Topics in Stereochemistry, Volume 14

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TOPICS IN STEREOCHEMISTRY

VOLUME 14

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TOPICS IN

STEREOCHEMISTRY

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VOLUME 14

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INTRODUCTION TO THE SERIES

During the past two decades several texts in the areas of stereochemistry and conformational analysis have been published, including *Stereochemistry of Carbon Compounds* (Eliel, McGraw-Hill, 1962) and *Conformational Analysis* (Eliel, Allinger, Angyal, and Morrison, Interscience, 1965). While the writing of these books was stimulated by the high level of research activity in the area of stereochemistry, it has, in turn, spurred further activity. As a result, many of the details found in these texts are already inadequate or out of date, although the student in stereochemistry and conformational analysis may still learn the basic concepts of the subject from them.

For both human and economic reasons, standard textbooks can be revised only at infrequent intervals. Yet the spate of periodical publications in the field of stereochemistry is such that it is an almost hopeless task for anyone to update himself by reading all the original literature. The present series is designed to bridge the resulting gap.

If that were its only purpose, this series would have been called "Advances (or "Recent Advances") in Stereochemistry." It must be remembered, however, that the above-mentioned texts were themselves not treatises and did not aim at an exhaustive treatment of the field. Thus the present series has a second purpose, namely, to deal in greater detail with some of the topics summarized in the standard texts. It is for this reason that we have selected the title *Topics in Stereochemistry*.

The series is intended for the advanced student, the teacher, and the active researcher. A background for the basic knowledge in the field of stereochemistry is assumed. Each chapter is written by an expert in the field and, hopefully, covers its subject in depth. We have tried to choose topics of fundamental import aimed primarily at an audience of inorganic and organic chemists but involved frequently with fundamental principles of physical chemistry and molecular physics, and dealing also with certain stereochemical aspects of biochemistry.

It is our intention to bring out future volumes at intervals of one to two years. The editors will welcome suggestions as to suitable topics.

We are fortunate in having been able to secure the help of an international board of editorial advisers who have been of great assistance by suggesting topics and authors for several chapters and by helping us avoid

duplication of topics appearing in other, related monograph series. We are grateful to the editorial advisers for this assistance, but the editors and authors alone must assume the responsibility for any shortcomings of *Topics in Stereochemistry*.

N. L. ALLINGER
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PREFACE

In the first of four chapters in this volume of *Topics in Stereochemistry*, Michinori Ōki presents a comprehensive review of atropisomerism with special reference to the literature of the past two decades. The review summarizes restricted rotation about sp^2–sp^2, sp^2–sp^3, and sp^3–sp^3 bonds and it concludes with an analysis of reactions of isolated rotational isomers. It places particular emphasis on the magnitude of rotation barriers as a function of structure (incidentally identifying some of the largest barriers yet measured to conformer interconversion) and on the isolation of stable single-bond rotational diastereomers.

The second chapter, by Jan Sandström, deals with stereochemical features of "push–pull" ethylenes. The focus is on rotational barriers, which span a large range of values. The ease of twisting is partly a matter of electron delocalization and partly a matter of steric and solvent effects. Electronic structure and such related items as dipole moments and photoelectron spectra for these systems are discussed. The chapter also deals with the structure and chiroptical properties of twisted ethylenes that do not have push–pull effects, such as *trans*-cyclooctene.

In the third chapter, Hans Hirschmann and Kenneth R. Hanson provide a detailed analysis of the principles of stereochemical classification or factorization. In contrast to the system earlier proposed by Cahn, Ingold, and Prelog (and recently extended and modified by Prelog and Helmchen) featuring centers, axes, and planes of chirality, Hirschmann and Hanson here present an alternative scheme not limited to chiral structures. This scheme for the factorization of stereoisomerism uses as principal elements the center and line of stereoisomerism. Numerous examples are given.

In the fourth and final chapter, Howard Haubenstock discusses asymmetric reduction of organic molecules. Within this general topic of wide and continuing interest, Haubenstock's chapter deals with chiral derivatives of lithium aluminum hydride, their preparation from suitable amino or hydroxy compounds, and their use in reducing carbonyl groups. Related reactions of the Meerwein–Ponndorf–Verley type or involving trialkylaluminum reagents are also presented.

Professor Guy Ourisson, who served as one of our editorial advisors since the beginnings of *Topics of Stereochemistry* some 15 years ago, has now relinquished his position; we are grateful to him for his valuable

advice over the years. In turn, we welcome two new members to our Editorial Advisory Board: Professor Jean-Marie Lehn (Collège de France, Paris) and Professor John B. Stothers (University of Western Ontario, London, Ontario, Canada) who will help us maintain—and even extend—the world-wide representation of our advisors.

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Athens, Georgia
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CONTENTS

TOPICS IN STEREOCHEMISTRY

VOLUME 14

Recent Advances in Atropisomerism

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I. INTRODUCTION

A. Atropisomerism

The word *atropisomerism* was coined by Kuhn (1) to cover isomerism caused by "freezing" the internal rotation about a single bond in a molecule. Indeed,

free rotation about a single bond had been accepted in chemistry, since no sign of the presence of isomers in molecules of XYZC—CX′Y′Z′ had been apparent. The first example of stable isomers due to restricted rotation, 2,2′-dinitro-6,6′-diphenic acid, was resolved by Christie and Kenner (2). Since then many biphenyl derivatives have been resolved into optical isomers (3). The term *atropisomerism* in its original meaning was coined to encompass the optical isomers of the biphenyls.

The concept of atropisomerism developed to a considerable extent following other developments in chemistry, especially those in spectroscopy. Early work by Kohlrausch (4) and Mizushima (5), based on Raman spectra and dipole moment studies, established that rotational isomers—*rotamers*—must exist in 1,2-dichloroethane. Pitzer established that there are three energy minima when ethane is rotated about its C—C axis (6). Rotamers about single bonds have been found in a wide variety of organic compounds since then, mainly as a result of the application of vibrational spectroscopy to organic molecules (7).

Those organic compounds that exhibit separate signals in vibrational or other kinds of spectroscopy due to rotamers do not necessarily give rise to atropisomers in the classical sense of Kuhn. It is now well known that, in order to recognize two isomers by a spectroscopic method, the mean lifetime (τ) of the isomer must exceed

$$\tau = \frac{1}{2\pi\Delta\nu}$$

where $\Delta\nu$ is the difference in frequencies (8). Since a difference of 20 cm^{-1} is a typical value in vibrational spectroscopy, a mean lifetime of 10^{-12} sec will suffice to give separate signals. This means that vibrational spectroscopy can detect individual atropisomers having lifetimes of more than about 10^{-11} sec. Isolation of rotamers detected by vibrational spectroscopy is not realistic, because these lifetimes are too short for isolation by conventional methods. In addition, vibrational spectroscopy does not give information about the rates of rotation, because rotamers usually have long enough lifetimes to exhibit independent signals characteristic of the respective isomers. If one takes the barrier to rotation of 3 kcal/mol, which is that of ethane (6), one calculates the rate constant for rotation of ethane, using the Eyring equation (9), to be ca. 10^{11} sec^{-1}. This is too slow for vibrational spectroscopy to give information about the rotation.

The introduction of microwave and far-infrared spectroscopy changed the situation somewhat. These techniques give the barriers to rotation if they are on the order of a few kilocalories per mole (10). Such values are still too low for the chemical isolation of atropisomers.

NMR spectroscopy changed the whole story drastically. If we deal with ^1H NMR signals, the difference in chemical shifts between two signals will typically

be 10 to 100 Hz. Thus, if the lifetimes of two exchanging sites exceed about 10^{-1} to 10^{-2} sec, they are detected by NMR spectroscopy as distinct entities. If the exchange rates exceed 10 to 100 sec^{-1}, the two sites give a single, time-averaged signal at a chemical shift determined by the chemical shifts of the contributing species and their populations (11).

A strong point of NMR spectroscopy, from the standpoint of investigation of rotational isomerism, is that information at various temperatures can be obtained without difficulty. When the temperature is lowered to make the exchange rate slow enough for NMR spectroscopy to detect two sites, two signals appear, whereas a sole signal, corresponding to an average of the two sites, is seen at higher temperature. The reverse occurs if the exchange rate is slow at low temperature and the temperature is raised. The merging of the two signals is called *coalescence*. At temperatures slightly above or below coalescence, the line shapes of NMR spectra change dramatically. Analysis of the line shapes can be used to give the rate constant of the exchange at a given temperature (11); this analysis requires the use of computer simulation. If only $\Delta G^{\ddagger}$, the free energy of activation, is required, and a high degree of accuracy is not demanded, a simple approach, called the *coalescence temperature method*, may be used. The coalescence temperature is the lowest temperature at which two signals merge and no minimum is seen between them. If two equally populated sites give two singlets at low temperatures, then the rate (k_c) of site exchange and the free energy of activation ($\Delta G_c^{\ddagger}$) at the coalescence temperature are given by eqs. [1] and [2], where T_c is the coalescence temperature.

$$k_c = \frac{\pi}{\sqrt{2}} \Delta\nu \qquad [1]$$

$$\Delta G_c^{\ddagger} = 4.57\, T_c \left[10.32 + \log_{10} \left(\frac{T_c}{\Delta\nu} \right) \right] \qquad [2]$$

If the nuclei interact with each other and give an AB quartet signal, then k_c and $\Delta G_c^{\ddagger}$ are given by the following equations:

$$k_c = \frac{\pi}{\sqrt{2}} \sqrt{\Delta\nu^2 + 6J^2} \qquad [3]$$

$$\Delta G_c^{\ddagger} = 4.57\, T_c \left[10.32 + \log_{10} \left(T_c / \sqrt{\Delta\nu^2 + 6J^2} \right) \right] \qquad [4]$$

where $\Delta\delta$ is the chemical shift difference between the two sites and J_{AB} is the coupling constant. Since NMR spectroscopy deals with subtle differences in frequencies, the line shape method, or dynamic NMR (11), gives useful information about the possibility of isolating rotamers. Table 1 gives the free energy

Table 1
Free Energies of Activation ($\Delta G^{\ddagger}$) Necessary to Give a Half-Life of 1000 Seconds

	$\Delta G^{\ddagger}$ (kcal/mol)	
Temperature (K)	$K = 1.0$	$K = 10^a$
200	14.73	14.49
250	18.52	18.23
300	22.34	21.98
350	26.17	25.75
400	30.01	29.53
450	33.87	33.33
500	37.74	37.14

[a]Free energies of activation required when the isomerization starts from the pure isomer that is the less favored one at equilibrium.

of activation for rotation that gives a half-life of 1000 sec at various temperatures. This half-life is considered the minimum requirement for chemically isolating an isomer. Tables 2 and 3 summarize the free energies of activation for rotation at a coalescence temperature with a given chemical shift difference between two sites, when there is no coupling (Table 2), or when coupling results in an AB quartet between the two nuclei (Table 3). Since the entropy of activation for rotation is believed to be small, especially when the molecule in question is a hydrocarbon, the $\Delta G_c^{\ddagger}$'s at a coalescence temperature may, as a first approximation, be used as the barrier to rotation at any temperature. Then $\Delta G_c^{\ddagger}$ gives a good estimate as to whether the rotamer in question can be isolated at a given temperature.

Table 2
Free Energies of Activation ($\Delta G_c^{\ddagger}$) for the Exchange Obtained by the Coalescence Method at a Given Chemical Shift Difference and a Given Temperature

Chemical Shift Difference (Hz) / T_c (K)	10	20	50	100
	$\Delta G^{\ddagger}$ (kcal/mol)			
200	10.30	10.03	9.66	9.39
250	12.99	12.64	12.19	11.85
300	15.69	15.28	14.74	14.32
350	18.42	17.94	17.30	16.82
400	21.15	20.60	19.88	19.33
450	23.90	23.28	22.47	21.85
500	26.66	25.98	25.07	24.38

Table 3
Free Energies of Activation ($\Delta G_c^{\ddagger}$) for the Exchange Obtained by the Coalescence Method at a Given Chemical Shift Difference and a Given Temperature with a Coupling Constant of 14 Hz (AB Spins)

Chemical Shift Difference (Hz) / T_c (K)	10	20	50	100
	$\Delta G_c^{\ddagger}$ (kcal/mol)			
200	9.80	9.75	9.59	9.36
250	12.36	12.30	12.09	11.82
300	14.94	14.87	14.62	14.29
350	17.53	17.46	17.16	16.78
400	20.14	20.06	19.72	19.28
450	22.77	22.67	22.29	21.80
500	25.40	25.30	24.88	24.32

B. Scope of This Chapter

As has been mentioned, the term *atropisomerism* has a broad meaning. If we discuss atropisomerism from the standpoint of vibrational spectroscopy, then almost all organic compounds would give rise to atropisomers. If we are discussing atropisomerism from the standpoint of NMR spectroscopy, then it is necessary to specify the temperature at which we measure the spectrum. The strength of the main magnetic field (or observation frequency) is also a concern. Eliel discussed the term *residual isomerism* in this connection (12). Since we cannot cover all types of atropisomerism here, the present discussion will be confined to atropisomerism wherein isomers are isolated chemically.

Even though we define the atropisomerism as above for present purposes, there remain some ambiguities. *sym*-Tetrabromoethane was obtained in different modifications according to the method of crystallization at low temperature (13). These were found by spectroscopy to correspond to rotamers. Similar situations occur in other alkyl halides and acetates (14,15). Such cases will not be included in the discussion, mainly because crystalline atropisomers are isolated at far lower temperatures than the ambient, and their barriers to rotation have not been determined by equilibration. Also excluded is the isolation of chlorocyclohexane (16). The isolation of the equatorial and axial conformational isomers was possible only by crystallization of the former at $-150°C$, although it was possible to observe equilibration between the equatorial and the axial forms at higher temperatures.

The main purpose of this chapter is to review cases where stable rotamers are isolated at room temperature or above. This means that free energies of activation of more than ca. 23 kcal/mol separate the atropisomers focused on in

this chapter. Owing to the development of NMR spectroscopy, it is now possible to discuss the effect of structure and substituents on rotational barriers and populations of rotamers, and these points will be discussed in detail. The end result should be an informative rather than exhaustive review.

Furthermore, several types of atropisomers will be excluded from discussion even though they fall within the category just delimited. The most classical example comprises biphenyls and related compounds, which continue to attract the interest of chemists even today (17). Atropisomers of cyclophanes and related compounds constitute classical examples as well (18). Since these compounds do not give stable diastereomers but only enantiomers, they will not be discussed in detail. Paquette and his co-workers have done interesting work on optically active cyclooctatetraene derivatives (19), as have Mislow et al. on triarylmethanes and analogs (20). Although the latter work includes diastereomers (21), in addition to enantiomers, it is not discussed because it is concerned with correlated rotations of several single bonds. Thus, this review is confined to the discussion on atropisomerism that can be seen at about room temperature or above by chemical means, involves one single bond, and gives rise to stable diastereomers.

The final class of compounds excluded from this chapter is that of the cis–trans isomers of olefins. Olefins do give rise to diastereomers due to restricted rotation, but have been dealt with in a previous volume of this series (22).

C. Nomenclature of Atropisomers

Since atropisomers are conformational isomers, their stereochemistry should be designated by IUPAC nomenclature rule E (23). For the convenience of the reader, the rule will be outlined here. A sequence number is given to substituents connected to the rotational axis according to the Sequence Rule (24), as follows.

If a ligand is connected to an atom of a rotational axis through an atom of higher atomic number than others, then that ligand precedes others. If the sequence number is not determined by the first atom, then the next atom of highest atomic number farther away from the axis is considered. Thus an ethyl group precedes a methyl because the ethyl has a carbon (CH_3) atom attached to the ligated carbon (CH_2), whereas the methyl has only hydrogens.

For descriptions of conformations, additional rules are necessary:

1. If the molecule in question has an XYZC— group where the carbon atom forms part of the axis of rotation, then the ligand (X, Y, or Z) of highest precedence among the three in the Sequence Rule is taken as the reference.
2. If the molecule has an XY_2C— group, the unique group X is taken as reference, irrespective of the precedence according to the Sequence Rule.
3. For an ethane-type molecule, a Newman projection is written and the

angle made by two reference substituents is considered. If the angle falls in the sc region ($\tau = 30 \sim 90°$), the conformation is called sc (see Fig. 1). If the angle corresponds to ap ($\tau = 180 \pm 30°$), the conformation is ap. Although the IUPAC rule does not recommend the use of signs as in ±sc or ±ac, signs will be used throughout this chapter where appropriate, because their use avoids misunderstandings in certain cases.

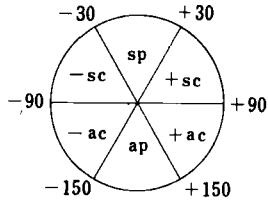
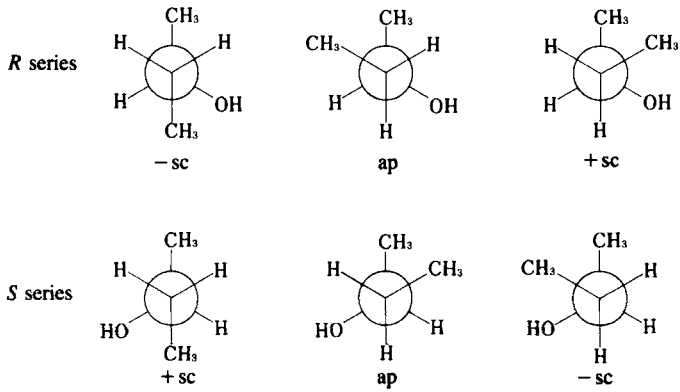


Figure 1

There is another point of nomenclature that must be discussed, namely where a chiral center is involved. Taking the simple case of 2-butanol, $CH_3CH(OH)CH_2CH_3$, we can explain the point as follows (Scheme 1). Two configurations are possible at the chiral center. In both the *R* and the *S* series, three conformations are possible. The +sc form in the *R* series and the −sc form in the *S* series are enantiomers and their free energies must be the same under achiral conditions. However, the −sc form in the *R* and that in the *S* series differ in free energies. Therefore, it is not sufficient to call a conformation −sc if a chiral center is involved. In this case we may have to call such conformations −sc(*R*) and −sc(*S*) to distinguish them.

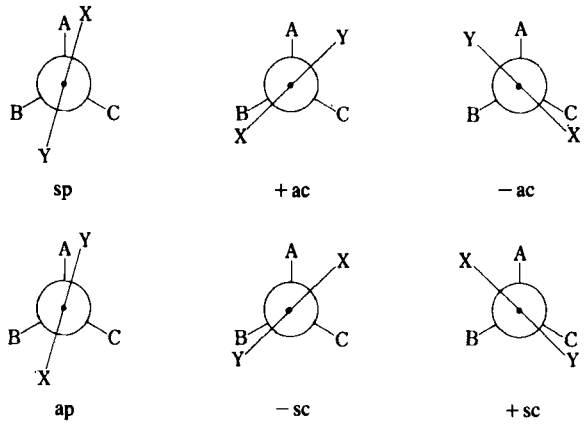
It is recommended in rule E of the IUPAC nomenclature that *RS* be used when the compound in question is a racemate. Then the conformations −sc(*R*)



Scheme 1

and $+sc(S)$ may be written as $\mp sc(RS)$. But this conformational description can cause confusion for the following reasons: If there are two chiral centers connected by a single bond and we discuss the conformations, it is apparent from the foregoing discussion that we have to give the absolute configurations of both chiral centers. Then we had better reserve the description (RS) for the conformation concerned with an R chiral center and an S chiral center. The symbols $sc^*(R^*)$ will be used throughout this chapter to describe a racemic mixture of $+sc(R)$ and $-sc(S)$. Likewise, $sc^*(S^*)$ means a racemic mixture of $+sc(S)$ and $-sc(R)$. The symbols ap and sp may be used instead of $ap^*(R^*)$ because both enantiomeric conformations are equal in energy irrespective of the absolute configuration of the chiral center, as far as we discuss conformations about a bond involving only one chiral center.

Conformations about an sp^3–sp^2 bond may be similarly designated. It is known that in these cases the stable conformation involves the eclipsing of a double bond by a single bond (25). Therefore, the following symbols are given if A>B>C and X>Y in the Sequence Rule (Scheme 2).



Scheme 2 (R series)

Again, the configuration of the chiral center must be considered if one is present, because the conformational energy of the $+ac$ conformation in the S series is the same as that of the $-ac$ conformation in the R series, but different from that of $+ac$. Here $ac^*(R^*)$ will be used to indicate a mixture of $+ac(R)$ and $-ac(S)$ conformations. Similar symbols may be used to designate other pairs of enantiomeric conformations. Again, sp and ap would suffice to designate a pair of enantiomers, because their conformational energies are the same irrespective of the absolute configuration at the chiral center.

Conformations about an sp^2–sp^2 bond can also be designated by the foregoing rule; that is, the conformation s-cis in the older designation is sp, whereas the

s-trans becomes ap. However, it is now more common to use the symbols *E* and *Z* for ap and sp conformations, respectively (26), and this practice will be followed here.

II. ATROPISOMERISM ABOUT sp^2–sp^2 BONDS

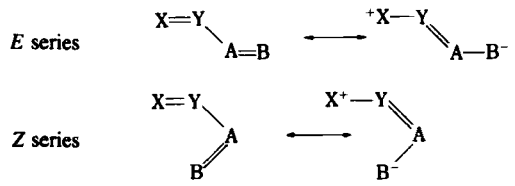
The most classical examples of atropisomerism, biphenyls, fall into this category. They form enantiomers because the two benzene rings are not coplanar and both rings are substituted unsymmetrically so that the plane passing through the pivot bond and one of the benzene rings cannot be a σ plane. If we consider the conformations of biphenyls in more detail, we recognize that there are two diastereomeric conformations possible, as depicted in Scheme 3 for a compound

Scheme 3

of given configuration. There are a few reports about conformations of this type in biphenyls (27), but the barrier for their interconversion is too low for the isolation of rotamers at ambient temperatures and barrier heights are not reported.

This type of isomerism is possible not only in biphenyls, but also in compounds in which rotation about an sp^2–sp^2 bond is restricted and the two planes involving the sp^2 center are noncoincident and substituted unsymmetrically. In addition to enantiomers, diastereomers are possible. There are some examples reported of restricted rotation about an aromatic ring-to-carbonyl bond or aromatic ring-to-nitrogen bond (28). Since these reports make no mention of diastereomers but only of enantiomers, they will receive no further mention here.

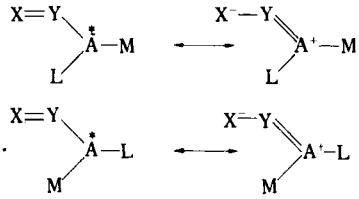
If two planar unsaturated groups are linked by a single bond (conjugated), the planar conformation is stabilized. In terms of valence bond theory, the planar structure is stabilized due to the contribution of resonance forms (Scheme 4).



Scheme 4

In other words, if the two halves of the molecule rotate out of the plane, the potential energy increases and a barrier exists. The barrier is expected to be higher if the contribution of the dipolar structure is large. *E* and *Z* diastereomers can in principle be isolated.

This type of conjugation is also possible if an atom with a lone pair of electrons is connected to an sp^2 center, because once again the planar structure is stabilized by resonance. Such molecules give rise to *E* and *Z* isomers as shown in Scheme 5. (The asterisk in Scheme 5 and in **1** and **2** indicates the lone pair in the orbital at a right angle to the plane of the paper.)

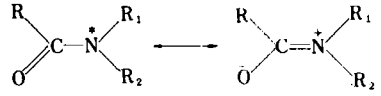


Scheme 5

The amides, nitrosamines, and enamines discussed in this chapter fall in this category. Diastereomeric atropisomers of the X=Y—A=B type have never been isolated, because high enough stabilization of the ground state (planar structure) can be realized only when one end of the sp^2–sp^2 bond is strongly electron donating and the other is strongly electron accepting. This point will be clear from the discussion given in the following sections.

A. Amides

Amides possess planar or almost planar structures (**1** and **2**). Their rotational ground state is stabilized because the amino group is a strongly electron-donating group and the carbonyl function is strongly electron accepting. Excellent reviews on this topic have been published (28,29,30), and should be consulted by readers interested in amide rotation.



1 **2**

Restricted rotation about the C—N bond of amides was studied by Gutowsky and Holm in the earliest days of NMR spectroscopy (31). A number of papers have been published since then. However, due to various difficulties, the barriers

to rotation about the amide C—N bond that were reported in those early days are not necessarily reliable, in contrast to later data obtained by total line shape analysis of the NMR signals. Barriers based on recent data (if such are available) are discussed below. However, readers should note that a subtle difference in barriers to rotation is usually not significant in discussing whether or not atropisomers of the compound in question are isolable at room temperature.

Barriers to rotation about the C—N bond of *N,N*-dimethylformamide are known to be affected by concentration and the nature of the solvent. As expected, polar solvents tend to increase the barrier by stabilizing the polar structure (**2**). Therefore, it is not surprising that, whereas the barrier to rotation of *N,N*-dimethylformamide is about 21 kcal/mol in solution, the barrier becomes as low as 15.6 kcal/mol in the gas phase (32). In the practical question of isolating atropisomers, it is the magnitude of the barrier in solution that matters.

Barriers to rotation about the amide C—N bond are sensitive to the steric effects of both of the substituents on nitrogen and of that within the acyl group. Typical examples of *N,N*-dimethylalkanamides, as studied by dynamic NMR (33), are listed in Table 4. Clearly, the bulkier the substituent, the lower the barrier. This is usually attributed to a raising of the ground state energy of the amide. Since the barrier to rotation is the difference in energy between the ground state and the transition state for rotation, it is, however, difficult to discuss precisely where the effect of substituents occurs. Generally only the effect presumed to be of greatest importance, in either the ground state or the transition state, is discussed.

The effects of the substituents on nitrogen on rotational barriers were discussed by Yoder and Gardner (34) for formamides and acetamides. The pertinent data, given in Table 5, suggest that the barriers to rotation of formamides are not affected by the bulkiness of the alkyl group on nitrogen, but such a conclusion

Table 4
Effect of the Alkyl Groups of *N,N*-Dimethylalkanamide [$RCON(CH_3)_2$] on the Barrier to Rotation (33)

R	$\Delta G^{\ddagger}_{298.2}$ (kcal/mol)
H[a]	20.6
CH_3[a]	18.2
C_2H_5[a]	18
$(CH_3)_2CH$[b]	16.2
$(CH_3)_3C$[c]	12.2

[a]Pure liquid.
[b]*o*-Dichlorobenzene solvent (concentration not given).
[c]Dichloromethane solvent (10 mol %).

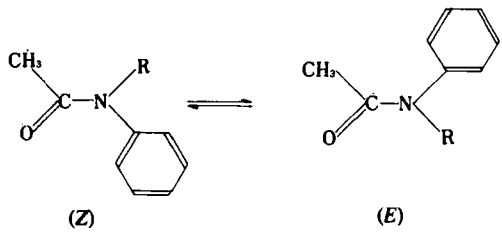
Table 5
Effect of Substituents on Nitrogen on the Barrier to Rotation of Formamides and Acetamides ($RCONR'_2$)[a]

R	R'	$\Delta G^{\ddagger}_{289.2}$ (kcal/mol)
H	CH_3	20.6
H	C_2H_5	20.9
H	$(CH_3)_2CH$	20.6
H	$(CH_3)_2CHCH_2$	21.0
CH_3	CH_3	18.1
CH_3	C_2H_5	17.8
CH_3	$(CH_3)_2CH$	16.2

[a]Compiled by Yoder and Gardner (34) from various sources.

may be premature until a bulkier substituent, such as *tert*-butyl, is introduced. An isopropyl group may take on a conformation in which its effective size is not much different from that of a primary alkyl group. In contrast, the *N,N*-dialkylacetamides definitely show a decrease in barrier height when the alkyl group becomes larger. This is again attributed to the steric interaction which raises the energy of the ground state.

The bulkiness of the substituents in amides affects their conformational equilibria. The situation in formamide again contrasts with that in other amides. Because it is smaller than oxygen, the hydrogen atom in formamides favors the conformation in which the bulkier substituent on nitrogen takes the conformation syn to it, whereas in acetamides, for example, the bulkier group takes the conformation syn to oxygen rather than to methyl. A typical example is provided by acetanilide derivatives. In acetanilide (**3**, R = H), the *Z* conformation predominates and none of the *E* form can be detected. However, when an *N*-alkyl group is introduced into acetanilide (**3**, R = alkyl), the presence of the *E* conformation becomes detectable. *N*-Methylacetanilide is known to be stable in the *E* conformation, which constitutes 99.5% of the molecules in pyridine solvent. X-ray crystallography of this compound was carried out, confirming that the *E* conformation exists in the solid state. In addition, X-ray diffraction results re-



(*Z*) (*E*)

3

vealed that the benzene ring in *N*-methylacetanilide is orthogonal to the amide plane (35).

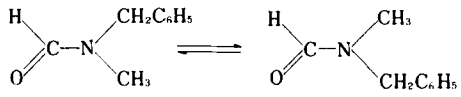
Barriers to rotation about the amide bond are expected to be affected by the electronic effect of the *R* substituent, because the electronic effect of the substituent should either stabilize or destabilize the canonical structure **2**. Rogers and Woodbrey (36) found that the barriers to rotation of *N,N*-dimethylcarbamic acid derivatives were lower than those of *N,N*-dimethylformamide and *N,N*-dimethylacetamide, and they attributed this phenomenon to the cross-conjugation of the carbonyl group, which disfavors the canonical structure **2**. They also introduced some strongly electron-withdrawing substituents in the acyl part of the molecule, but it was difficult to analyze the results because both electronic and steric effects are operative. Likewise, a substituent on nitrogen (R_1, R_2) that disfavors structure **2** decreases the barrier to rotation. Since the lone pair of electrons on nitrogen in pyrrole is a part of the π sextet, acetylpyrrole is expected to have a low C—N barrier, and the observed barrier is indeed low (37). Acetylimidazolide and aceto-1,2,4-triazolide have similarly low barriers.

Neuman and Jonas (38) summarized these results, although the number of examples they considered was rather small. According to their study, the difference in barriers to rotation between a given substituent and a methyl group in the acyl part of *N,N*-dimethylamides is given by the following equation:

$$\Delta\Delta G^{\ddagger}/2.3RT = (-\Delta G^{\ddagger}_{R} + \Delta G^{\ddagger}_{CH_3})/2.3RT = \rho^*\sigma^* + sE_s \qquad [5]$$

where the $\Delta G^{\ddagger}$'s are the free energies of activation, and R and CH_3 refer to the values for the substituent in question and CH_3 (acetamide), respectively. The σ^* is a substituent constant referring to inductive effects and E_s is a substituent constant referring to the steric effect, while ρ^* and s are reaction constants. If we empirically adopt the values of -1 for ρ^* and -2 for s, a good linear relationship results. Yoder and Gardner (34) elaborated on this work and found that the steric effect is more important than the electronic effect in determining the barrier to rotation. They point out that the ν value introduced by Charton (39) as a steric parameter gives better fits than E_s for the barriers to rotation of amides.

As has been discussed, ordinary formamides have a barrier of about 21 kcal/mol, which is a little less than that required for the isolation of atropisomers at room temperature. This means that, at a temperature slightly lower than ambient, it may be possible to obtain stable rotamers. This possibility was first realized by Gutowsky, Jonas, and Siddall (40). They used a uranyl nitrate complex of *N*-benzyl-*N*-methylformamide (**4**) crystallized from dichloromethane. When the crystals were washed with ice water to strip off the uranyl nitrate, a mixture of *E* and *Z* forms (*Z*/*E* = 1.6) was obtained. Since the equilibrium mixture gives a *Z*/*E* value of 0.8, it was possible to perform a kinetic study of equilibration



(*E*) (*Z*)

4

on this mixture, and $\Delta G^{\ddagger}_{373.1}$ was found to be 21.6 ± 0.7 kcal/mol. The equilibrium constant reflects the fact that the benzyl group is larger than the methyl; the larger group favors the position sp to the hydrogen in the formyl group.

It is well known in organic chemistry that, due to the steric effect of the 2,6-substituents, the carbonyl group and the mesitylene plane in a mesitoyl (2,4,6-trimethylbenzoyl) group cannot be coplanar. The barrier to rotation about the C_{Ar}—CO bond in this group is expected to be high from the analogy of 2,6-disubstituted styrenes, which were isolated as stable enantiomers (41). Mannschreck, Staab, and Wurmb-Gerlich (37) studied the possibility of using this fact to raise the barrier to rotation of amides. Severe interaction is expected between R_1 or R_2 with the mesityl group in the transition state for rotation about the N—CO bond. They found that 1-mesitoylpyrrole indeed has a much higher barrier to rotation (T_c of signals due to pyrrole 2-H and 5-H, 60°C) than 1-acetylpyrrole (T_c of signals due to the same protons, 37°C). Introduction of a methyl group into the 2-position of the imidazole ring of mesitoylimidazolide raised the barrier to rotation greatly (T_c over 180°C).

As an extension of this work, Mannschreck prepared a series of mesitamides (42). He found the barrier to rotation in *N,N*-dimethylmesitamide (**5**, $R_1 = R_2 = CH_3$) to be 22.5 kcal/mol, which is high enough to see the transient rotamer species if R_1 and R_2 are not the same. Indeed, he was able to isolate the pure *Z* form of *N*-benzyl-*N*-methylmesitamide (**5**, $R_1 = CH_3$, $R_2 = CH_2C_6H_5$). On dissolution of the amide in carbon tetrachloride, isomerization of the *Z* form to the *E* was observed with a $\Delta G^{\ddagger}_{38.2}$ of 22.9 kcal/mol, giving a mixture of *Z*/*E* = 1.0 : 0.36. The *E* form was enriched up to 69% in the mother liquor of crystallization of the *Z* form. The results summarized in Table 6 show that the barriers to rotation are raised when the substituents on nitrogen become larger, but the effect is rather small. The equilibrium constants are as expected from the steric effect. Being a large group, mesityl disfavors the conformation in which a larger group on nitrogen occupies the position syn to it.

Staab and Lauer introduced *tert*-butyl groups into the benzene ring of the acyl

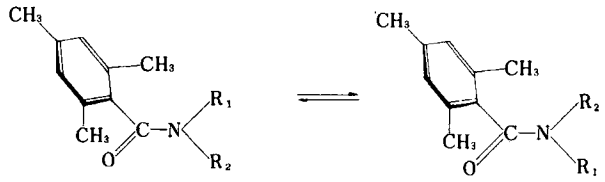


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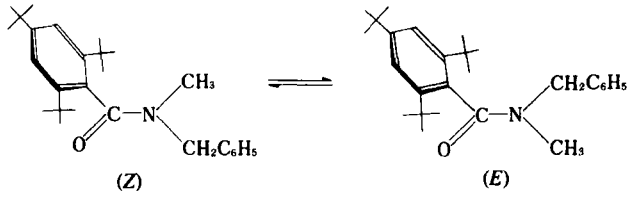
Table 6
Barriers to Rotation of Some Mesitamides (**5**)

R_1	R_2	Solvent	$\Delta G^{\ddagger}$ (kcal/mol)[a]	K (E/Z)	T (°C)
CH_3	$CH_2C_6H_5$	CCl_4	22.9	0.36	38.2
CH_3	$CH_2C_6H_5$	Quinoline	23.4	0.38	40.6
CH_3	Cyclohexyl	CCl_4	23.2	0.43	38.8
$CH_2C_6H_5$	$(CH_3)_2CH$	Quinoline	23.9	0.28	38.8

[a]For the process from the stable form to the less stable.

group (43). They were able to isolate atropisomers of *N*-benzyl-*N*-methyl-2,4,6-tri-*tert*-butylbenzamide (**6**) by fractional crystallization. The barrier to rotation was examined by equilibration at 160–180°C in 1-chloronaphthalene-α,α,α-trichlorotoluene solution and $\Delta G^{\ddagger}_{393}$ was found to be 32.0 kcal/mol for the process $Z \rightarrow E$. The equilibrium constant (E/Z) at this temperature was 0.12, which was as expected on steric grounds. The higher barrier of compound **6** relative to



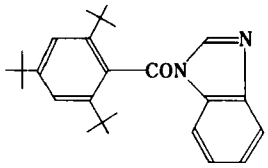
(*Z*) (*E*)

6

compound **5** is attributable to the steric effect of the *tert*-butyl groups; that is, the transition state for rotation is raised in energy relative to the ground state.

Mannschreck et al. (44) examined the effect of substituents on the barriers to rotation in 2,4,6-trisubstituted benzamides. In *N*-benzyl-*N*-methyl-2,4,6-tribromobenzamide, the rotational barrier ($\Delta G^{\ddagger}$) is 23.8 kcal/mol at 35.8 to 40.6°C for the $Z \rightarrow E$ process in quinoline (44). This should be compared with $\Delta G^{\ddagger}$ of 23.4 kcal/mol for the same process with the trimethyl compound (**5**). It is seen that steric effects are of primary importance, inasmuch as the van der Waals radii of the methyl and bromo groups are almost the same.

Having obtained stable rotamers of compound **6**, Staab and Lauer (45) extended the work to see whether rotamers of amides that normally have lower barriers as a result of a disfavored canonical structure **2** due to electronic effects are also isolable. They found that the rotamers of 2,4,6-tri-*tert*-butylbenzobenzimidazolide (**7**) were isolable, but those of the corresponding imidazolide (**8**) were not. The barrier to rotation of the former in hexachlorobutadiene solution was 28.7 kcal/mol for the $E \rightarrow Z$ process at 80°C. The barrier to rotation of the latter was estimated at less than 23 kcal/mol. It is possible to attribute this result to electronic effects that raise the ground state energy, because the aromatic



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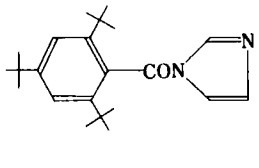

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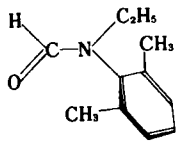
character of imidazole is stronger than that of benzimidazole, leading to less $^{-}O—C{=}N^{+}$ double-bond character. However, the steric effect, which will certainly raise the transition state energy for rotation, should not be forgotten. The benzimidazolyl group should give larger steric effects with the 2,4,6-tri-*tert*-butylphenyl group in the (planar) transition state for rotation than the smaller imidazolyl group.

As was discussed earlier, *N*-substituted acetanilides take on conformations in which the amide and the phenyl groups are orthogonal to each other. In this conformation, the electron-withdrawing ability of the phenyl group is diminished because of the inhibition of resonance. Thus it is expected that the canonical structure **2** is not destabilized by N–Ar resonance but only by the $-I$ effect of the phenyl group. The feasibility of isolating atropisomers of amides of this type becomes great, since, in the transition state for rotation of the amide group, the steric interaction between the *N*-substituents of the amide moiety and the phenyl group becomes large if the phenyl group carries substituents in the 2,6-positions. In these compounds, it is also possible to observe restricted rotation about the $N—C_{Ar}$ bond but this type of atropisomerism will not be dealt with here.

Siddall and his co-workers (46) have examined the barriers to rotation of a series of 2,6-disubstituted anilides. *N*-Ethyl-*N*-(2,6-xylyl)formamide (**9**) was recrystallized as a uranyl nitrate complex, and one isomer, which at equilibrium was favored by a factor of 3 : 1, was enriched up to a 30 : 1 ratio. The kinetics of rotation were examined at 0 to 29°C. The Arrhenius activation energy was 26 ± 3 kcal/mol and log *A* was 18.5 ± 2.4 hr^{-1}. Siddall and Garner (47) were able to obtain an almost pure isomer (which also predominated at equilibrium: 1.3 : 1 for the ethyl compound and 1.1 :1 for the methyl compound) of *N*-alkyl-*N*-(2-methyl-4,6-dibromophenyl)-1-naphthamide (**10**). The half-lives of



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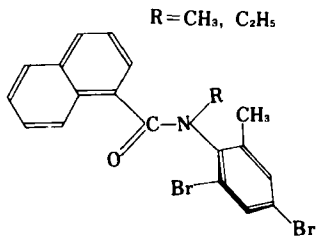

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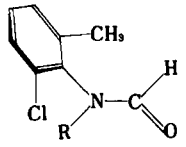
the methyl and the ethyl compounds at 25°C in chloroform-*d* solutions were 22 and 70 min, respectively. Apparently there is a steric effect by the alkyl group which raises the energy of the transition state for rotation.

Siddall (48) also reported that the barriers to rotation in *N*-substituted *N*-(2-chloro-6-methylphenyl)formamides (**11**) were high, but not high enough for the isolation of atropisomers. The exact barriers were not reported but, if one compares them with those in compound **9**, the barriers to rotation of these compounds are lowered by the substitution of the chloro group for the methyl on the aromatic ring.



R = C_2H_5, $-CHC_6H_5$ (CH₃)

11

A similar kind of steric effect was examined by Chupp and Olin (49), although the system contained a halogen atom in the acetyl moiety. The results are given in Table 7. The assignment of stereochemistry of the isomers was possible by taking into account the ring current effect in ^1H NMR spectroscopy. Although it was noted that the chemical shift differences become smaller as R and R_1 become larger, the assignment of stereochemistry was clear and was supported by aromatic solvent induced shifts. The Arrhenius activation energy for rotation ($Z \rightarrow E$) in **12** for R = *tert*-butyl, R_1 = ethyl, X = Br was 26.3 kcal/mol, whereas that in **12** for R = R_1 = *tert*-butyl, X = I was 27.8 kcal/mol. In both cases the entropy of activation was very close to zero. The results in Table 7

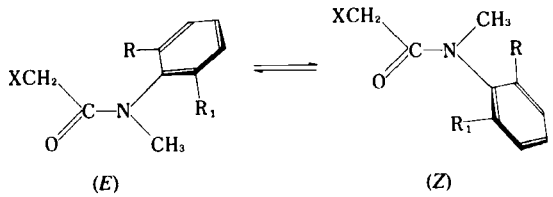
Table 7

Effect of Substituents on the Rotational Barriers and Equilibrium Constants of *N*-(2,6-Disubstituted phenyl)-*N*-methyl-haloacetamides (**12**)

Substituents				
R	R_1	Halogen	K (E/Z)[a]	$k \times 10^7$ (sec^{-1}, $Z \rightarrow E$)[a]
$(CH_3)_3C$	CH_3	Cl	0.078	25
$(CH_3)_3C$	C_2H_5	Cl	0.078	32
$(CH_3)_3C$	C_2H_5	Br	0.081	10
$(CH_3)_3C$	C_2H_5	I	0.12	5.9
$(CH_3)_3C$	$(CH_3)_3C$	Br	0.136[b]	164[b]
$(CH_3)_3C$	$(CH_3)_3C$	I	0.132[b]	165[b]

[a]Data obtained with carbon tetrachloride solutions at 25°C.

[b]Data obtained at 101°C. Other conditions not specified.

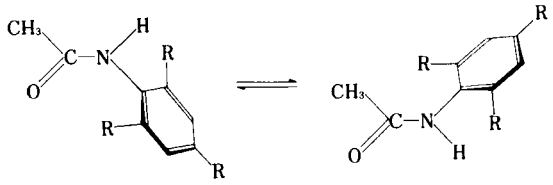


(*E*) (*Z*)

12

indicate that the effect on K of the second substituent in combination with the *tert*-butyl group in the aromatic ring is rather small, yet the E conformation becomes more favored when the bulkiness of the substituent increases. The rates of isomerization are, as expected, dependent on the size of the substituent: A *tert*-butyl group gives the highest barrier to rotation. A solvent effect on the barrier was also noticed; the more polar the solvent, the higher the barrier due to stabilization of the canonical structure **2**. The effect of halogens in the haloacetyl group on the barrier to rotation is appreciable in 2-*tert*-butyl-6-ethyl compounds, but is not apparent in 2,6-di-*tert*-butyl compounds.

Kessler and Rieker (50) studied the barriers to rotation and equilibrium constants of a series of *N*-(2,4,6-trialkylphenyl)acetamides (**13**). The barriers, which are generally low relative to those in the corresponding *N*-methyl compounds, and equilibrium constants are summarized in Table 8. The barrier is large when



(*Z*) (*E*)

13

Table 8

Effects of Alkyl Substituents on the Rotational Barriers and Equilibrium Constants of 2,4,6-Trialkylacetanilides (**13**)

R	K (E/Z)[a]	$\Delta G_c^{\ddagger}$ (kcal/mol)[b]	T_c(°C)[c]
CH_3	—	18.3	85
C_2H_5	31/69	18.8	95
$(CH_3)_2CH$	37/63	19.6	115
$(CH_3)_3C$	45/55	24.2[d]	150

[a]Data in chloroform-*d* solution.

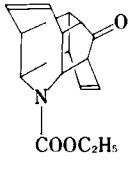
[b]Data in bromoform solution calculated from T_c and $\Delta\nu$ of the acetyl protons.

[c]Coalescence temperature of acetyl protons.

[d]Obtained from the *tert*-butyl protons.

the substituents are *tert*-butyl, and is then sufficient for the isolation of atropisomers at room temperature. Indeed, the *Z* conformation of **13**, R = *tert*-butyl, was isolated in more than 95% purity by thin-layer chromatography (TLC) carried out below 5°C. It is interesting that in this series the *Z* form is more stable than the *E*, although if the nitrogen is methylated, the *E* form is favored.

Ito and his co-workers (51) noticed that an adduct (**14**) of tropone with *N*-ethoxycarbonylazepine appeared to undergo slow internal rotation by ^{1}H NMR, the barrier at 83°C being 18.3 kcal/mol. As was discussed earlier, the ethoxycarbonyl group gives a lower barrier than those of acetyl and formyl derivatives. Indeed, by changing the *N*-substitutent from ethoxycarbonyl to acetyl, the barrier was raised to 20.0 kcal/mol. The formyl derivative showed a barrier to rotation of 23.0 kcal/mol at 20°C. It was possible to isolate a pure *Z* isomer and a nearly pure *E* isomer of the formyl derivative (**15**) by TLC. The free energy of activation



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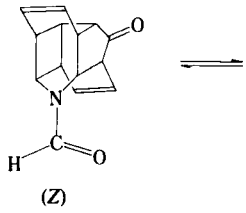

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for rotation was 23.5 ± 0.1 kcal/mol at 20°C, as determined by equilibration. The *Z* conformation was slightly more stable than the *E* form. The barriers to rotation of these compounds were all higher than those in corresponding open-chain compounds. This was attributed to the fact that, due to rigidity of the molecule, bond angle deformation of the nitrogen requires more energy: Since the hybridization of nitrogen changes from sp^2 in the ground state to sp^3 in the transition state for rotation, such a change in bond angle must occur during *Z–E* interconversion.

B. Thioamides and Selenoamides

Thioamides are known to exhibit higher barriers to rotation about their C—N bonds than the corresponding amides. The barrier in *N,N*-dimethylthioformamide corresponds to an Arrhenius activation energy of 27.9 ± 1.1 kcal/mol and a frequency factor of 4.4×10^{13} sec^{-1} for the neat liquid (52). Similarly, for *N,N*-diisopropylthioformamide, the Arrhenius activation energy is 31.8 ± 2.8 kcal/mol and the frequency factor was 8.9×10^{14} sec^{-1} when the line shapes given by pure liquid were analyzed. These tendencies were confirmed by more sophisticated analyses (53). The higher barriers of thioamides are attributed to a higher degree of contribution of the dipolar form (**17**) because the double bond

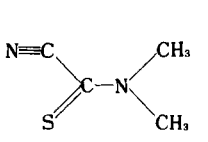
16 17

between carbon and sulfur is not as stable as that in a carbonyl. The stability of the polar structure is supported by the large dipole moment of thioamides (54). This consideration suggests that the effect of solvents on the barrier must be important, and that the concentration in solution should also affect the barrier. This expectation is found to be correct. At the extreme, *N,N*-dimethylthioformamide has a barrier to rotation as low as 22.5 kcal/mol at 420 K in the gas phase. This is about 3 kcal/mol lower than that obtained with the pure liquid (55).

Siddall and his co-workers studied the barriers to rotation of various thioamides by total line shape analysis (53). Barriers to rotation of thioformamides were about 24.5 kcal/mol and were not much affected by the nature of the alkyl groups on nitrogen. In thioacetamides, the barriers are slightly affected by the alkyl groups on nitrogen: the larger the alkyl group, the lower the barrier. *N,N*-Dimethylthioacetamide has a barrier of 21.8 kcal/mol at 136°C. This lowered barrier to rotation in thioacetamides may be attributed to a steric effect (CH_3 and R_1 interaction), which raises the ground state energy of the molecule. At any rate, thioformamides have higher barriers to rotation than the corresponding formamides by ca. 3.6 kcal/mol. This barrier should be high enough for isolation of stable isomers at room temperature, if $R_1 \neq R_2$ in **16**. The barriers to rotation of thioacetamides are ca. 3.0 kcal/mol higher than those in the corresponding oxygen compounds, but are not high enough for chemical isolation of atropisomers at room temperature.

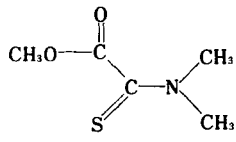
Barriers to rotation of various heteroatom substituted thioamides have been examined by several groups of investigators. Sandström reported that the barriers were uniformly lowered—as was the case with amides—when a heteroatom was introduced at the thiocarbonyl carbon (56). This is true also for fluoro and chloro atoms. However, if the substituent on the thiocarbonyl group is either cyano or ethoxycarbonyl, the barriers are high enough for the isolation of atropisomers at room temperature, although such an attempt has not been reported. Hobson and co-workers (57) carried out a similar investigation using the technique of total line shape analysis. The results are generally in good agreement with those reported by Sandström. In addition to *N,N*-dimethylcyanothioformamide (**18**) and *N,N*-dimethylmethoxycarbonylthioformamide (**19**), *N,N,N',N'*-tetramethyldithiooxamide (**20**) has a barrier to rotation high enough for the isolation of rotamers at room temperature, if the substituents on nitrogen are different (58).

As early as 1963, Walter and Maerten (59) noticed that *N*-benzyl-*N*-methylthioformamide (**21**) has a single conformation in the crystalline state but iso-



18

$\Delta G\dagger$ 23.2 ± 0.9 kcal/mol



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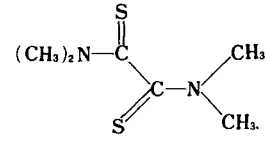
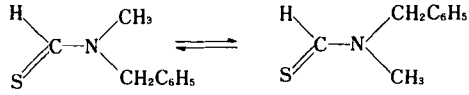
23.4 ± 0.4 kcal/mol



20

23.9 ± 1.5 kcal/mol

merizes to give new IR bands when the crystal is dissolved to make a solution. They compared the results with ^{1}H NMR spectral data and concluded that they had isolated an atropisomer of the thioamide. This is a reasonable assumption, because the barrier to rotation in *N,N*-dimethylthioformamide in solution is ca. 24.5 kcal/mol. Later, Walter and his co-workers (60) concluded that the crystalline compound they had isolated previously was the *E* form, and that the *Z* form could be concentrated up to 75% purity. The structure was confirmed by X-ray crystallography. The rates of rotation were measured at various temperatures and the Arrhenius activation energy and log *A* for the $E \rightarrow Z$ process were obtained as 25.16 ± 0.46 kcal/mol and 14.16, respectively. The free-energy difference between the two rotamers was less than 0.2 kcal/mol. This indicates that at equilibrium the populations of the *E* and *Z* forms of **21** are

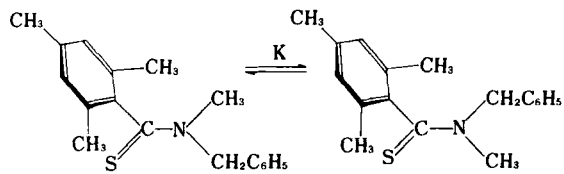


(*Z*) (*E*)

21

almost equal. The steric effect of the benzyl group may be suppressed because the C=S bond is much longer than C=O (*vide supra*).

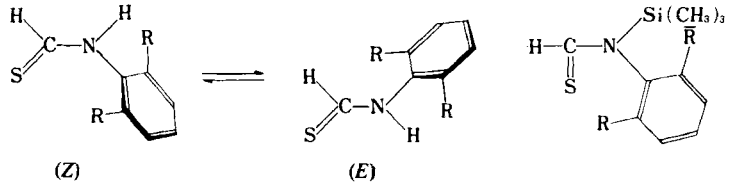
Mannschreck (61) was able to isolate atropisomers of *N*-benzyl-*N*-methylthiomesitamide (**22**) as an extension of his work on amides. The *Z* form was found to be more stable, *K* being 32/68 at 50°C. The free energy of activation for rotation was 27.3 kcal/mol for the $Z \rightarrow E$ process, and that for the $E \rightarrow Z$ process was 26.8 kcal/mol. The barriers were ca. 5 kcal/mol higher than those of the oxygen analogs. The barriers are also higher than those in **21**, of which isomers were isolated by Walter and associates. The higher barrier was attributed to the steric effect of the mesityl group (interaction with N—CH_3).



(*Z*) (*E*)

22

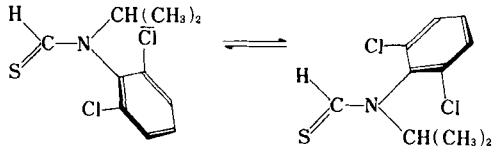
Walter and Schaumann (62) investigated the effect of the alkyl group on the barrier to rotation of 2,6-dialkylthioformanilides (**23**). The results, shown in Table 9, clearly indicate that the size of the ortho alkyl group is responsible for determining the barrier to rotation. This is probably due to both steric and electronic effects. Introduction of the alkyl substituents favors the *Z* form. This may be attributed to the nonplanarity of the phenyl group with respect to the thioamide, when the substituents are introduced. If the hydrogen of the amide is replaced by a trimethylsilyl group (**24**), the barrier to rotation is lowered by 2 to 4 kcal/mol. This may be attributed to both the electron-donating ability of the trimethylsilyl group, and its steric effect, which destabilizes the planar ground state (63).



(*Z*) (*E*)

23 **24**

Walter and Becker (64) have investigated the barrier to rotation of *N*-isopropyl-*N*-(2,6-dichlorophenyl)thioformamide (**25**). Its *Z* form crystallized, but on dis-



(*Z*) (*E*)

25

solution in carbon tetrachloride it slowly isomerized. The free energy of activation for rotation was 22.02 kcal/mol for the $Z \rightarrow E$ process and 22.31 kcal/mol for the reverse. The free energies of the two forms are almost the same. The low barrier is reasonable because a chlorine atom is smaller than a methyl group.

Table 9

Populations and Barriers to Rotation of 2,6-Disubstituted Thioformanilides (**23**) in Methanol-d_4 at 0°C

		$\Delta G^{\ddagger}$ (kcal/mol)	
R	*Z*(%)	$Z \rightarrow E$	$E \rightarrow Z$
H	9	20.5	21.7
CH_3	75	23.5	22.9
$(CH_3)_2CH$	70	24.5	23.8

(Z) (E)

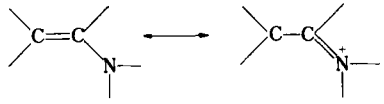
26

Simple *N*-monosubstituted thioformamides (**26**) exhibit rather low barriers, according to Walter and his co-workers (65). They found that these compounds were isolable in almost pure form by TLC at − 15°C; half-lives at that temperature were ca. 4 weeks. The *Z* forms of these *N*-alkylthioformamides are generally favored over the *E* forms due to the dipole compensation of the C—N bond with the C=S in the *Z* form. *N-tert*-Butylthioformamide constitutes an exception to this rule: Its *E* form is more stable than the *Z* form for steric reasons.

From the foregoing line of discussion rationalizing the higher barriers to rotation in thioamides compared to amides, it might naturally be expected that selenoamides would have still higher barriers. This expectation seems to be borne out, although there are not many examples reported. Svanholm (66) investigated the barriers to rotation in some selenoamides and compared them with those of oxygen and sulfur analogs. Schwenker and Rosswag (67a) compared the barriers to rotation of *N,N*-dimethylbenzamide, thiobenzamide, and selenobenzamide. Jensen and Sandström (67b) estimated the barrier to rotation in *N,N*-dimethylselenoacetamide. The results shown in Table 10 clearly indicate the trend, although the solvents are not the same in all cases. Reeves and coworkers (68) obtained the barrier to rotation of *N,N*-dimethylselenourea in chloroform-*d* as $\Delta G^{\ddagger}$ 14.58 kcal/mol (298.2 K), E_a 14.31 ± 0.33 kcal/mol, and $\Delta S^{\ddagger}$ −2.88 ± 1.10 e.u. at 298.2 K. This barrier is considered to be higher than that of the corresponding sulfur compound by ca. 1 kcal/mol.

C. Enamines and Hydrazones

Enamines (**27**) are expected to show high barriers to rotation about their C—N bonds, especially when the carbon–carbon double bond is connected to an electronegative group, leading to stabilization of the canonical structure (**28**). Kramer and Gompper (69) studied the dynamic NMR of 3-dimethylaminopropenal (**29**,



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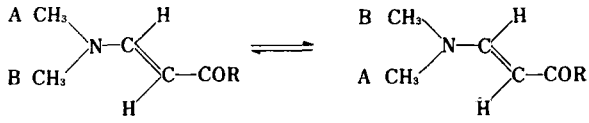

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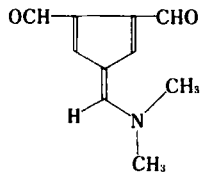
Table 10
Comparison of the Barriers to Rotation of Amides, Thioamides, and Selenoamides [$RCXN(CH_3)_2$]

R	X	Solvent	$\Delta G^{\ddagger}$ (kcal/mol)[a]	Reference
H	O	$C_6H_5NO_2$	17.7 (57)	66
H	S	o-$Cl_2C_6H_4$	24.1 (117)	53
H	Se	$C_6H_5NO_2$	25.8 (196)	66
CH_3	O	o-$Cl_2C_6H_4$	17.7 (57)	53
CH_3	S	o-$Cl_2C_6H_4$	20.6 (124)	53
CH_3	Se	o-$Cl_2C_6H_4$	22.8 (178)	67b
C_6H_5	O	C_6H_5Cl	7.5[b]	67a
C_6H_5	S	C_6H_5Cl	15.4[b]	67a
C_6H_5	Se	C_6H_5Cl	21.1[b]	67a

[a]Temperature in parentheses.
[b]Arrhenius activation energy.

R = H) and its derivatives (**29**, R = C_6H_5 or OC_2H_5) and found that the barrier was ca. 15 kcal/mol. Hobson and Reeves (70) introduced two cyano groups at the terminus of the same system and found the free energy of activation to be 17.7 kcal/mol at 25°C in 1,1,2,2-tetrachloroethane solution.

Mannschreck and Kölle examined various systems in which the dipolar structure **28** was stabilized by delocalization of the negative charge to the other end of enamines. The highest barrier to rotation in their work in 1967 (71) was obtained with 2,3-diformyl-6-dimethylaminofulvene (**30**). The ^1H NMR spectrum of the compound did not change up to 185°C, and the barrier to rotation was estimated to be >25 kcal/mol. Another candidate that provided stable rotamers was 4-(dimethylaminomethylene)-1,2-diphenyldiazolidine-3,5-dione (**31**).



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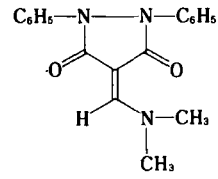
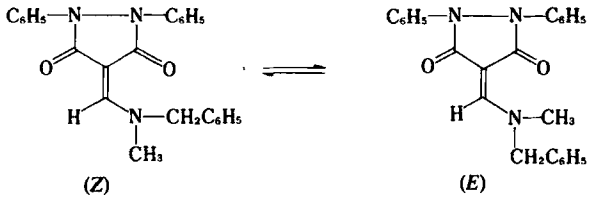


31

The barrier to rotation was 21.5 kcal/mol at 160°C. They extended this work in 1969 and were able to isolate the atropisomers of 4-(*N*-benzyl-*N*-methylaminomethylene)-1,2-diphenyl-1,2-diazolidine-3,5-dione (**32**). The *E* isomer was isolated pure, and the *Z* isomer 93% pure (72). An equilibrium mixture in chloroform-*d* solution at 28.5°C contained 40% *Z* and 60% *E*. To distinguish the barriers to rotation about the C=C and the C—N bonds, the barriers were

obtained with a compound carrying an *N*-methyl group instead of one of the phenyls on the nitrogens in the ring. The barrier to rotation about the C—N bond was 21.3 kcal/mol, and that about the C=C bond was 19.2 kcal/mol.

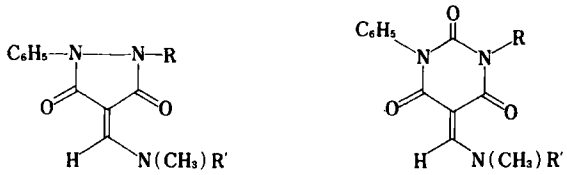


(*Z*) (*E*)

32

The high barriers in compounds **31** and **32** may be attributed to the fact that in these compounds the two carbonyl groups are coplanar with the enamine moiety, whereas such a coplanar structure is impossible for the open-chain compounds. Based on this point of view, Kölle and associates extended the work further and were able to isolate a series of compounds (**33**, **34**) in one crystalline atropisomeric form (73).

In these instances the barriers were rather low, as shown in Table 11. Inter-



33 **34**

Table 11

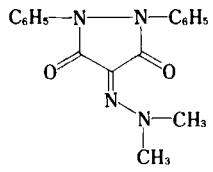
Barriers to Rotation about the C—N Bond of Enamines Derived from Malonhydrazide and Barbituric Acid

R	R′	$\Delta G^{\ddagger}$ (kcal/mol)	Temperature (K)	Solvent
		Malonhydrazides (**33**)		
CH_3	$CH_2C_6H_5$	21.3 ± 0.3	289	$CDCl_3$
C_6H_5	$CH_2C_6H_5$	22.0 ± 0.1	288.5	$CDCl_3$
H	$CH_2C_6H_5$	20.4 ± 0.5[a]	399	C_2HCl_5
2,4-$(NO_2)_2C_6H_3$	$CH_2C_6H_5$	23.7 ± 0.3	316	$CDCl_3$
		Barbituric Acids (**34**)		
C_6H_5	CH_3	20.4 ± 0.2[a]	385	DMSO-d_6
C_6H_5	$CH_2C_6H_5$	22.3 ± 0.6	300	$CDCl_3$
CH_3	$CH_2C_6H_5$	20.6 ± 0.3	317	$CDCl_3$

[a]Obtained by coalescence temperature method.

estingly, the barriers are affected by both the ring size and the substituent remote from the enamine moiety in question. Electronegative substituents on the ring tend to raise the barrier to rotation. The higher barrier of the 5-membered ring compounds (**33**) relative to the 6-membered one (**34**) is attributed to the more nearly coplanar structure of the former.

Hydrazones are analogs of enamines. Their barriers to rotation about the N—N bond are expected to be analogous to those discussed for the enamines. However, the barriers to rotation of hydrazones **35** and **36**, which are analogs of enamines that afforded stable atropisomers, were found to be lower. The barrier in **35** was only 16.7 kcal/mol. The barrier is again higher for the 5-membered compound **35** than for the 6-membered **36**.



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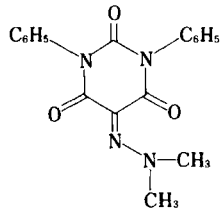

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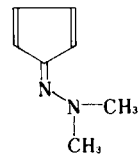


37

The barrier to rotation of the cyclopentadienone hydrazone **37** is reported to be less than 11 kcal/mol (71). Introduction of a formyl group into the 2-position of the cyclopentadienylidene ring raised the barrier to 11.8 kcal/mol (71).

D. Nitrosamines

A ^{1}H NMR spectrum of *N,N*-dimethylnitrosamine (**38**) was obtained as early as 1957, and the free energy of activation for rotation was determined to be ca. 23 kcal/mol at 215°C (74). This high a barrier in nitrosamines is reasonable because the canonical structure **39** is stabilized by the strongly electron-donating ability

38 **39**

of the amino group and the strongly electron-accepting ability of nitroso group. The barrier to rotation seems again affected by the environment of the molecules, because in the gas phase it is only 21.1 kcal/mol at 158°C (75).

Looney and associates (74) examined the NMR spectra of *N*-benzyl-*N*-methylnitrosamine and obtained an Arrhenius activation energy for rotation of 23

kcal/mol and a frequency factor of 0.7×10^{13} sec^{-1}. Although they found only one signal for the methyl group of *N*-methyl-*N*-phenylnitrosamine and could not conclude whether this was due to fast rotation or to the presence of a single isomer, Forlani and co-workers (76) investigated diphenylnitrosamine by dynamic ^{13}C NMR and concluded, from coalescence temperature measurements, that the free energy of activation for rotation was 19.1 ± 0.1 kcal/mol at various temperatures in dimethyl sulfoxide-d_6. This lowering of the barrier in aromatic nitrosamines is expected because of the electron-withdrawing ability of the aromatic ring.

The populations of the rotamers are affected by steric effects. Karabatsos and Taller (77) examined the populations of unsymmetrical nitrosamines and found that in methyl-*tert*-butylnitrosamine only one isomer was observable. Nelsen and associates (78) similarly found that the populations of conformers of 2-nitroso-2-azabicyclo[2.2.2]octanes (**40**) are affected by the substituent in the 3-position.

syn anti

40

If the substituents are all hydrogen, the syn conformer is present to the extent of 100%, but the syn–anti ratio is 13 : 87 when the 3-position is substituted by two methyl groups.

Mannschreck (61,79) was able to concentrate one of the isomers of *N*-benzyl-*N*-isopropylnitrosamine (**41**) up to 94% by crystallization from carbon disulfide

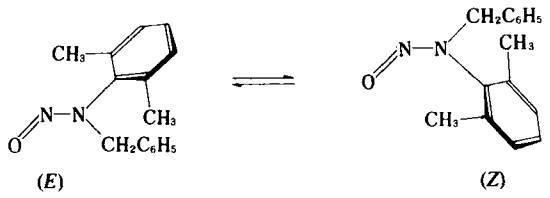
(*E*) (*Z*)

41

at −60°C. The mother liquor contained the other isomer which was enriched up to 75%. The half-life of the crystalline conformer, which was *E*, was 8.2 ± 2.0 min at 36°C in carbon tetrachloride. The equilibrium was, as expected, in favor of the *E* form (81 : 19).

Mannschreck (80) extended this work, and the barrier to rotation of *N*-benzyl-*N*-neopentylnitrosamine (**41**) was measured as 22.1 kcal/mol at 100°C by equilibration. At equilibrium, the *E* form is slightly favored.

2,6-Disubstituted phenyl groups were introduced into nitrosamines. *N*-Benzyl-*N*-2,6-xylylnitrosamine (**42**) was separated into two atropisomers. The free en-

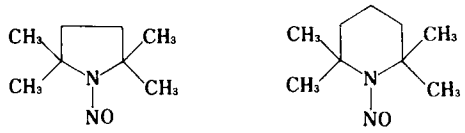


(*E*) (*Z*)

42

ergy of activation for rotation was 23.9 ± 0.2 kcal/mol at 36.5°C in carbon tetrachloride for the $E \rightarrow Z$ process, and 24.2 ± 0.2 kcal/mol for the reverse (79,81). The cause for the slight favoring of the *Z* isomer should again be the steric factor, since a methyl group is larger than the half-thickness of the aromatic ring, which is inclined with respect to the N—N—O plane.

Barriers to rotation of nitrosamines in which the amino part is embedded in a cyclic system seem generally to be smaller. However, Harris and associates (82) reported that the barrier of *N*-nitroso-2,2,5,5-tetramethylpyrrolidine (**43**) was over 22.6 kcal/mol. This must be higher than the barrier required for isolation of rotamers at room temperature, and is even higher than that in *N*-nitroso-2,2,6,6-tetramethylpiperidine (**44**). Harris and Pryce-Jones attribute the high barrier of **43** relative to **44** to the more stable ground state of the former. If the pyrrolidine derivative is properly substituted, the atropisomers are expected to be isolable at room temperature.



43 **44**

E. Esters

The barriers to rotation of esters deserve mention here, especially in comparison to amide barriers. The ^{1}H NMR spectra of some nitrites (**45**) were measured in 1957 (83). The temperature had to be lowered to −58°C at 30 MHz to see the separate signals of propyl nitrite. The barriers to rotation were ca. 10 kcal/mol. This result may be rationalized by considering the lesser electron-donating ability of the alkoxy relative to the dialkylamino group. The dipolar canonical form (**46**) of nitrite esters is not as stable as that of nitrosamines.

45 **46**

Likewise, carboxylate esters (**47**) have less double-bond character in their C—O bonds relative to the C—N in amides. There are two additional factors that should be taken into account when one considers the conformations of esters.

47

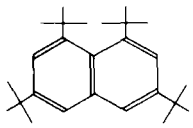
One is the steric effect. As in the case of amides, the *E* conformation is disfavored by the steric effect when R is equal to or larger than a methyl group. The second factor is the dipole moment. The *E* conformation is much more polar than the *Z* conformation. Because of these factors, esters usually assume the *Z* conformation and no *E* conformation is observed. To observe the latter, a special probe is needed. From the foregoing discussion, it is apparent that if R is hydrogen and R′ a large group, the *E* conformation might be present. Thus the *E* form of *tert*-butyl formate was detected by ^{1}H NMR spectroscopy at low temperature (84). The barrier was found to be ca. 11 kcal/mol (85).

Evidently, very special circumstances will be required to make the *E* conformation of esters so stable that atropisomers can be isolated at ambient temperatures.

III. ATROPISOMERISM ABOUT sp^2–sp^3 BONDS

Restricted rotation in aromatic compounds has been one of the favorite areas of atropisomerism since the early success in optical resolution of biphenyls. *ortho*-Substituents played a decisive role in determining the barriers to rotation of aryl-to-carbon (or nitrogen) bonds. Thus attempts were made to determine the barriers to rotation of aromatic compounds with two, or sometimes three, bulky groups ortho to each other (28). Through such efforts an interesting fact emerged. That is, rotation about an aryl–carbon bond can be frozen on the NMR time scale when the steric interference is seemingly moderate, whereas for compounds carrying large groups, the barrier to rotation is too low to observe by the NMR technique at room temperature. For example, a ^{1}H NMR spectrum of 1,3,6,8-tetra-*tert*-butylnaphthalene (**48**) at room temperature showed only a singlet for the *tert*-butyl groups in the 1,8-positions (86). Similarly, an NMR spectrum of *o*-di-*tert*-butylbenzene (**49**) at room temperature suggested that the rotation was fast on the NMR time scale (87). Ōki and Nakamura (88) reported that the rotation of a *tert*-butyl group in 1-*tert*-butyl-4,6,8-trimethylazulene (**50**) was slow on the NMR time scale only at ca. −80°C, and the barrier is probably about 10 kcal/mol. Anderson and associates (89) were eventually able to see the slow rotation

of the *tert*-butyl groups in **48** by ^{1}H NMR at very low temperatures; the broadening began at $-80°C$ and separate signals were observed at $-153°C$.



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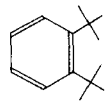

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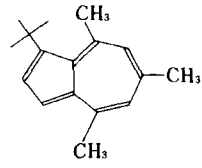

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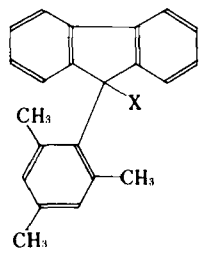
These low barriers to rotation for congested molecules are undoubtedly due to the energy of the ground states of the molecules being raised relative to the transition states so as to make the energy gap smaller. X-ray crystallography of 1,3,6,8-tetra-*tert*-butylnaphthalene indeed supports a highly distorted ground state (90), and the strained structure can be reproduced by force-field calculations (90,91). Therefore, it is necessary to explore compounds that are less congested in the ground state, but possess severe interaction between the parts of the molecule in the transition state for rotation, to make it possible to isolate atropisomers at room temperature.

A. 9-Arylfluorenes

The first report suggesting the possibility of isolating atropisomers about an sp^2–sp^3 bond appeared in 1968. Chandross and Sheley (92) happened to prepare 9-mesitylfluorene derivatives (**51**), because of their interest in finding stable radicals that do not easily dimerize. Upon examining the NMR spectra of compound **51** (X = OH), they found that the two methyl groups ortho to the connecting bond between the mesityl and the fluorenyl groups were nonequivalent, and that coalescence of the signals was not observed up to 150°C. When they changed the hydroxy to a hydrogen, the NMR spectrum showing nonequivalent methyls in the 2- and 6-positions of the mesityl group did not change, even when the sample solution was heated up to a temperature of 200°C. Thus the



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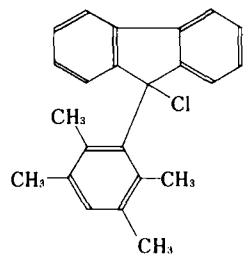

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barrier to rotation about the mesityl-to-fluorenyl bond must be higher than 26 kcal/mol, suggesting that if the mesityl group is properly substituted stable rotamers should exist in this compound.

When the hydroxy group was changed to chloro (**51**, X = Cl), the compound showed a sharp signal due to the 4-methyl of the mesityl group, but broad signals due to the 2- and 6-methyls at ambient temperature. Chandross and Sheley attributed this low barrier in the exchange of the magnetic environments of the two methyls to a facile ionization followed by ion pair return. A lower barrier for a duryl compound (**52**) was cited in support of the ionization mechanism. Although this mechanism was disproved by other workers (see following discussion), it was clearly demonstrated that the barrier to rotation about the aryl-to-fluorenyl bond was actually lowered when the bulkiness of the substituent was increased.

Siddall and Stewart (93) also reported the barrier to rotation in 9-mesitylfluorene to be over 26 kcal/mol. The barrier to rotation of 9-(2,6-xylyl)-9-fluorenol in hexachlorobutadiene was 21.3 kcal/mol (at 200°C), in agreement with the qualitative work of Chandross and Sheley (92). At almost the same time, Rieker and Kessler (94) measured the barrier to rotation about the aryl-to-fluorenyl bond in two series of 9-arylfluorenes. The results, shown in Table 12, clearly indicate the general tendency for the barrier heights to decrease as the bulkiness of the substituent in the 9-position of fluorene increases; apparently the rise in the ground state energy is responsible for the observed barriers. It is also interesting to note that the barriers to rotation are lowered considerably when the two methyl groups ortho to the pivot bond are replaced by methoxy groups. This result suggests that the steric interaction in the transition state for rotation is reduced considerably because of the smaller size of the methoxy group. (Presumably the ground state of the dimethoxy compound is less crowded than that of the methyl compound.)

Table 12
Barriers to Rotation about the Aryl-to-Fluorenyl Bond in 9-Arylfluorenes[a]

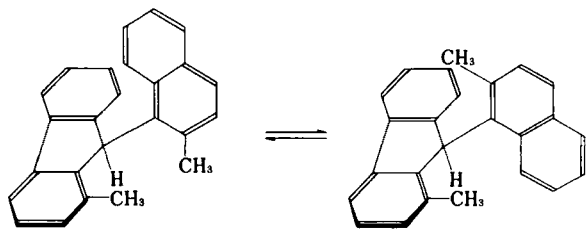
	$\Delta G^{\ddagger}$ (kcal/mol)	
9-Substituent	Mesityl	2,6-Dimethoxyphenyl
H	>25 (>190)[b]	20.6 (145)[b]
OH	20.2 (145)[b]	14.4 (24)[c]
Cl	16.2 (66)[b]	9.2 (−81)[d]

[a]Numbers given in parentheses are coalescence temperatures (°C) where the free energy of activation for rotation was obtained.
[b]1,2,4-Trichlorobenzene solvent.
[c]Chloroform-*d* solvent.
[d]Dichloromethane solvent.

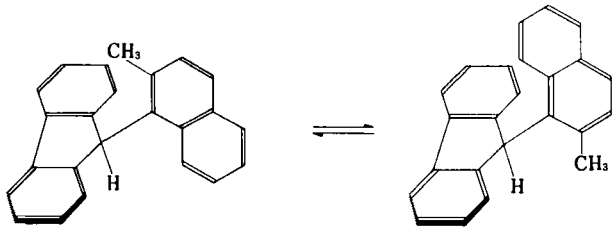
The mechanism of the exchange of the two methyl groups in 9-mesityl-9-chlorofluorene (as observed by NMR spectroscopy) proposed by Chandross and Sheley aroused the interest of several chemists. A weak point in this mechanism is that the rate of exchange was not affected by solvent polarity, although a solvent effect should clearly be observed if the exchange were ionic in nature. This flaw was noted by Rieker and Kessler (94), who preferred a rotation mechanism. The matter was further elaborated on by Ford and associates (95), who considered three possible mechanisms for the exchange of magnetic environment of the two ortho methyls in 9-mesitylfluorenes. They are as follows:

1. Rotation about the aryl-to-fluorene bond.
2. Dissociation of the bond, either heterolytic or homolytic.
3. A hydrogen shift to make the rotation easier.

Ford et al. prepared 1-methyl-9-(2-methyl-1-naphthyl)fluorene (**53**) in the hope that, if rotation were the true mechanism, the introduction of the 1-methyl group in the fluorene nucleus would raise the barrier by increasing the steric interaction in the transition state for rotation. They found that the barrier to rotation from the sc*(*S**) isomer to the ac*(*R**) isomer was 33.3 ± 0.3 kcal/mol at 166°C in hexachlorobutadiene. If this value is compared with the barrier of 9-(2-methyl-1-naphthyl)fluorene (**54**), 29.2 kcal/mol at 116°C, which was determined by Siddall and Stewart (93), it is clear that the introduction of the methyl group into the 1-position of the fluorene ring raises the barrier to rotation.



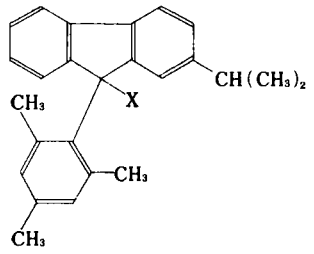
sc*(*S**) **53** ac*(*R**)



sp **54** ap

They further measured the rates of exchange with the addition of *p*-toluenesulfonic acid, and found that the barrier was not affected. This result rules out the possibility that the exchange takes place via ionization.

Ford et al. (95) further prepared 9-substituted 9-mesityl-2-isopropylfluorene (**55**) to disprove the dissociation mechanism for the exchange. In these com-



X=H, OH, Cl

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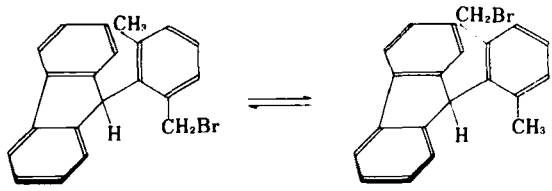
pounds C_9 is a chiral center and the isopropyl methyls are diastereotopic. If the substituent dissociates and recombination occurs from the other side of the fluorene ring, this corresponds to racemization. This occurrence would be reflected in the NMR spectrum as a site exchange of the diastereotopic pair of methyl groups, which would appear homotopic on the average. The isopropyl group in the 2-position should not affect the barrier to rotation, because in the transition state for rotation the main steric interference occurs between the C(1)–H group and the ortho substituent in the aryl group. Indeed, the barrier to rotation in **55** (X = OH) was 20.8 kcal/mol, in good agreement with that in 9-mesityl-9-fluorenol (**51**, X = OH).

During the exchange of the ortho methyls in the mesityl group, the line shape of the isopropyl methyls was not affected, indicating that the dissociation mechanism is not operative. In particular, the chloro compound (**55**, X = Cl) did not exhibit any sign of line broadening for the isopropyl carbons, although other signals coalesced. Ford and associates (95) thus concluded that, even in the chloro compound, rotation was responsible for the exchange of the magnetic environment of the methyls in 9-mesitylfluorenes.

They further heated fluorene-9,9-d_2 without solvent. There was no detectable increase in the amount of 9-H, indicating that there were no significant hydrogen shifts to other positions.

Nakamura and Ōki (96) isolated the rotamers of 9-(2-bromomethyl-6-methylphenyl)fluorene (**56**), and found that the Arrhenius activation energy for rotation was 27.1 kcal/mol for the sp → ap process, log *A* being 10.8. For the reverse process, the values were 27.1 kcal/mol and 11.4, respectively. This is direct proof that the energy barrier obtained by the dynamic NMR technique is useful for diagnosing the possibility of isolating atropisomers, since the barrier



sp ap

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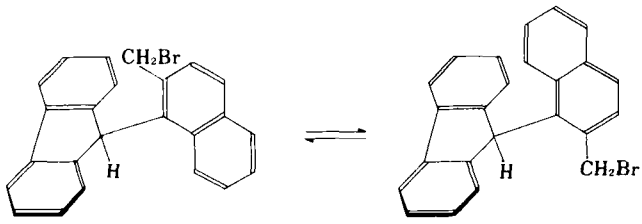
determined by dynamic NMR was over 26 kcal/mol for 9-mesitylfluorene. The equilibrium constant was 3.6 ± 0.2 in favor of sp and was independent of temperature in the range of 80 to 121°C.

One might be tempted to explain this equilibrium constant by saying that a bromomethyl group is larger than a methyl, and that therefore placement of the bromomethyl group in the more crowded position over the fluorene ring is disfavored, relative to where it is in the other conformation (which is sp). However, if we consider the ap conformation and interacting parts therein, we realize that it is CH_2, in both bromomethyl and methyl groups, that interacts with the fluorene ring. In this sense then, the steric interaction should be approximately the same in both conformations. The present reviewer believes, therefore, that important factors responsible for the equilibrium constant are solvation and entropy. The solvation will undoubtedly be stronger with the bromomethyl group than with the methyl. If the bromomethyl group is over the fluorene ring, a part of the solvation shell cannot be completed, thus making the ap conformation relatively unfavorable. The indication of a temperature-independent equilibrium constant, implying entropy control, may support this hypothesis. At the same time, due to the steric effect of the bromine atom, a conformation in which the bromine is close to the fluorene ring is of high energy in the ap form, whereas the steric effect in the sp form is not severe. This results in a decrease in entropy when one goes from the sp to the ap form.

Siddall and Stewart (93) prepared 9-(2-methyl-1-naphthyl)fluorene as an extension of their work on 9-mesitylfluorene. They were able to concentrate one of the isomers to over 90% purity; this isomer displayed its methyl NMR signal at a lower field than the other, which was concentrated up to 7/5 by fractional crystallization. These atropisomers were later isolated in pure forms by Nakamura and Ōki (97). The assignment of conformation was made by considering the ring current effect of the fluorene moiety. Since the methyl group in the sp conformation is placed over the fluorene ring, it must show the methyl signal at a higher field relative to its diastereomer. Thus the compound originally concentrated to over 90% by Siddall and Stewart is the sp form. The rates of rotation were measured at various temperatures by Siddall and Stewart, an Arrhenius activation energy of 29.8 kcal/mol and log *A* of 12.9 being obtained. The equilibrium constant was 1.0 in the temperature range examined.

Apparently the 9-(2-methyl-1-naphthyl) group has a higher barrier to rotation about the pivot bond than does the mesityl group. Although the steric effect of a methyl group at an ortho position in a benzene nucleus is often compared with the corresponding effect of a peri hydrogen at the 1-position of naphthalene, the results suggest that the barriers to rotation in the foregoing cases are somewhat different from the normal. There are two reasons to be considered. One is the rigidity of the naphthalene ring. Probably the rigid structure of the 1-naphthyl group will make its steric interaction in the transition state for rotation more severe than that of the less rigid *o*-tolyl group. Another factor deserving mention here is the relative size of the methyl and the annelated benzene ring. The van der Waals radius of a methyl group is known to be larger than the half-thickness of the benzene ring. Thus the steric interaction of the naphthyl group with the 9-hydrogen (as well as that with the fluorene ring in the ap conformation) will be smaller than that of *o*-tolyl, where a methyl group is close to the 9-hydrogen, provided that the naphthyl group avoids the 9-hydrogen by changing the torsion angle slightly. Thus the ground state is believed to be more stable in the naphthyl, relative to the xylyl compound.

It may be argued that direct comparison of the barrier of 9-(2-methyl-1-naphthyl)fluorene with that of 9-(2-bromomethyl-6-methylphenyl)fluorene is not fair, because the latter carries a bromine atom. However, the discussion just presented is valid because Saito and Ōki (98) found the Arrhenius activation energy for rotation of 9-(2-bromomethyl-1-naphthyl)fluorene (**57**) for the process ap → sp



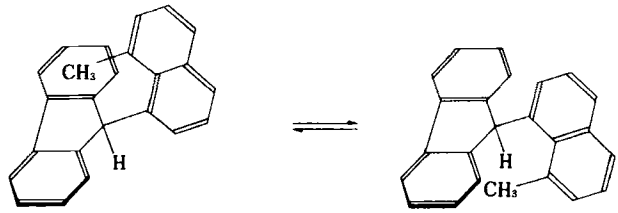
ap sp

57

to be 29.0 ± 0.6 kcal/mol with log *A* being 12.4 ± 0.4. These activation parameters are almost the same as those reported for the hydrocarbon, and the barrier is clearly higher than that in 9-(2-bromomethyl-6-methylphenyl)fluorene (*vide supra*). Interestingly, the equilibrium constant (sp/ap) for **57** was 2.8 in the temperature range of 95 to 124°C in hexachlorobutadiene. Relative to the hydrocarbon (equilibrium constant 1.0), the ap form becomes less favored on introduction of the bromo atom. The causes for this phenomenon must again be the steric effect on solvation and the entropy factor. An examination of both the barrier to rotation and the equilibrium constant of 9-(2-methoxymethyl-1-naphthyl)fluorene indicates that, whereas the barrier to rotation is about the same as

for the related compounds (**54** and **57**), the equilibrium constant was 2.3. Apparently the equilibrium constant is affected by the substituent remote from the site of direct interaction through the effects on solvation and entropy.

The effect of the 2-substituent on the barrier to rotation of 9-(2-substituted 1-naphthyl)fluorene seems to be large because 9-(1-naphthyl)fluorene has a barrier to rotation of only 18.0 kcal/mol at 60°C (93). The barrier was later redetermined and a similar result (99) was obtained. This means that the methyl group in the 2-position of the naphthalene ring plays an important role by interacting with the C(1)–H group of fluorene in the transition state for rotation, just as molecular models suggest. Investigation of molecular models further suggests that a methyl group introduced into the 8-position of the naphthalene in 9-(1-naphthyl)fluorene should also raise the transition state energy for rotation. However, since the 8-methyl group interacts strongly with the fluorene ring, even in the ground state of the ap form, the barrier to rotation may be small in the process ap → sp. Indeed, although the ap form of **58** could be made by



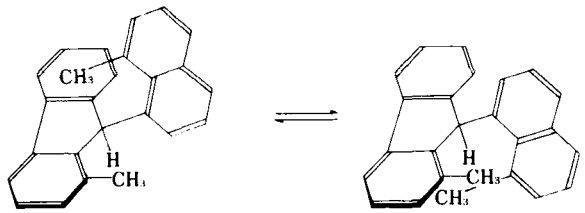
ap sp

58

protonation of the corresponding lithium compound, it rotates with a free energy of activation of 23.9 kcal/mol at 307 K, the equilibrium constant (sp/ap) at that temperature being 25 (100). Although isolation of a stable ap form at room temperature was not possible, it is noteworthy that the barrier to rotation (ap → sp) in this compound is higher by about 6 kcal/mol than that in the parent hydrocarbon. The large equilibrium constant reflects the strain in the ground state of the ap form.

As Ford and associates pointed out (95), introduction of a methyl group into the 1-position of the fluorene group in 9-(1-naphthyl)fluorene raises the barrier. This effect was examined in several compounds. The barrier to rotation in 1-methyl-9-(1-naphthyl)fluorene was 21.4 kcal/mol at 433 K, which is ca. 4 kcal/mol higher than that in the parent compound (101). Introduction of a 1-methyl group into 9-(8-methyl-1-naphthyl)fluorene raised the barrier for the sc*(*S**) → ac*(*R**) process to 25.2 kcal/mol at 307 K. Thus it was possible to isolate the sc*(*S**) isomer (**59**). Another pair of enantiomers, ac*(*R**), was isolated. The equilibrium constant was again very large, 33 in favor of ac*(*R**) (100).

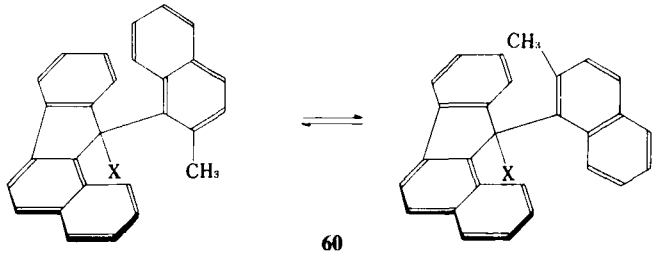
Introduction of substituents into the 1-position of the fluorene ring seems to



sc*(*S**) ac*(*R**)

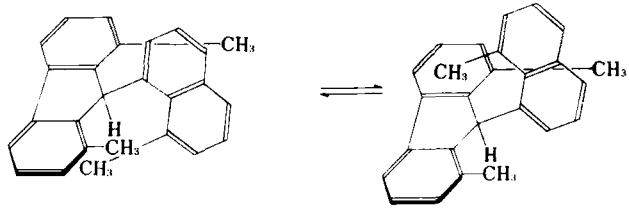
59

raise the barrier to rotation of 9-aryl-9-fluorenols considerably. Thus Ford et al. (95) suggested that the barrier in 1-methyl-9-(2-methyl-1-naphthyl)fluoren-9-ol was over 26 kcal/mol. Kajigaeshi and co-workers were able to isolate one of the rotamers (ap) of a benzo-annelated 9-(2-methyl-1-naphthyl)fluoren-9-ol (**60**, X = OH). The barrier to rotation was 24.6 kcal/mol at 50°C. In this case also, however, the corresponding hydrocarbon (**60**, X = H) gives a higher barrier of 32.8 kcal/mol at 170°C for the sc*(*S**) → ac*(*R**) process (102).



ap sc*(*S**) **60** X = OH X = H sp ac*(*R**)

From the foregoing discussion, it might be expected that if two methyl groups are introduced into the 1- and 8-positions of the fluorene ring the barriers would become very high. This expectation has been proved to be unwarranted. 1,8-Dimethyl-9-(8-methyl-1-naphthyl)fluorene (**61**) showed a barrier to rotation of 26.1 kcal/mol for the ap → sp process and 27.6 kcal/mol for the sp → ap process. This barrier is higher than that in analogs lacking one of the methyls on the



sp ap

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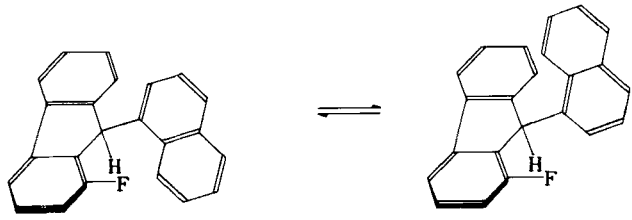
fluorene ring by only ca. 1 kcal/mol. The same is true for 1,8-dimethyl-9-(1-naphthyl)fluorene. The barrier here was 20.6 kcal/mol at 370 K for the ap → sp process and 21.1 kcal/mol for the reverse (103), almost the same as that for 1-methyl-9-(1-naphthyl)fluorene. Kajigaeshi et al. (104) have obtained similar results in the 9-(2-methyl-1-naphthyl)fluorene series; the free energy of activation for rotation (ap → sp) in 1,8-dimethyl-9-(2-methyl-1-naphthyl)fluorene at 166°C was 34.0 kcal/mol, which is an increase of only 0.7 kcal/mol relative to 1-methyl-9-(2-methyl-1-naphthyl)fluorene (**53**).

These results seem puzzling at first glance but are explained by the strain in the ground state. Introduction of a substituent into the 1-position of the fluorene ring in 9-(1-naphthyl)fluorene causes not only an increase in the transition state energy, but also an increase in the ground state energy. If substituents are introduced into both the 1- and the 8-position of fluorene, the ground state energy will be further raised.

This kind of consideration is supported by X-ray crystallographic data of sc*(*S**)-1-methyl-9-(8-methyl-1-naphthyl)fluorene (**59**) (103). In this molecule, the C—C bond connecting the naphthyl and the fluorene ring is not parallel with the CH_3—C_1-(naphthyl) bond, thus indicating that internal strain has accumulated. Even more strikingly, 1-fluoro-9-(1-naphthyl)fluorene (**62**) has a lower

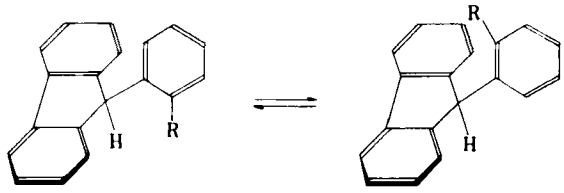


ac*(*S**) sc*(*R**)

62

barrier to rotation than the parent hydrocarbon; the barrier is 18.1 kcal/mol for the ac* → sc* process shown but 18.7 kcal/mol for the analogous process for 9-(1-naphthyl)fluorene in hexachlorobutadiene. If the fluorine substituent is in the 2-position, then the barrier to rotation is the same as that of the parent hydrocarbon.

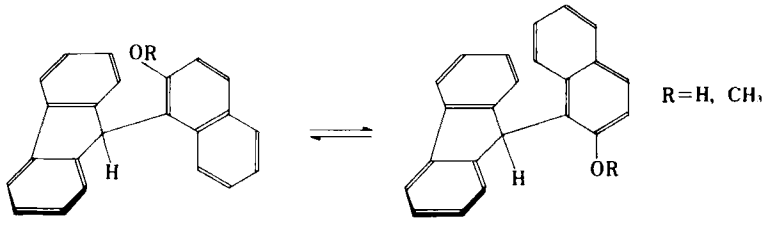
Barriers to rotation about the aryl-to-fluorene bond in 9-arylfluorene (**63**), where the aryl group is an *o*-alkylphenyl, were examined by two groups of investigators (93,105). Results given by Nakamura and Ōki are shown in Table 13. Both the free energy of activation for rotation and the equilibrium constant are affected by the size of the substituent. Especially noteworthy is the case of 9-(2-*tert*-butylphenyl)fluorene, where the equilibrium is quite lopsided and the barrier for the process sp → ap is very large. The ap form of this compound was prepared by protonation of the corresponding lithio compound, and equi-



63

librium rates were measured immediately. The observed $\Delta G^{\ddagger}_{273}$ was 20.3 kcal/mol for the ap → sp process.

So far, the 9-arylfluorenes discussed carry hydrocarbon groups that control the transition state for rotation. Some heteroatom analogs in this series have been prepared. Nakamura and Ōki (106) prepared compounds (**64**) carrying a hydroxy



64

or a methoxy group which interferes maximally in the transition state for rotation. The results summarized in Table 14 indicate a few interesting points (106).

The first is the fact that these compounds have low barriers to rotation relative to the corresponding methyl or substituted methyl compounds. This is in line with the fact that 9-(2,6-dimethoxyphenyl)fluorene has a lower barrier than 9-mesitylfluorene (94). This must be again a reflection of the fact that the effective size of the oxygen is smaller than that of methyl.

The second point is that the naphthyl derivatives give higher barriers to rotation

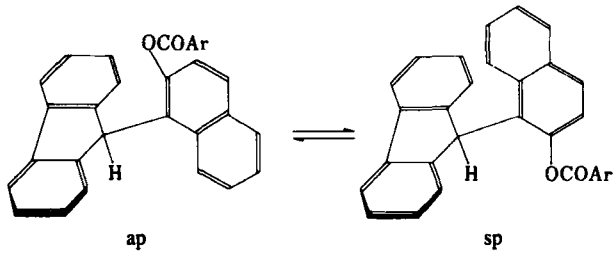
Table 13

Barriers to Rotation and Equilibrium Constants at 0°C for 9-(*o*-Substituted Phenyl)fluorene Rotamers (**63**) in Chloroform-*d*

	$\Delta G^{\ddagger}$ (kcal/mol)		
Substituent	ap → sp	sp → ap	*K* (ap/sp)
CH_3	16.3	16.6	1/1.6
C_2H_5	17.3	17.9	1/3.3
$(CH_3)_2CH$	18.0	18.3	1/2.4
$(CH_3)_3C$	20.3	>23	<1/100

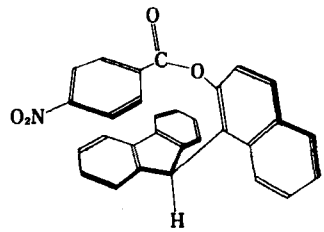
than the 2-methylphenyl derivatives, a point discussed earlier. The third point of interest concerns the equilibrium constants. One sees in Table 14 that the sp form is favored over the ap if the substituent is a methoxy group, whereas the opposite is true when the substituent is hydroxy. Yet the barriers to rotation for the processes sp → ap in the methoxy and the hydroxy compounds are almost the same. This is reasonable because the effective sizes of the hydroxy and the methoxy groups are mainly determined by the oxygen atom; their ground states and transition states for rotation must, by and large, be the same in terms of energy. Thus the barriers to rotation are also nearly the same. Since the energies of the transition states for both the hydroxy and the methoxy compounds are nearly the same, if the barriers to rotation for the ap → sp processes are different, that difference must reflect the difference in stabilities of the ground states. Examination of the difference in these energies reveals that the ap forms of the hydroxy compounds are more stable by ca. 1 kcal/mol than those of the methoxy compounds. The reason for this stability difference is the presence of attractive interactions due to hydrogen bonding between the hydroxy group and the π-electron system in the fluorene group. The presence of OH···π interaction was confirmed by IR spectroscopy. The anomalies in equilibrium constants are explained on this basis.

Barriers to rotation of 9-(2-hydroxy-1-naphthyl)fluorene benzoates (**65**) reveal



ap sp

65



66

another interesting point. The data are shown in Table 15 (107). From mere steric considerations, the barriers to rotation are all expected to be the same, because the variation in the aroyl group occurs in a remote place from the site

Table 14

Barriers to Rotation and Equilibrium Constants of Arylfluorenes Carrying a Hydroxy or a Methoxy Group in the 2-Position of the Aryl Group at 56.3°C in Chloroform-*d*

Substituent	Process	$\Delta G^{\ddagger}$ (kcal/mol)	K (ap/sp)
	9-(2-Substituted 4,6-dimethylphenyl)fluorenes		
OCH_3	sp → ap	25.0 ± 0.1	1/3.30
	ap → sp	24.1 ± 0.1	
OH	sp → ap	24.7 ± 0.1	1.80
	ap → sp	25.1 ± 0.1	
	9-(2-Substituted 1-naphthyl)fluorenes (**64**)		
OCH_3	sp → ap	25.9 ± 0.1	1/3.56
	ap → sp	25.1 ± 0.1	
OH	sp → ap	25.8 ± 0.1	2.30
	ap → sp	26.3 ± 0.1	

of interaction in the transition state for rotation. The facts bear out the expectation except for two compounds. Since one of the exceptions involved an *o*-methyl group, this may impact the carbonyl group sterically, which, in turn, may affect both the transition state and the ground state. An unusual situation is found in the *p*-nitrobenzoate, which displays a large equilibrium constant in favor of the ap form. This is also reflected in the barriers to rotation; the free energy of activation for rotation for the process sp → ap of the *p*-nitrobenzoate is about the same as for the others, but that for the process ap → sp is larger by about 0.5 kcal/mol. Therefore, the large K value and the enhanced barrier to rotation

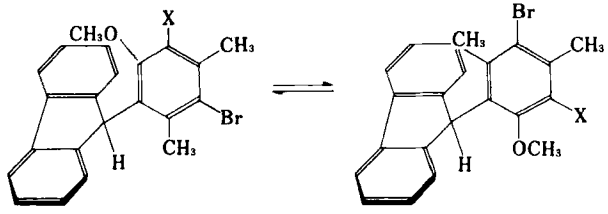
Table 15

Barriers to Rotation and Equilibrium Constants of 9-(2-Hydroxy-1-naphthyl)fluorene Benzoates (**65**) in Chloroform-*d* at 69°C

Substituent on benzoyl group	K (ap/sp)	Process	$\Delta G^{\ddagger}_{324}$ (kcal/mol)
4-CH_3O	0.82 ± 0.03	sp → ap	27.3 ± 0.1
		ap → sp	27.2 ± 0.1
4-CH_3	0.83 ± 0.03	sp → ap	27.3 ± 0.1
		ap → sp	27.2 ± 0.1
2-CH_3	0.67 ± 0.03	sp → ap	27.6 ± 0.1
		ap → sp	27.4 ± 0.1
H	0.90 ± 0.03	sp → ap	27.3 ± 0.1
		ap → sp	27.3 ± 0.1
4-NO_2	2.9 ± 0.2	sp → ap	27.3 ± 0.1
		ap → sp	28.1 ± 0.1

for the ap → sp process must be attributed to some special stabilization of the ap form rather than to destabilization of the sp form. A charge transfer interaction as is represented by structure **66** is postulated for the stabilization of the ap form. Although this conformation has the disadvantage of requiring the *E* conformation of the ester, which is usually unstable, the *E* form of the ester becomes stable relative to the *Z* form when the phenol moiety carries two substituents in ortho positions (84).

Buttressing effects are known to raise the barrier to rotation in the biphenyl series by preventing bond angle deformations of a substituent involved in direct interaction in the transition state. Similar effects were found in the 9-arylfluorene series (108). The barrier to rotation of 9-(3-bromo-6-methoxy-2,4-dimethylphenyl)fluorene (**67**, X = H) in chloroform-*d* at 56.3°C is 25.7 kcal/mol for



ap sp

67

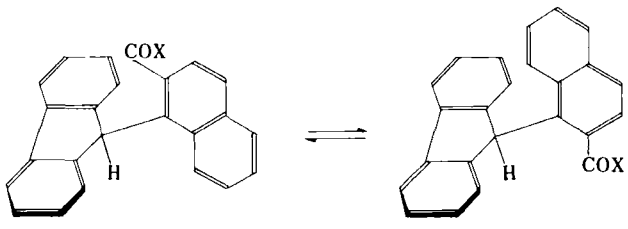
the sp → ap process, and that for the ap → sp process is 24.9 kcal/mol (the barriers for the parent compound at 56.3°C were 25.0 and 24.1 kcal/mol for the sp → ap and ap → sp processes, respectively); the equilibrium constant is 3.5 in favor of the sp form. When another bromine atom is added, 9-(3,5-dibromo-2-methoxy-4,6-dimethylphenyl)fluorene (**67**, X = Br) under the same conditions displays a barrier to rotation of 27.1 kcal/mol for the sp → ap process, and 25.8 kcal/mol for the ap → sp process; the equilibrium constant is 7.0 in favor of the sp form.

Clearly the buttressing effect is larger when a bromine atom is introduced ortho to the methoxy group than when it is placed ortho to methyl. This may be attributed to the following factors. Compound **67** (X = Br), having two bromine atoms, has a barrier to rotation higher by ca. 1.5 kcal/mol than that of the monobromo compound. Since the sp conformation of the monobromo and dibromo compounds are probably not very different in energy because of a similar steric environment, this increase may be taken as a net increase in barrier. However, in going from 9-(2-methoxy-4,6-dimethylphenyl)fluorene to the monobromo compound (**67**, X = H), the increase in the barrier is less than 1 kcal/mol. This is probably caused by making the effective size of the methoxy group larger by forcing the methyl group of the methoxy to take a conformation away from the bromine, in addition to the normal buttressing effect. The change in equilibrium constants also deserves mention. The sp forms become more stable,

relatively speaking, when the bromine atoms are introduced. This is probably because the methoxy group cannot be coplanar with the naphthyl group, in addition to the steric inhibition of solvation in the ap form.

As to the buttressing effect, it seems perplexing at first glance to note that 9-duryl-9-chlorofluorene has a greater rate of exchange between methyls than 9-mesityl-9-chlorofluorene (92). This might be taken as an indication that ionization is the true mechanism for the exchange of the methyls in the former. However, the buttressing effect can lower barriers to rotation, as will be discussed later. Further study seems necessary to draw a definite conclusion.

Barriers to rotation of some carbonyl derivatives (**68**) of 9-(1-naph-



ap sp

68

thyl)fluorene have been determined by Saito and Ōki and are listed in Table 16, together with population ratios of the rotamers (109). Apparently the barriers for the process sp → ap are almost the same. Probably the transition states for rotation of these compounds are nearly the same in energy. In contrast, the barriers to rotation for the process ap → sp vary according to the substituent on the carbonyl group, and this variation is reflected in the equilibrium constants.

Table 16

Barriers to Rotation and Population Ratios of 9-(1-Naphthyl)fluorenes Carrying Carbonyl Substituents at the 2-Position of the Naphthyl at 55°C

Carbonyl group	Process	$\Delta G^{\ddagger}$ (kcal/mol)	K (sp/ap)	Solvent
CHO	sp → ap	26.9	1.5	C_4Cl_6[a]
	ap → sp	26.7		
COOH	sp → ap	25.7	~20	DMSO
	ap → sp	23.8		
$COOCH_3$	sp → ap	26.6	7	C_6D_6
	ap → sp	25.3		
C_6H_5CO	sp → ap	26.5	13	C_6D_6
	ap → sp	24.9		
CH_3CO	sp → ap	26.3	12	C_6D_6
	ap → sp	24.6		

[a]Hexachlorobutadiene.

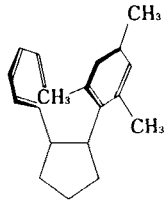
Molecular models suggest that the aldehyde (**68**, X = H) can assume a coplanar conformation with the naphthyl group, whereas such a coplanar conformation is not possible for any of the other compounds. This situation is reflected in the infrared carbonyl stretching frequencies. The ap forms of these compounds absorb generally at higher frequencies than do their sp counterparts.

Since the solvent properties of dimethyl sulfoxide are widely different from those of hydrocarbons and halogenated hydrocarbons, it may be difficult to compare the kinetic and thermodynamic data for the CO_2H group (Table 16) directly with others. However, heating the carboxylic acid (**68**, X = OH) in toluene affords the sp isomer almost exclusively. Probably, the observed results with the carboxylic acid derive from difficulty in the formation of a hydrogen bond owing to a steric effect, in addition to the nonplanar conformation of the carboxyl group relative to the naphthalene.

Comparing the barrier to rotation of the aldehyde (**68**, X = H) with that of the corresponding methyl compound (**54**), one sees that the barrier in the former is diminished to some extent. This phenomenon may be attributed to the small size of the CHO group relative to methyl, which causes diminution of the interaction in the transition state for rotation.

B. Other sp^3-Carbon-to-Aryl Systems

When two benzene rings are placed with their faces opposing each other at close range, it is to be expected that rotation of one ring will require a relatively high energy, if the other is fixed. Thus atropisomerism should be possible. One possibility for realizing this expectation is to place two benzene rings in a ring system. However, the rotational barrier of *cis*-(1-phenyl-2-mesitylcyclopentane (**69**) was found to be low, 11 kcal/mol (110). To manifest a high barrier to rotation, rigidity of the molecule may be required. Although this required rigidity was provided by the naphthalene system and 1,8-di(*o*-tolyl)naphthalene (**70**) was



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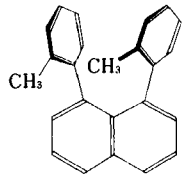


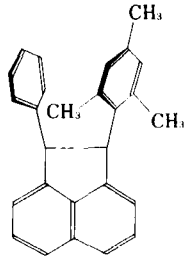
Only cis-form is shown.

70

separated into cis and trans atropisomers (111), this will not be further discussed here because this is an sp^2–sp^2 system similar to biphenyl.

The required rigidity of a nonaromatic ring carrying two aryl groups was

provided by acenaphthene. Miller and Curtin (112) prepared *cis*-1-phenyl-2-mesitylacenaphthene (**71**) and *cis*-1-phenyl-2-(2,4,6-triisopropylphenyl)acenaphthene (**72**). From the NMR data at high temperatures, they concluded that the barrier to rotation of the mesityl group in **71** is 23 to 26 kcal/mol, and that of the triisopropylphenyl group in **72** is >26 kcal/mol at 200°C.



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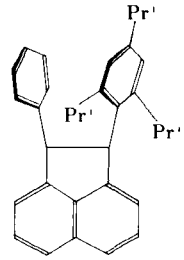

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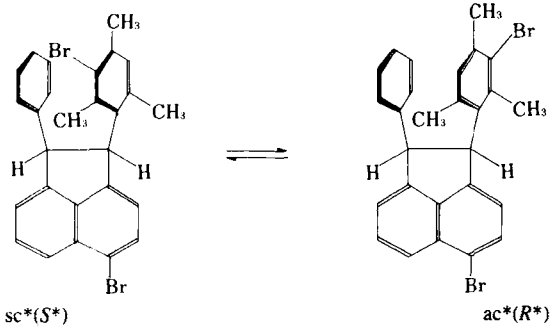
Such barriers are high enough for the isolation of atropisomers if the benzene ring is properly substituted. Miller and Curtin (112) brominated **71** and were able to isolate 86% pure ap isomer of the dibromo compound (**73**). The barrier



73

to isomerization in carbon tetrachloride was 25.6 ± 0.3 kcal/mol for the ap → sp process at 76°C, and the equilibrium constant was 0.63 ± 0.01 in favor of ap.

Lomas and Dubois (113a) treated di-*tert*-butyl ketone with *o*-tolyllithium and obtained a mixture of rotamers of *o*-tolyl-di-*tert*-butylcarbinol (**74**), which were

74

isolable at room temperature. The conformations of these isomers were confirmed by X-ray crystallography, which revealed that the distance between the *o*-methyl and the oxygen of the hydroxy group in the sp isomer is only 2.66 Å and the C—O bond of the carbinol makes a dihedral angle of 11.6° rather than being coplanar with the benzene ring. The barrier to rotation for the ap → sp process was 25.9 kcal/mol in dodecane. This indicates that introduction of a methyl ortho to the carbinol moiety raised the barrier by more than 4 kcal/mol, since the barriers to rotation of aryl-di-*tert*-butylcarbinols lacking the *o*-substituent are known to be 19 to 21 kcal/mol (114,115). No ap form was detected at equilibrium, and this result was attributed to the raising of the ground state energy due to severe steric interaction between the two *tert*-butyl groups and the *o*-methyl.

Substituent effects on the rates of isomerization of aryl-di-*tert*-butylcarbinols have been studied. The results are shown in Table 17 (116). The substituent effect on the barrier is, as expected, small if the substituent is in either the 4- or the 3-position. However, a buttressing effect of the substituents in 2,3,4,5-tetramethylphenyl-di-*tert*-butylcarbinol is apparent. The barrier is raised by ca. 1 kcal/mol in this case.

Lomas, Luong, and Dubois (116) have reported another interesting point, namely, the effect of base on the barriers to rotation in **74**. As can be seen in Table 18, there is a large decrease in barrier, and both the equilibrium constants and the rates of rotation are dependent on the concentration of added butyllithium. This large decrease is attributed to the increase in size of the alkoxy group due to aggregation of lithium alkoxide and butyllithium and a consequent increase in ground state energy. The change in the equilibrium constant is explained on the same basis.

Lomas and Dubois (113b) also reported that by substitution of 1-adamantyl group(s) for one or two of the *tert*-butyl group(s) of di-*tert*-butyl-*o*-tolylcarbinol (**74**), the barrier to rotation was considerably raised, $\Delta G^{\ddagger}$ at 200°C being 33.9 and 39.1 kcal/mol, respectively, for the mono-1-adamantyl and di-1-adamantyl compounds in dodecane. Being rigid, the 1-adamantyl group causes more steric interference in the transition state for rotation than does the *tert*-butyl.

Table 17

Rates and Kinetic Parameters for the Internal Rotation of Substituted 2-Methylphenyl-di-*tert*-butylcarbinol (**74**) in Dodecane (ap → sp)

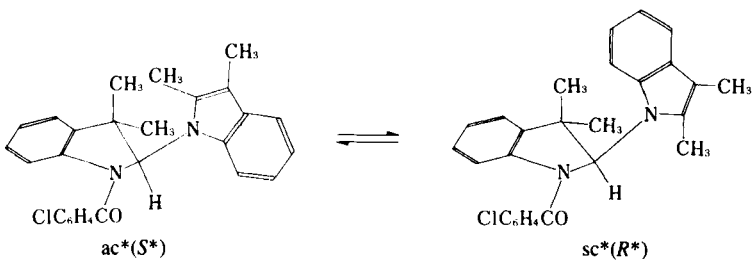
Substituent	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (e.u.)	$k \times 10^4$ (sec^{-1}, 130°C)
4-CH_3O	25.1 ± 0.5	−9.3 ± 1.2	18.3
4-CH_3	25.2 ± 0.5	−9.3 ± 1.3	16.9
5-CH_3	25.5 ± 0.4	−9.0 ± 0.9	13.6
H	25.9 ± 0.4	−8.2 ± 0.9	12.6
5-Cl	25.7 ± 0.4	−8.9 ± 1.0	11.2
3,4,5-$(CH_3)_3$	26.6 ± 0.6	−9.0 ± 1.5	3.40

Table 18
Effect of Butyllithium Concentration on the Rate of Isomerization and Equilibrium Constant of 2-Methylphenyl-di-*tert*-butylcarbinol (**74**) in Hexane at 25°C

		10^3k (sec^{-1})	
[BuLi] (mol/liter)	K (sp/ap)	ap → sp	sp → ap
0.08	10.1		
0.16	6.88	2.43	0.35
0.48	3.44	2.99	0.87
0.80	2.27	3.90	1.72
1.12	1.78	4.90	2.75
1.60	1.15	5.90	3.75

C. Atropisomerism about Nitrogen-Containing Bonds

Taguchi and associates (117) treated 3,3-dimethyl-3H-indole with *p*-chlorobenzoyl chloride in pyridine, and obtained two crystalline compounds in addition to 1-(*p*-chlorobenzoyl)-3,3-dimethylindolin-2-ol. These two products had the molecular formula $C_{27}H_{25}ON_2Cl$, and a tricyclic structure with two benzo moieties was assigned. Dave and co-workers (118) questioned the structure on the basis of mechanistic considerations, and presented evidence that the products are atropisomers of 1-(*p*-chlorobenzoyl)-2-(2,3-dimethyl-1-indolyl)-3,3-dimethylindoline (**75**) about the C—N axis. The barrier to rotation about the C—N bond

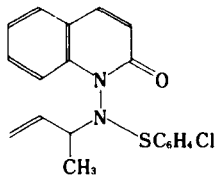


75

was >30 kcal/mol, because equilibrium had not been reached after heating 1 hr in boiling toluene. When equilibrium is reached by heating above the melting points, 204 to 206°C and 133 to 135°C, the higher-melting isomer predominates (ca. 7 : 3). Other acyl derivatives were also found to contain stereoisomers that were not separated (119). Reduction of the *p*-chlorobenzoyl group of each isomer gave the respective *N*-*p*-chlorobenzyl compound. Although the latter was heat sensitive, one isomer was ca. 40% converted to the other at 145°C (118). From the ^{1}H NMR data, the low-melting isomer of the *p*-chlorobenzoyl compound was assigned the ac*(*S**) conformation. The substituent on the nitrogen of the indoline ring is important in making the barrier to rotation high, because when

the *p*-chlorobenzoyl group is removed both stereoisomers afford the same product. The ^{1}H NMR spectra of the latter showed separate signals that coalesced at 60°C. The conformations of the stereoisomers of **75** were confirmed by X-ray analysis (120).

Atkinson and co-workers treated *p*-chlorophenyl 2-butenyl sulfide with 1,2-dihydro-2-quinolon-1-ylnitrene, and found two isomers in the product **76**, between which equilibrium was reached by heating at 100°C for 30 min (121). The barrier was later determined to be 26.1 kcal/mol (122). A similar phenomenon was observed for the product obtained when 3-methyl-2-butenyl phenyl sulfide was used. However, the product (**77**) from *N*-phthalimidonitrene afforded



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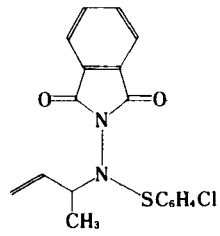

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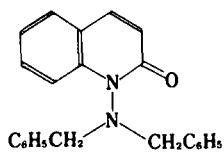
a single isomer. If the *p*-chlorophenylsulfenyl group is removed from **76**, the barrier for the exchange becomes so low as to show coalescence of NMR signals at ca. 20°C.

As an extension of this work, Atkinson and co-workers (123) prepared 1-dibenzylamino-1,2-dihydro-2-quinolone (**78**) and 1-(*N*-benzyl-*N*-carboxymethyl)amino-1,2-dihydro-2-quinolone (**79**). The benzylic protons of **78** showed an AB quartet that did not coalesce up to 180°C, and **79** was resolved into optical isomers. The E_a for racemization was 26.2 ± 0.4 kcal/mol. Various attempts were made to elucidate the possible pathways for isomerization in these quinolone derivatives (123). Radical dissociation, a sigmatropic shift followed by rotation, and restricted rotation about the S—N bond were excluded. The aforementioned authors (123) also excluded the possibility of nitrogen inversion and preferred restricted rotation about the N—N bond as an explanation for the existence of stereoisomers. They supported this explanation by examining the steric effects



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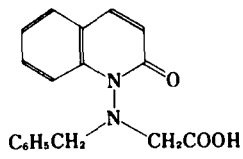

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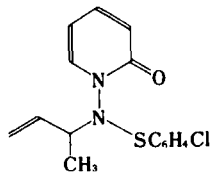

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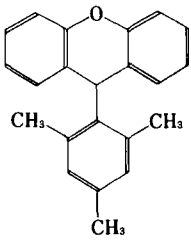
on isomerization. Although bulky substituents are known to lower the barrier to inversion of nitrogen, the rate of isomerization was smaller for the quinolone (**76**) than for the phthalimide or a pyridone (**80**).

The postulate by Atkinson and associates would be convincing if the sulfenamide nitrogen in compound **76** assumed a planar structure. However, the nitrogen is definitely pyramidal according to X-ray crystallography (124). The AB NMR signal of compound **78** also suggests that the nitrogen is pyramidal and its inversion is slow. Therefore, further work is needed to establish that restricted rotation about the N—N bond does indeed explain the barrier to isomerization of **76**.

D. Some Potential Atropisomers about sp^3-Carbon-to-Aryl Bonds

There are two other systems known that show barriers to rotation of more than 23 kcal/mol, although no isolation of atropisomers has been reported in these systems. It is a surprise to note that the barrier to rotation in 9-mesitylxanthene (**81**) is low (125), after knowing that the barriers to rotation in 9-mesitylfluorenes are very high. This phenomenon is a result of the structure of these compounds. Compound **81** is unstable in the equatorial conformation because the central 6-membered ring assumes the boat form (126). The mesityl group then takes the axial position (**82**), where steric hindrance to rotation is not high.



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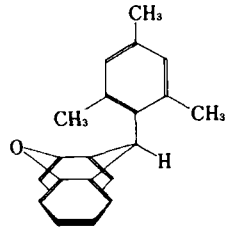

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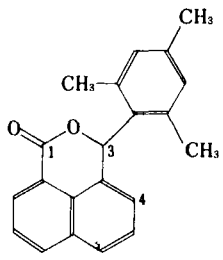
A similar kind of ring flip followed by rotation—which, however, gives rise to a high barrier to rotation—has been reported by Miller (127) in naphthopyrane derivatives **83** to **85**. The mesityl groups in these compounds exist in an equatorial conformation, according to proton NMR evidence. If rotation of the mesityl group occurred in this conformation, the barriers in these compounds should not differ greatly. The observed results shown in Table 19 reveal, however, that the barrier is affected by the substituent in the 1-position. This is because the hydrogen in the 4-position locks the rotation of the mesityl in the equatorial conformation, so the oxygen-containing ring must invert before rotation can occur.



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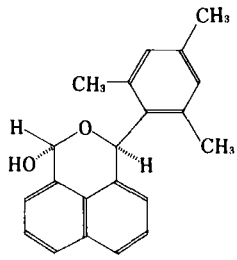

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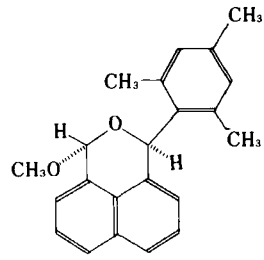

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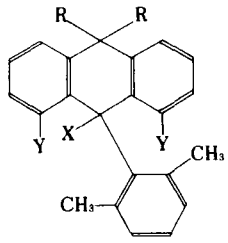
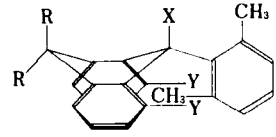
Thus the barriers are reasonably explained by the steric effect due to the hydrogen across the ring when the mesityl group rotates in the axial position. Being a larger group, the methoxy group gives a larger buttressing effect to the hydrogen in the 1-position and raises the barrier. Therefore, the barrier to exchange in this case is the sum of the barriers for the ring flip and for rotation of the mesityl group.

Nakamura and Ōki (128) provided a technique to lock a 2,6-xylyl group in the equatorial position of 9-(2,6-xylyl)-9,10-dihydroanthracene, namely the introduction of two alkyl groups into the 10-position. Now, in either conformation of the central ring there is an alkyl group to oppose the axial substituent in the 9-position, thus making the xylyl axial conformation unstable. Yet the barriers to rotation of the 2,6-xylyl group, summarized in Table 20, indicate that the effect of the substituent in the 10-position is large. This suggests that the xylyl group actually does rotate in the axial conformation. It is interesting that the barrier is decreased if X = OH and Y is changed from Cl to H, whereas the barrier for Y = H is higher than that for Y = Cl when X = H. This phenomenon was explained by assuming that the 2,6-xylyl group rotates in the axial conformation, in which three dipoles (C—Cl, C—OH, C—Cl) must be arranged parallel in the transition state for rotation in **86** (X = OH, Y = Cl). Therefore, the energy of the transition state for rotation of **86** (X = OH) is raised by the introduction of the two chlorine atoms (because the axial conformation becomes



86



87

Table 19
Kinetic Parameters for the Mesityl Site Exchange in Naphthopyrane Derivatives (**83**, **84**, **85**)

Compound	T_c (°C)	$\Delta G_c^{\ddagger}$ (kcal/mol)
83[a]	51 ± 1	16.3 ± 0.1
84[b]	175 ± 3	22.8 ± 0.2
85[b]	198 ± 3	24.0 ± 0.2

[a]Chloroform-*d* solvent.
[b]1,2,4-Trichlorobenzene solvent.

less favorable), and this rise is responsible for the high barrier. In contrast, when X = H no such interaction occurs. Thus the introduction of the chlorine atoms, in the case of X = H, raises the ground state (**87**) energy more than that of the transition state for rotation.

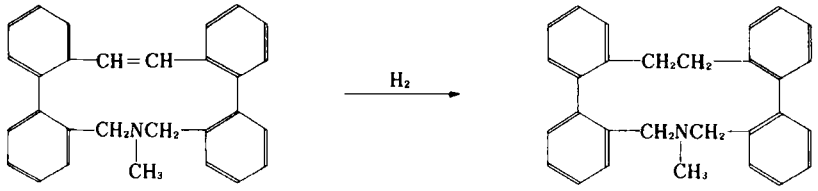
IV. ATROPISOMERISM ABOUT sp^3–sp^3 BONDS

Despite the fact that many groups of scientists have been interested in finding systems with high barriers to rotation, purely open-chain hindered aliphatic systems such as di-*tert*-butyl(2,2,3,3-tetramethylbutane) showed barriers to rotation of ca. 16 kcal/mol at the most (129). Recent studies (130) on similar systems agree with the earlier ones. Evidently some device is necessary to lock the conformation of the open-chain compound.

Wittig and associates (131) had noticed that the cis and trans forms of 1-methyl-1-aza-3,4,5,6,9,10,11,12-tetrabenzocyclotrideca-3,5,7,9,11-pentaene (**88**) yield different forms of the corresponding saturated compounds (**89**) on hydrogenation. They attributed this phenomenon to the existence of stable ±sc and

Table 20
Kinetic Parameters for the 2,6-Xylyl Rotation in 10,10-Disubstituted 9-(2,6-Xylyl)-9,10-dihydroanthracenes (**86**) in Hexachlorobutadiene

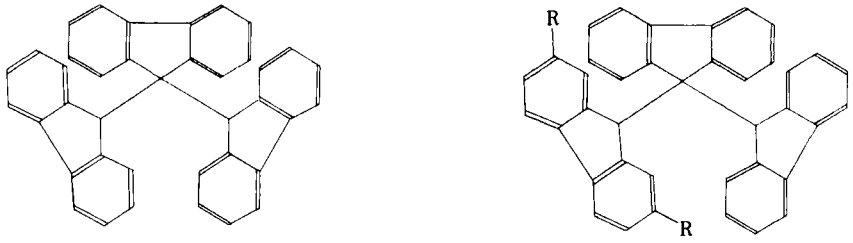
X	Y	R	T_c (°C)	$\Delta G_c^{\ddagger}$ (kcal/mol)
OH	H	CH_3	48	15.4
H	H	CH_3	126	19.6
OH	Cl	CH_3	172	21.6
H	Cl	CH_3	36	15.0
OH	H	$CH_2C_6H_5$	138	19.6
OH	Cl	$CH_2C_6H_5$	>200	>22.7



88 **89**

ap conformers about the CH_2—CH_2 bond. They were able to equilibrate these. However, since more than one bond must rotate to convert one isomer to the other in this example, it will not be discussed further.

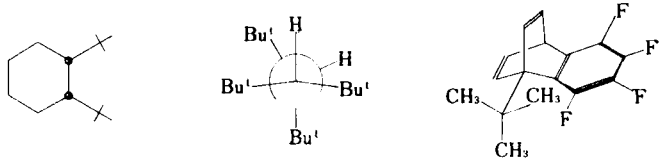
The existence of stable rotamers of 9,9-di(9-fluorenyl)fluorene (**90**) has been postulated (132). However, work by Kajigaeshi and associates (133) has revealed that the barrier to rotation of a series of related compounds (**91**) is at most 20.9



90 **91**

kcal/mol at 120°C. Therefore this type of compound cannot exist as stable rotamers at room temperature. Another claim (134) that atropisomers were isolated in a steroid system was refuted by X-ray crystallography (135).

Kessler and co-workers (136) reported that the barrier to rotation in *cis*-di-*tert*-butylcyclohexane (**92**) was 16.3 kcal/mol at 298 K. This relatively low



92 **93** **94**

barrier must be attributed to the raising of the ground state energy caused by very large steric interactions. Indeed, force-field calculations on this compound showed distortion of the molecule from the normal cyclohexane geometry (137).

Brownstein and associates (138) found that 1,1,2,2-tetra-*tert*-butylethane ex-

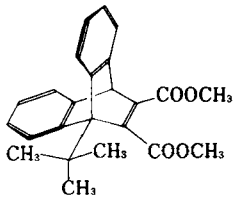
ists in a distorted ±sc conformation (**93**) because of the bulkiness of the *tert*-butyl group. The free energy of activation for rotation of this compound is estimated to be >23 kcal/mol at 140°C where irreversible decomposition sets in. Therefore, this compound, in principle, should give stable enantiomers at room temperature if an appropriate method of resolution were available.

The first indication of high barriers to rotation in compounds in which synthetic modification of the molecule is facile has been provided by Brewer and associates (139). During their work on polyhalogenated benzynes, they treated *tert*-butylbenzene with tetrafluorobenzyne and observed the ^{1}H NMR spectrum of the product (**94**). The *tert*-butyl protons gave two kinds of methyl signals in 1 : 2 intensities and these signals coalesced at 120°C. Although they did not report the barrier to rotation of this compound, it could be calculated from the available data to be ca. 20 kcal/mol.

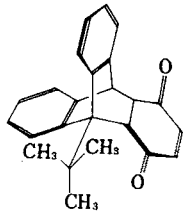
Although this compound itself does not have a high enough barrier to rotation for the isolation of atropisomers, the skeleton may be modified: If one or two benzeno bridges are added to the benzotricyclo[2.2.2]triene system (**94**), it was speculated that the barrier to rotation might be raised considerably and might finally make it possible to isolate atropisomers. With this expectation Ōki and associates carried out a series of investigations of 9-substituted triptycenes and related compounds, and the following is an account of their work.

A. Atropisomerism about *tert*-Alkyl-to-Triptycyl Bonds and Related Systems

Ōki and Suda (140) treated 9-*tert*-butylanthracene with dimethyl acetylenedicarboxylate and with *p*-benzoquinone, respectively, to obtain the Diels–Alder adducts **95** and **96**. Compound **95** exhibited two kinds of high-field methyl signals in its ^{1}H NMR spectrum and **96** three methyls. The two methyl signals of **95**



95

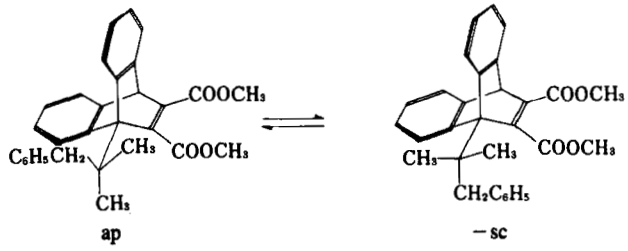


96

did not coalesce, although the spectrum was recorded at temperatures as high as 132°C. Thus the free energy of activation for rotation is calculated as more than 25 kcal/mol, which is high enough for the isolation of atropisomers.

The *tert*-butyl group must obviously be modified in order to obtain atrop-

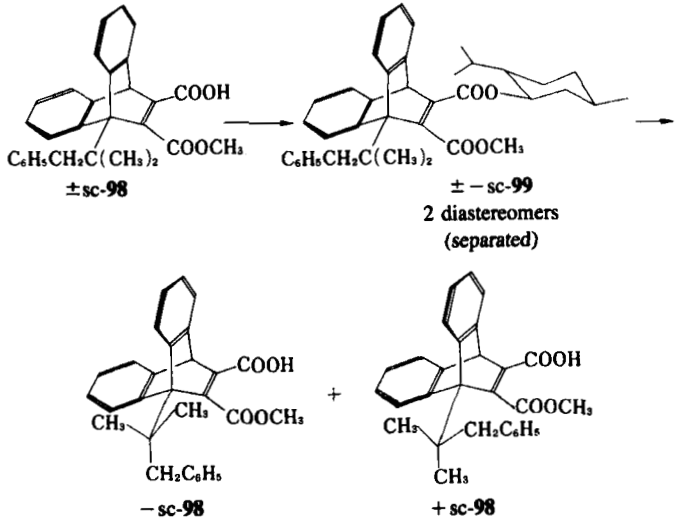
isomers of this type. The first attempt at isolating rotamers of a compound carrying an isopropyl group instead of the *tert*-butyl group in **95** failed because of a low barrier to rotation. Then Yamamoto and Ōki (141) modified one of the methyls of the *tert*-butyl in **95** by substituting a phenyl group for a hydrogen. The compound **97** initially prepared was the ap isomer. After equilibration,

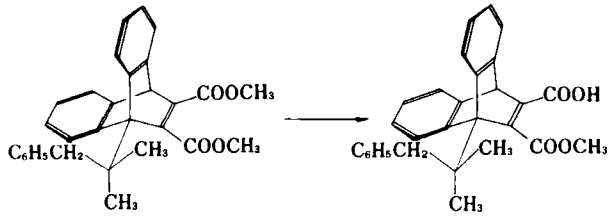


97

chromatography of the mixture afforded the ±sc isomer. The assignment of the stereostructures is straightforward because, having a plane of symmetry in the molecule, the ap form gives a single methyl signal and a singlet for the methylene in its ^{1}H NMR spectrum, whereas the ±sc form gives two methyl signals and an AB quartet for the methylene.

Treatment of either the ±sc or the ap atropisomer of the diester (**97**) with potassium hydroxide effected the hydrolysis of only one of the ester groups for steric reasons, to afford monocarboxylic acid ±sc-**98** and ap-**98**, respectively. The ±sc isomer was converted into a menthyl ester (**99**) for resolution into optical isomers. Thus the three rotameric forms of the monocarboxylic acid (+sc, −sc, ap) were isolated (142).

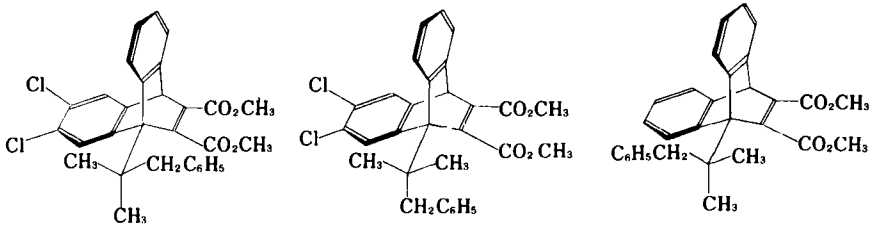




ap-**97** ap-**98**

The Arrhenius activation energy for rotation of the diester (ap → sc) was 33.2 kcal/mol with log *A* 13.3. The equilibrium constant (±sc/ap) was 3.0 throughout the temperature range of 111 to 152°C. The ±sc form is slightly favored above the statistical ratio of 2. This is probably due to the fact, that, being more flexible, the methoxycarbonyl group has a smaller steric interaction with the proximal benzyl group than does the fused benzene ring.

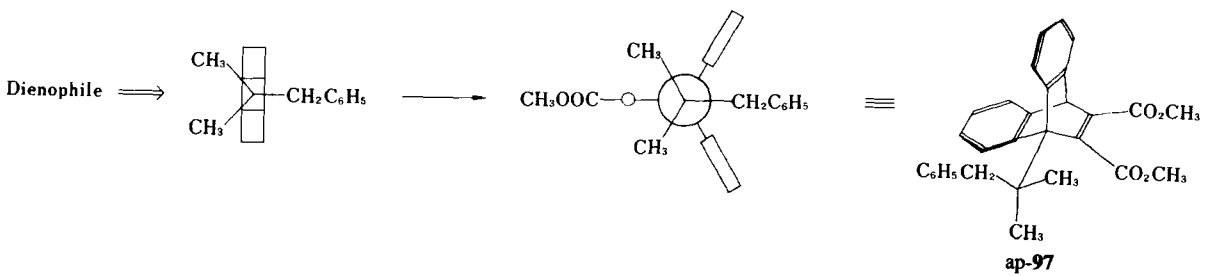
Isolation of another set of three rotamers, but without recourse to optical resolution, was accomplished by Yamamoto and Ōki (143) by suitably modifying the dibenzobicyclo[2.2.2]octatriene. The constitution of the compound separated is dimethyl 2,3-dichloro-9-(1,1-dimethyl-2-phenylethyl)-9,10-dihydro-9,10-ethenoanthracene-11,12-dicarboxylate (**100**). It should possess three diastereomeric



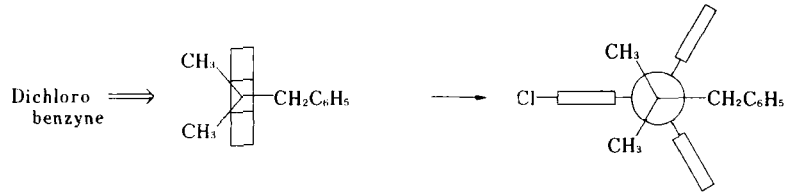
sc*(*S**)-**100** sc*(*R**)-**100** ap-**100**

pairs of enantiomers by internal rotation. These were isolated by chromatography. The barrier to rotation was about the same as that of compound **97** and the equilibrium populations were 3 : 3 : 2 for sc*(*R**), sc*(*S**), and ap at 150°C in chlorobenzene, in agreement with those (3 : 1) for the equilibrium of **97**. The chlorine substituents in the 2- and the 3-position hardly affect either the populations of the rotamers at equilibrium or the rotational barriers.

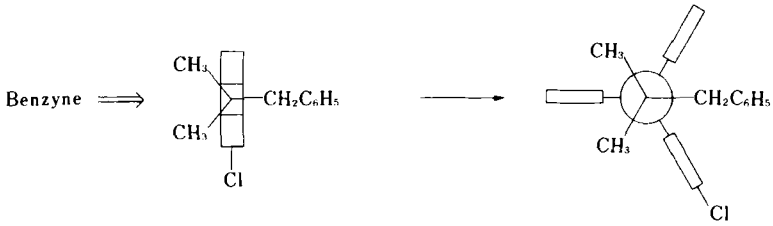
In the syntheses of these compounds, very high stereoselectivity was noted. In every case, the entering dienophile approaches the least hindered side of the substituted anthracene. Thus the ap isomer is the almost exclusive product of the reaction. As an extension of this finding, atropisomers of 9-(1,1-dimethyl-2-phenylethyl)-2,3-dichlorotriptycene (**101**) were prepared separately: the ap form by treating 9-(1,1-dimethyl-2-phenylethyl)anthracene with 4,5-dichlorobenzyne, and the ±sc form by treating 2,3-dichloro-9-(1,1-dimethyl-2-phenylethyl)-


Dienophile
CH3
CH2C6H5
CH3
CH3OOC
CH3
CH2C6H5
CH3
CO2CH3
C6H5CH2
CH3
CO2CH3
CH3

ap-97



ap-**101**

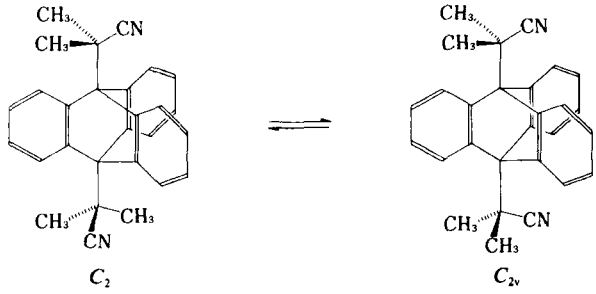


+sc-**101**

anthracene with benzyne (144). This type of stereoselectivity is found helpful for the preparation of pure atropisomers whose separation is often tedious.

The activation energy for rotation about the *tert*-alkyl-to-triptycyl bond was 36.6 kcal/mol for **101**, and the frequency factor was $10^{11.7}$ sec^{-1}. It should be noted that the barrier to rotation is raised by ca. 4 kcal/mol by going from a bis(methoxycarbonyl)etheno bridge to a benzeno bridge. The equilibrium constant (±sc/ap) was 2.0, as expected on statistical grounds.

Contemporaneously with these studies, Iwamura (145) described the separation of the C_2 and C_{2v} isomers of 9,10-bis(1-cyano-1-methylethyl)triptycene (**102**). The Arrhenius activation energy for rotation obtained was 37.7 kcal/mol,



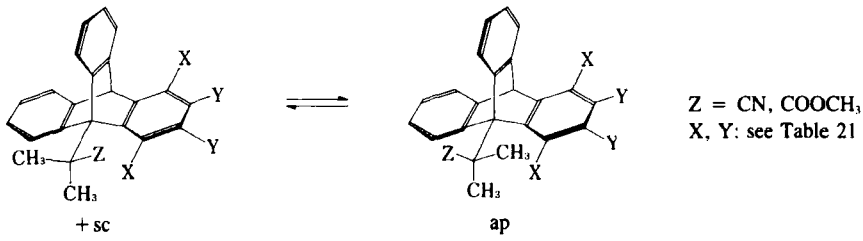
C_2 C_{2v}

102

and the frequency factor was 10^{13} sec^{-1}. The equilibrium constant (C_2/C_{2v}) was 65.5/34.5, close to the statistical value.

This result aroused interest because the barrier to rotation in **102** was higher by about 1 kcal/mol than that in compound **101**, which carries a tertiary alkyl

substituent. Since a benzyl group is larger than a cyano, the observed result is contrary to the expectation based on size. In order to see whether this result is due to the presence of a cyano group, several compounds bearing a 1-cyano-1-methylethyl or a 1-methoxycarbonyl-1-methylethyl group were prepared (146). The results shown in Table 21 are interesting. The barriers are dependent on the direction of interconversion, either ±sc → ap or ap → ±sc, because of a large difference in stabilities of the rotamers, but are generally lower than those of compound **102**. Based on the size of the peri substituent, the barriers to rotation of these compounds (**103**) were originally expected to be higher than the barrier in **102**.



103

In order to see the effect of the peri substituent on the barrier to rotation, 2,3-dichloro-9-(1-cyano-1-methylethyl)triptycene and 2,3-dichloro-9-(1-methoxycarbonyl-1-methylethyl)triptycene (**103**, X = H, Y = Cl) were prepared (147). The data are included in Table 21. The barrier to rotation becomes definitely higher when the peri substituent is removed. Thus the peri substituent in

Table 21
Kinetic Parameters for the Internal Rotation of 9-(1-Cyano- or 1-Methoxycarbonyl-1-methylethyl)triptycenes (**103**) in 1-Chloronaphthalene

Z	X	Y	Process	E_a (kcal/mol)	log A	K (sc/ap, 189°C)
CN	Cl	Cl	sc → ap	36.1	12.9	7.5
			ap → sc	33.8	12.7	
CN	CH_3	H	sc → ap	36.7	13.1	15
			ap → sc	35.4	13.6	
CN	H	Cl	sc → ap	40.3	14.8	2.24
			ap → sc	42.1	16.0	
$COOCH_3$	Cl	Cl	sc → ap	34.4	12.6	21
			ap → sc	31.2	12.4	
$COOCH_3$	CH_3	H	sc → ap	29.1	10.2	8.4
			ap → sc	24.4	9.0	
$COOCH_3$	H	Cl	sc → ap	34.7	13.0	2.80
			ap → sc	35.0	13.6	

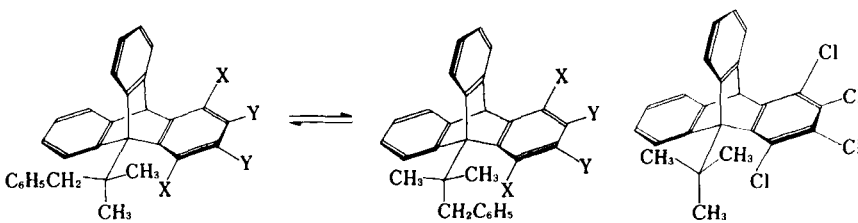
these cases works to raise the ground state energy more than that of the transition state for rotation.

Examination of the barriers to rotation of the cyano and methoxycarbonyl compounds reveals that the barriers are higher for the former if the peri substituent is the same. This may also be ascribed to a raising of the ground state energy caused by the methoxycarbonyl group extending into the gap between the two benzeno bridges of the triptycene skeleton.

The populations of rotamers show interesting trends. To a first approximation, the population ratio of the sc form and the ap should be 2 : 1 if there is no substituent in the peri position. The observed values (Table 21) are significantly larger than this, especially for the methoxycarbonyl compounds. The cause for this anomaly is not well understood, but is not due to dipolar effects because the ±sc isomers are more polar than the ap and the equilibrium was studied in relatively nonpolar 1-chloronaphthalene. When a substituent is introduced in the peri position, the equilibrium constant changes greatly in favor of the ±sc form. A rationale for this phenomenon can be given on steric grounds because, being smaller than methyl, a cyano or a methoxycarbonyl group engenders less steric repulsion with the peri substituent and thus favors the ±sc form.

Close examination of the population ratios of the peri substituted compounds (Table 21) shows another point. That is, whereas the ±sc form of the methoxycarbonyl compound is less favored relative to that of the cyano compound when the peri substituent is methyl, the situation is reversed when the peri substituent is chlorine. Weak attractive interactions between a carbonyl moiety and a peri substituent bearing a lone pair of electrons are known in triptycene systems, and the methoxycarbonyl group is a stronger electron acceptor than cyano (148). This attractive interaction may be the cause for the seemingly anomalous populations.

Establishing that a smaller substituent in the peri position can raise the barrier, Ōki and co-workers (149) were interested in finding the peri substituent effect on the barrier to rotation, and prepared a series of 9-(1,1-dimethyl-2-phenylethyl)triptycenes (**104**). Data in Table 22 indicate that the barrier to rotation



104 **105**

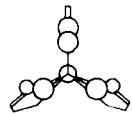
passes through a maximum as the size of the peri substituent is increased systematically.

Table 22
Kinetic Parameters and Equilibrium Constants for the Internal Rotation of 9-(1,1-Dimethyl-2-phenylethyl)triptycenes (**104**) (ap → sc) in 1-Chloronaphthalene

X	Y	$\Delta G^{\ddagger}_{500}$ (kcal/mol)	K (sc/ap)[a]
H	Cl	40.4	2.0 (259)
F	F	44.3	1.42 (259)
OCH_3	H	42.4	1.22 (259)
Cl	Cl	38.2	0.48 (208)
CH_3	H	38.6	0.41 (212)

[a]Temperature (°C) in parentheses.

X-ray crystallography was carried out by Saito and associates (150) with 9-*tert*-butyl-1,2,3,4-tetrachlorotriptycene (**105**). The results indicate that the molecule has a large amount of internal strain. Especially noteworthy is the fact that, although the four chlorine atoms do not deviate appreciably from the plane of the benzene ring to which they are attached, the C(1)—Cl bond is bent considerably against the C—$C(CH_3)_3$ pivot bond. Conversely, the C—C pivot bond is also tilted against the C(1)—Cl bond. This means that the introduction of a peri substituent gives rise to considerable internal strain and, at the same time, that the pivot bond connecting the *tert*-butyl group and the C(9) of triptycene is not collinear with the line passing through C(9) and C(10) of the triptycene. Then if we consider the *tert*-butyl as a rigid rotor, there is a lag between the time when the maximum interaction occurs between one of the methyls and one of the peri CH moieties and that when another methyl has the maximum interaction with another peri CH as shown in Scheme 6. This should tend to lower



Scheme 6

the energy of the transition state. The contribution of this effect along with ground state strain and perhaps other factors must result in lowering the barrier when the peri substituent becomes large.

The equilibrium constants in Table 22 suggest that the larger the peri substituent, the less favored is the sc form. Since the phenyl group takes a conformation in which it does not directly interact with the peri CH group, this result may originate in the ease or difficulty of solvation in addition to an entropy factor due to limitations of certain conformations.

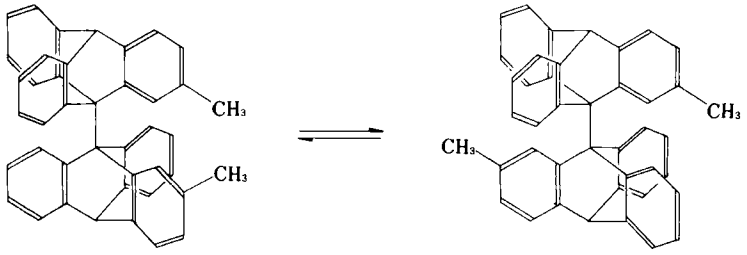
Close examination of the data in Table 22 indicates that the barriers of the

chloro and the methyl compounds are anomalous. Although, from the general trend, the larger methyl group should give a lower barrier to rotation than the smaller chlorine, the opposite is the case. To clarify this point and to investigate a potential buttressing effect of the chloro groups in the benzeno bridge, 1,4-dichloro-9-(1,1-dimethyl-2-phenylethyl)triptycene (**104**, X = Cl, Y = H) was prepared, and its barrier to rotation was measured. The free energy of activation for rotation at 500 K was 39.8 kcal/mol. There is a rise in barrier by ca. 1.6 kcal/mol on removal of the buttressing 2-chloro group. Although this is a "reverse buttressing effect," it is to be expected since internal strain is relieved to some extent when a buttressing group is removed. This will result in lowering the energy of the ground state, as well as in keeping the transition state energy almost the same or slightly higher by matching the timing of maximum interactions (151).

These results suggested examination of the buttressing effect in bromo compounds, so 1,2,3,4-tetrabromo- and 1-bromo-9-(1,1-dimethyl-2-phenylethyl)-triptycenes were prepared. As expected, the tetrabromo compound had a relatively low barrier of 35.1 kcal/mol at 500 K. In contrast, the free energy of activation for rotation of the monobromo compound was 39.2 kcal/mol. The difference amounts to 4.1 kcal/mol (151). The "reverse buttressing effect" can be large if the substituents concerned are large.

Since, in the case of the *tert*-butyltriptycene skeleton, the maximum barrier to rotation is realized when the substituent in the peri position is medium sized, it was of interest to see whether a similar result would be obtained with other tertiary alkyl groups. Thus to complete the series, 1,2,3,4-tetrafluoro- and 1,4-dimethoxy-9-(1-cyano-1-methylethyl)triptycenes (**103**, X = Y = F or X = CH_3O, Y = H) were prepared. The free energies of activation for rotation of the fluoro and the methoxy compounds were 39.9 and 38.9 kcal/mol, respectively, at 462 K (152). It may be too early to draw a general conclusion in the tertiary alkyl series, but it is tempting to consider that the highest barriers are obtained when the peri substituent in this series is fluorine.

It has become clear that a high barrier to rotation exists in principle in 9-*tert*-alkyltriptycenes, but that their ground states are congested. Thus a high barrier is in fact expected if the ground state is relaxed by removing strong steric interactions. Schwartz and associates (153) presented a beautiful example of this sort, 2,2′-dimethylbitriptycyl (**106**), although in this molecule the transition state for rotation is also raised in energy. One of the isomers, probably the ±sc form, could be concentrated up to 2.1 : 1.0 by repeated crystallization. The other isomer was concentrated up to 1.0 : 0.44. Heating solutions of these isomers in naphthalene at 300°C for 171 hr led to no significant interconversion. If a frequency factor of 10^{13} is assumed, which is the normal value for internal rotation, the Arrhenius activation energy is calculated to be in excess of 54 kcal/mol.

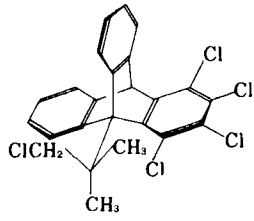


+sc ap

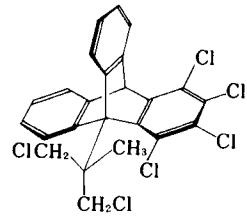
106

Since the barrier to rotation is so high in the 9-*tert*-alkyltriptycene series, one may wonder if the mechanism of rotation might involve radical dissociation. Although no positive evidence for exclusion of a homolytic mechanism has been obtained, there are two indirect pieces of evidence. One is the experiment of Schwartz and associates (153), who heated compound **106** at 300°C for 171 hr without significant change. This means the triptycyl radicals are not produced significantly under these conditions. Although other triptycenes examined possess *tert*-alkyl groups which, after dissociation, can give more stable radicals than triptycyl, the temperatures required for the isomerization were much lower than 300°C. We may assume, therefore, that radical dissociation does not occur appreciably during the isomerization. Another point is that no isomerization of the 9-(1,1-dimethyl-2-phenylethyl) substituent was observed during the exchange of rotamers in compound **104**. If homolysis intervenes, neophyl radicals would be formed, which should isomerize quite easily (154). It is especially so here, because ground state strain would be relieved if the neophyl rearrangement took place and the 2-methyl-2-phenylpropyl radical recombined to form a triptycene derivative.

Chlorination of 9-*tert*-butyl-1,2,3,4-tetrachlorotriptycene yielded ap and ±sc monochlorinated compounds (e.g., **107**) and ap and ±sc dichlorinated compounds (e.g., **108**). The barriers to rotation were found to be 36 kcal/mol at 400



ap-**107**

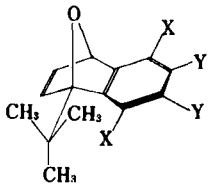


+sc-**108**

K for both compounds (155). These values are a little smaller than that for 1,2,3,4-tetrachloro-9-(1,1-dimethyl-2-phenylethyl)triptycene (**104**, X = Y = Cl),

but the difference is probably not significant, since these halogenated compounds tend to decompose during the heating for isomerization, and barrier measurements are therefore approximate. Interestingly, the population ratios of the atropisomers of these compounds at equilibrium (sc/ap) were 0.96 and 1.80 respectively, for **107** and **108** in the temperature range of 187 to 218.5°C. The equilibrium constant for **107** is larger than that of the phenyl analog (**104**), and that for **108** is very close to the statistical value. These results may be attributed to attractive interactions between the chloro group in the peri position and the chloromethyl group on the substituent, as suggested for other triptycene derivatives on the basis of conformational populations (156).

As for compounds having modified bridges in a bicyclo[2.2.2]octatriene system, 1-*tert*-butyl-1,4-dihydronaphthalene 1,4-endoxides (**109**) and 9-*tert*-butyl-1,2,3,4-tetrachloro-9,10-dihydro-9,10-ethenoanthracene (**110**) were prepared. The



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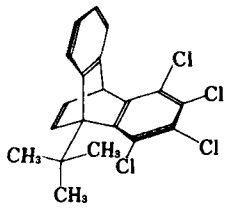

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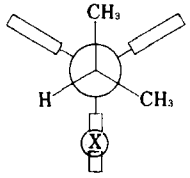
barriers to rotation in the endoxides were lower than 12 kcal/mol (157). It is interesting to note that the highest barrier was obtained when the peri substituent was chloro in the series X = bromo, chloro, fluoro, methoxy, hydrogen. The barrier to rotation in the ethenoanthracene was over 25 kcal/mol (158). If one of the methyls in the *tert*-butyl is modified, atropisomers should be isolable.

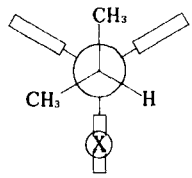
B. Atropisomerism about *sec*-Alkyl-to-Triptycyl Bonds and Related Systems

After finding that rotation of the *tert*-butyl group in dimethyl 9-*tert*-butyl-9,10-dihydro-9,10-ethenoanthracene-11,12-dicarboxylate (**95**) was locked on the laboratory time scale, Ōki and Suda introduced an isopropyl group in place of the *tert*-butyl group and found that the barrier was so much lowered (E_a = 15.4 kcal/mol) that the attempt to isolate atropisomers had to be abandoned (140). Since then, triptycene systems have been found to give higher barriers to rotation than the ethenoanthracene system. Thus it became attractive to examine the barriers to rotation about a *sec*-alkyl-to-triptycyl bond.

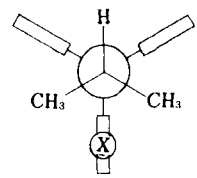
Ōki and associates (159) studied the barriers to rotation of 9-isopropyltriptycenes (**111**) by the dynamic NMR technique. The results shown in Table 23 reveal that, although the barrier to rotation is low when the peri substituent is



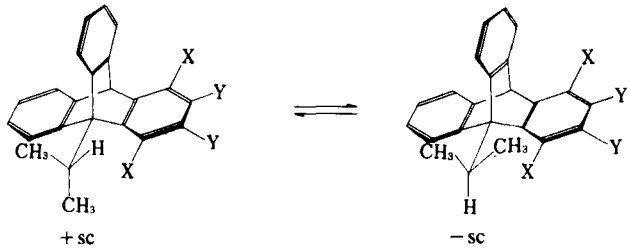
−sc-**111**



+sc-**111**



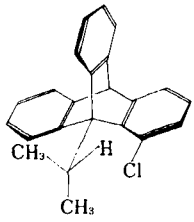
ap-**111**



111

hydrogen, when it is methoxy, chlorine, or bromine, the barrier is high enough for the isolation of atropisomers. Incidentally, these mono-peri-substituted isopropyl compounds exist exclusively in the ±sc conformations, and no ap form (with its single methyl signal) is detected by NMR spectroscopy. This is because in the ap form two methyl groups flank the peri substituent to raise the energy. This contrasts with the situation in dimethyl 9-isopropyl-9,10-dihydro-9,10-ethenoanthracene-11,12-dicarboxylate, which shows the existence of the ap form (160). Thus the isomerization we observe in the isopropyl compounds **111** is a racemization process, thanks to the substituent in the peri position; it is observed as a site exchange of the diastereotopic methyl groups of the isopropyl substituent.

In order to see the effect of buttressing and the effect of size of the peri substituent on the barrier to rotation, 1-chloro- (**112**) and 1,3-di-*tert*-butyl-9-isopropyltriptycene (**113**) were prepared (161). The barrier for **112** was 22.9 kcal/mol. Comparing this to the tetrachloro compound **111** (all substituents Cl), $\Delta G^{\ddagger}$ = 25.5 kcal/mol, a normal buttressing effect seems to operate, in contrast to what is observed for the 9-*tert*-butyltriptycenes as discussed in the previous section. The barrier to rotation in **113** was 20.8 kcal/mol, which is very low



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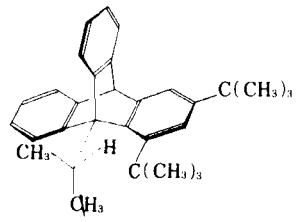


113

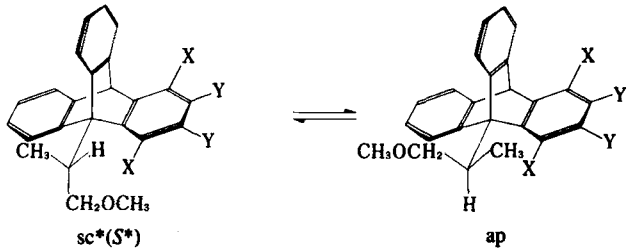
Table 23
Free Energies of Activation for Rotation of 9-Isopropyltriptycenes (**111**) at 25°C

Substituents	$\Delta G^{\ddagger}$ (kcal/mol)	Solvent
2,4-$(CH_3)_2$	19.9 ± 2.5	Tetrachloroethylene
1,4-$(CH_3)_2$	21.8 ± 1.1	Hexachlorobutadiene
1,4-$(CH_3O)_2$	23.6 ± 1.9	Hexachlorobutadiene
1,2,3,4-Cl_4	25.5 ± 2.3	Hexachlorobutadiene
1,2,3,4-Br_4	23.5[a]	Hexachlorobutadiene

[a]At 175°C.

relative to the 1-halo compound. Therefore, there is also a maximum barrier to rotation in the isopropyl series when the peri substituent is medium sized, similar to that seen earlier for tertiary groups. The maximum barrier seems to be realized with a chlorine atom as seen in Table 23. However, a large error in the barrier measurements prohibits a clear-cut conclusion.

Compounds of type **111** should, in principle, be resolvable into stable enantiomers if the barrier is high enough. However, these compounds do not carry a functional group convenient for resolution. Ōki and associates (162) modified one of the methyls in the isopropyl group to make the rotational isomers diastereomeric. They prepared 9-(2-methoxy-1-methylethyl)triptycenes (**114**) and



114

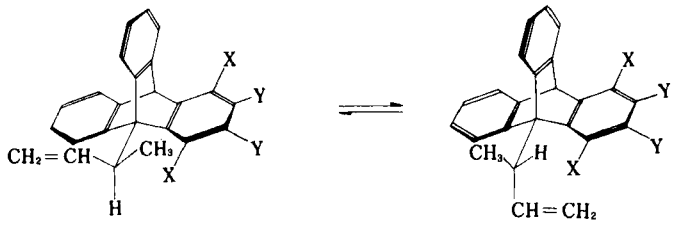
obtained one of the rotamers in the pure state by recrystallization. From the NMR spectra, the crystalline form was tentatively assigned the ap conformation. The barriers (Table 24) are generally in good agreement with those obtained by the dynamic NMR technique, but the errors are definitely smaller in this study. It is clear from these data that the methoxy compound indeed has a lower barrier to rotation than the halogen compounds. The chloro and bromo compounds show almost the same barrier heights. Since the assignment of conformation is tentative, we shall not discuss the stability of the conformers. But it is tempting to say that large groups in the peri position disfavor the sc conformation. The disadvantage of the sc form may include hindrance to solvation.

Table 24
Kinetic Parameters for Rotation (ap → sc) and Population Ratios of 9-(2-Methoxy-1-methylethyl)triptycenes (**114**) in Chloroform-*d*

Substituents	Temperature (K)	$\Delta G^{\ddagger}$ (kcal/mol)	K (sc/ap)
1,2,3,4-Cl_4	306	23.5	0.40
1,2,3,4-Br_4	307	23.4	0.28
1,4-$(CH_3O)_2$	306	22.9[a]	0.65

[a]Calculated from the kinetic parameters obtained by the dynamic NMR method.

Ōki and associates (163) further prepared 9-(1-methyl-2-propenyl) triptycenes (**115**) to see the effect of a vinyl substituent on the barrier to rotation. They were able either to isolate or to enrich one of the rotamers in crystalline form, and they examined the barrier both by equilibration and by the dynamic NMR tech-



ap sc*(*R**)

115

nique (Table 25). Barriers to rotation are about the same as those in compounds with the isopropyl (**111**) or 2-methoxy-1-methylethyl (**114**) groups. Since the bulkiness of the π system is less than that of methyl, it must be said that these 1-methyl-2-propenyl compounds possess rather high barriers. The atropisomers obtained as crystalline forms were tentatively assigned the ap conformation from the NMR spectra. Based on this assignment, the sc forms are less stable if the

Table 25
Activation Parameters for Rotation (ap → sc) of 9-(1-Methyl-2-propenyl)triptycenes (**115**) in Hexachlorobutadiene as Obtained by Dynamic NMR

Substituents	T_c (°C)	$\Delta G_c^{\ddagger}$ (kcal/mol)	K (sc/ap)[a]
1,2,3,4-Cl_4	176.4	24.3	0.81
1,2,3,4-Br_4	176.0	24.2	0.88
1,4-$(CH_3O)_2$	140.7	22.7	0.72
1,4-$(CH_3)_2$	137.2	22.3	1.5

[a]K was measured in the range of 20 to 50°C and was independent of temperature in this range.

peri substituent carries a lone pair of electrons. However, in the methyl compound (**115**, X = CH_3, Y = H) the sc isomer becomes the major conformation. Further study is needed to understand the switch in stabilities of these compounds.

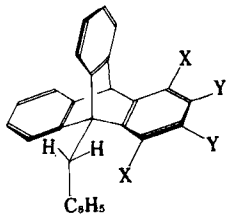
So far triptycenes carrying a secondary alkyl group in the 9-position have been found to give rather unstable atropisomers. To raise the barrier to rotation of the *sec*-alkyl group, the introduction of substituents in more than one peri position may be helpful; the same is true when there is a primary alkyl group at the 9-position (*vide infra*).

Summarizing the results related to the barriers to rotation of a secondary alkyl group in the 9-position of a 1-substituted triptycene, we note that the maximum barrier is realized when the peri substituent is chlorine or bromine. Evidently the size of the substituent that gives the maximum barrier to rotation is shifted from that in the 9-*tert*-alkyl systems. This is considered to be a reflection of the strain in the ground state, which is usually larger in the tertiary alkyl systems than in the secondary, if the same substituent is present in the peri position.

Ōki and associates (159) postulated earlier that there could be a cogwheeling arrangement between a peri methyl group and a 9-substituent to explain the observed low barrier relative to other substituents whose van der Waals radii are smaller than that of methyl. Mislow and co-workers (164) questioned this idea because the former authors neglected the buttressing effect. The buttressing effect is now found to be able to lower as well as to raise the barrier, depending on the situation. The results presented here suggest that mere consideration of the bulkiness of a methyl group may be sufficient to explain the low barrier for the *sec*-alkyl group.

C. Atropisomerism about Triptycyl-to-Primary Alkyl Bonds

From the trend in barriers of tertiary and secondary alkyl groups attached to the 9-triptycyl group, the barrier to rotation about a C(9)—C(CH_2) bond in 9-benzyltriptycenes (**116**) that carry a peri substituent is expected to be still lower, and it is only about 12 kcal/mol (165). However, if substituents are introduced at another peri position, the barriers are raised considerably. 1,2,3,4,5,6,7,8-



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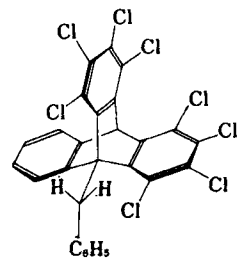

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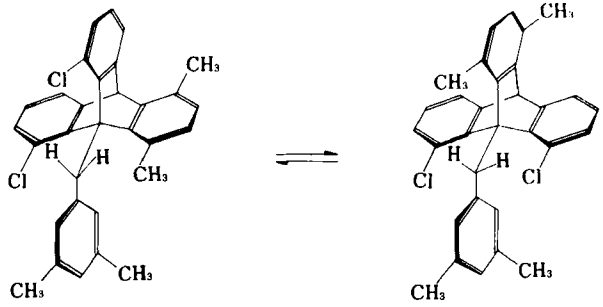
Octachloro-9-benzyltriptycene (**117**) shows a barrier to rotation of ca. 18 kcal/mol (166).

It is then expected that, if one introduces yet another peri substituent, the barrier may become high enough for the isolation of atropisomers. Thus Yamamoto and Ōki (167) prepared 8,13-dichloro-1,4-dimethyl-9-(3,5-dimethylbenzyl)triptycene (**118**) and succeeded in isolating the ap and ±sc atropisomers.

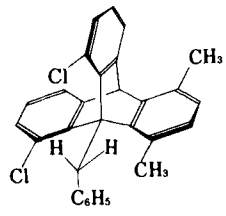


−sc ap

118

The barrier to rotation was 24.8 kcal/mol at 48°C, and the population ratio was 2.0 in chloroform-*d*, which is the statistical value. The size of the peri substituent has an important effect on the barrier to rotation about the CH_2—C(9) bond, because if a 1,4-dimethoxybenzeno bridge is introduced in place of the 1,4-dimethylbenzeno, the coalescence of the AB quartet due to the benzylic CH_2 protons is observed at 167°C corresponding to a free energy of activation of 22 kcal/mol, which is too low for isolation of the atropisomers at room temperature.

If the methyl substituents of the benzyl group are removed, the barrier (in **119**) is raised by ca. 1 kcal/mol, indicating that the effect of the methyl groups



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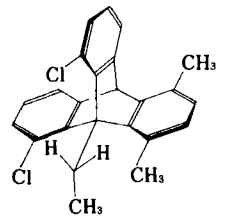

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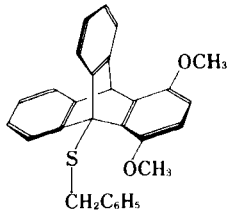
is to raise the energy of the ground state more than that of the transition state for rotation. The phenyl in the benzyl group seems to be important in maintaining a high-energy transition state for rotation, because if the phenyl is replaced by methyl, as in 9-ethyl-1,4-dimethyl-8,13-dichlorotriptycene (**120**), coalescence

of the signals due to the 1-methyl protons occurs at 94°C, and the free energy of activation is calculated to be 20.2 kcal/mol. Probably the phenyl group is so oriented as to interact with both of the peri substituents in the transition state for rotation, so as to raise the energy (168).

D. Atropisomerism about a Bond Involving a Heteroatom

Heteroatoms able to form tetrahedral arrangements of their ligands should also afford atropisomers if the bond in question is properly surrounded by large enough substituents. As a natural choice, triptycene derivatives in which the 9-position is connected to a heteroatom have been investigated.

Nakamura and Ōki (169) prepared 9-benzylthio-1,4-dimethoxytriptycene (**121**) and oxidized it to the corresponding sulfoxide (**122**) and sulfone (**123**). Although the barrier to rotation in **121** was low, slow rotation about the C(9)—S bond of the sulfoxide (**122**) was detected by ^{1}H NMR at about −40°C. In contrast, the sulfone (**123**) showed the presence of stable rotamers, which were isolated by



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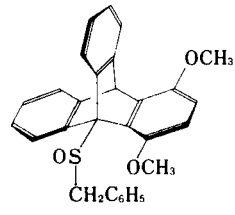

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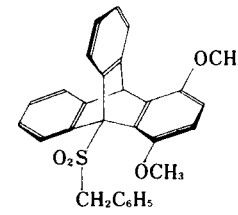
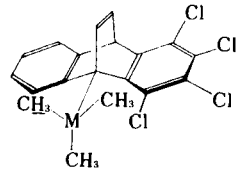


123

chromatography. The barrier to rotation for the process ap → sc was 31.5 kcal/mol at 400 K. The equilibrium constant (sc/ap) was 2.54 at 101°C. This indicates that the sc conformation is slightly more favored than the statistical value. The barrier may be affected by the long C—S bond and also by the sizes of the substituents. Further study is needed before these effects can be discussed.

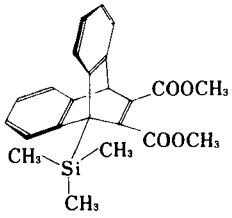
One point of interest is found in the study of the barrier to rotation of $(CH_3)_3M$ groups (where M is C, Si, Sn, or Ge) in 9-[trimethyl-M]-1,2,3,4-tetrachloro-9,10-dihydro-9,10-ethenoanthracene (**124**) (158). The results shown in Table 26 are interesting in that, when we descend the periodic table, the barrier becomes



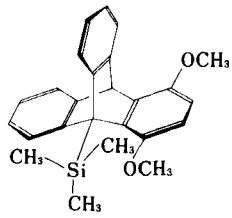
124

lower. Rigid molecular models do not predict this. On the contrary, they suggest that, as the M—CH_3 becomes longer, the CH_3–Cl interaction should become more severe (even though the C(9)–M distance also increases). However, these results may be explained by the smaller force constants for angle deformations for the atoms at the lower end of the periodic table, combined with the fact that a small bond angle deformation can cause a large displacement if the bond length is large. At any rate, if we compare the barriers to rotation about a C—M bond where M changes from the first row to the second, and then to the lower rows of the periodic table, the barrier becomes lower if the substitution pattern is otherwise the same.

In this context, it will be attractive to investigate whether or not it is possible to isolate rotamers of a silicon compound if a silyl group is attached to a triptycene system. Dimethyl 9-trimethylsilyl-9,10-dihydro-9,10-ethenoanthracene-11,12-dicarboxylate (**125**) exhibited a free energy of activation of 16.5 kcal/mol at 300



125



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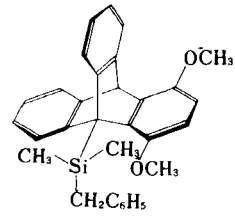


127

K. Therefore, the chloro group in compound **124** (M = Si) raises the barrier more than did the methoxycarbonyl group in **125**, when the skeleton is 9,10-dihydro-9,10-ethenoanthracene. As expected, when the skeleton was changed from dihydroethenoanthracene to triptycene, the barrier was raised. Thus 9-trimethylsilyl-1,4-dimethoxytriptycene (**126**) did not show coalescence of the methyl signals, although the solution was heated to 180°C. The barrier to rotation was thus estimated to be in excess of 25 kcal/mol. In order to confirm the indication from NMR spectroscopy that atropisomerism of this type should be

Table 26
Activation Parameters for Rotation in 1,2,3,4-Tetrachloro-9-trimethyl-M-9,10-dihydro-9,10-ethenoanthracenes (**124**)

M	T_c (°C)	$\Delta G^{\ddagger}$ (kcal/mol, 25°C)	Solvent
C	>200	>25	Hexachlorobutadiene
Si	112	19.9	Hexachlorobutadiene
Ge	64	17.2	Tetrachloroethene
Sn	−40	11.7	Carbon disulfide

observed at room temperature, 1,4-dimethoxy-9-(benzyldimethylsilyl)triptycene (**127**) was prepared (170). The almost pure ±sc form was obtained, which slowly isomerized to form the ap rotamer at 120°C. At equilibrium, the population ratio (±sc/ap) was 5/9. This value is much smaller than that of the corresponding carbon compound (**104**). Although the equilibrium temperatures are different, this large difference may be of fundamental significance.

V. FUTURE SCOPE OF THE CHEMISTRY OF ATROPISOMERS

A number of atropisomers reported in the literature have been discussed in this chapter. Obviously many more systems that can give rise to stable rotamers may be found both by chance and by systematic study, mainly through the dynamic NMR technique. Although in general we can say that such a system should have a relaxed ground state and a highly congested transition state for rotation, it is not an easy task at present to predict what systems may give stable atropisomers. Therefore, instead of trying to do this, we shall discuss possible developments in the field of atropisomerism that may be anticipated in the foreseeable future.

A. Reactions of Rotamers

It is well known that we usually deal with a mixture of rotamers in chemical reactions. If they are interconverted rapidly at a given temperature (eq. [6]), then the Curtin–Hammett relation (171) (eq. [7]) will explain the product dis-

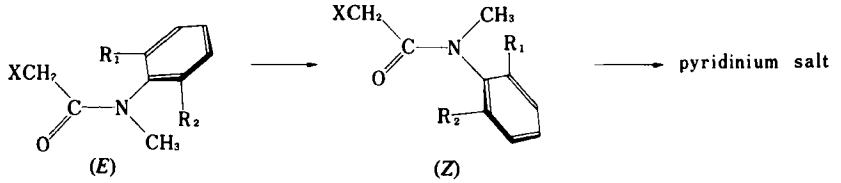
$$D \xleftarrow{k_4} A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B \xrightarrow{k_3} C \qquad [6]$$

$$[C]/[D] = k_3/k_4 \cdot K \quad \left(K = \frac{k_1}{k_2}\right) \qquad [7]$$

tribution. Normally we must know the rates of reactions (k_3 and k_4) as well as the ground state equilibrium constant $K = k_1/k_2$ to predict the product distribution. But k_3 and k_4 are not usually available. As a model for the conformational isomers, cyclohexane derivatives carrying a *tert*-butyl group (172) or *cis*-3,5-dimethyl groups have often been used, but they have limitations both in the functional groups that can be introduced into the system, and in the kinds of intramolecular interactions that are thus accessible. Much of the work in the past has been concerned with steric effects only. Moreover, it is often not certain if the conformation-anchoring groups (such as 4-*tert*-butyl or *cis*-3,5-dimethyl) are innocuous—that is, if they do not affect the reaction rate by direct steric or polar effects. If A and B (as atropisomers) can be isolated and investigated individually, an unobjectionable method for studying k_3 and k_4 would be at hand.

Knowledge of the reactivities of rotamers is becoming increasingly important, especially because, by aiming at highly selective reactions, synthetic organic chemists utilize low reaction temperatures and/or complexation with metals to lock molecules in desired conformations. It is to be hoped that, in the future, the reactivity of a locked conformation of this type might be predicted. Atropisomers might serve as models in this area.

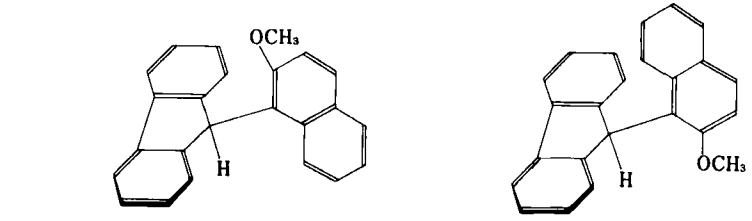
As early as 1967, after their success in isolating atropisomers of haloacetamide derivatives (**12**), Chupp and Olin (49) examined the separate reactivities of these atropisomers in Menschutkin reactions with pyridine (Scheme 7). They found



Scheme 7

that although the *Z* form reacted directly with pyridine, the reactivity of the *E* form was so low that it had to rotate to the *Z* form to react. Therefore, the rate-determining step of the *E* form is essentially the internal rotation.

A similar phenomenon was found by Nakamura and Ōki who investigated deprotonation of 9-(2-methoxy-1-naphthyl)fluorene (173) (Scheme 8). The ap

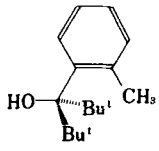


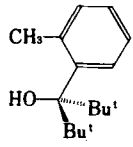
Scheme 8

form reacted at rates comparable with the ap form of 9-(2-methyl-1-naphthyl)fluorene (**54**), but the sp form reacted more than a thousand times faster. The reason for this difference is attributed to steric factors, in as much as butyllithium, normally a hexameric cluster (174) of relatively low reactivity, can, in the sp form, complex with the methoxy group, become disaggregated, and then react rapidly to remove the proximate proton. Part of the reaction of the ap form probably occurs through rotation to the sp rotamer.

Lomas and Dubois report that in the dehydration reaction of di-*tert*-butyl-*o*-

tolylcarbinols (**74**) the ap form reacts faster than the sp form by a factor of ca. 10^4. They attribute this result to the steric crowding in the ap form (175).

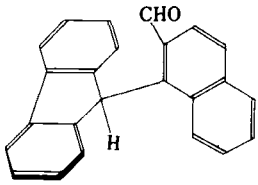


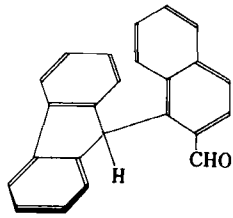


Relative rates of dehydration ca. 10^4 1.0

74

Saito and Ōki (109) tried to oxidize 9-(2-formyl-1-naphthyl)fluorene (**68**, X = H; see Scheme 9) to find that, whereas the sp form reacted normally to





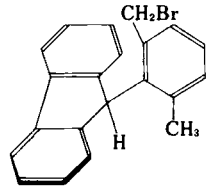
Oxidation with CrO_3 Resists oxidation Smooth oxidation

Scheme 9

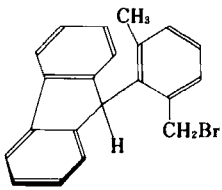
yield the corresponding carboxylic acid, the ap form resisted oxidation. Prolonged oxidation of the ap form afforded a lactone. This process is formally rationalized as follows. The 9-position is oxidized to form a hydroxy compound that rapidly rotates (see Section III-A), and consequently the formyl group is oxidized.

The foregoing examples of differential reactivities of rotamers may be summarized by saying that the reactivity is controlled by the steric factor. The difference in the reactivities of rotamers of 9-(2-bromomethyl-6-methylphenyl)fluorene (**56**) in S_N2 type reactions falls in the same category (176). However, the substituent effect is not limited to a steric one; there can be conformation-dependent electronic effects of substituents as well. A pertinent example is found in the reactivity of the bromomethyl compound (**56**) when the rotamers are heated in a trifluoroacetic acid solution (Scheme 10). The ap form gives rise to a cyclized product, whereas the sp form remains intact (176). The former must be reacting by participation of the π system of the fluorene ring.

The differential reactivity of the methyls in a *tert*-butyl group was first demonstrated by Ōki and co-workers (155) by halogenating the *tert*-butyl group in 9-*tert*-butyl-1,2,3,4-tetrachlorotriptycene (**105**). See Scheme 11. Evidence was



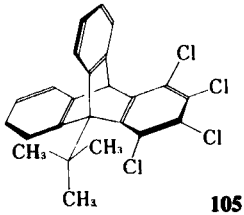
Heated in CF_3COOH — cyclization



no reaction

56 Scheme 10

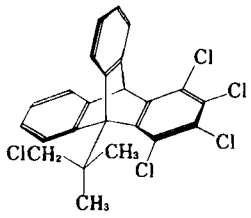
provided that the difference is caused by the electronic effect of the peri substituent.



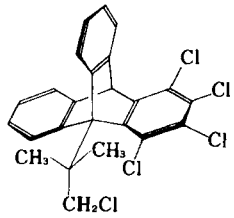
Chlorination with SO_2Cl_2
Relative reactivity:
ap-CH_3 1.0
± sc-CH_3 1.6

105 Scheme 11

Ōki and his co-workers (177) also found that these halogenated compounds (**107**) exhibited enormous differences in reactivity when they were treated with Lewis acids. The ±sc form undergoes a Friedel–Crafts type cyclization in the presence of titanium tetrachloride, which is a weak Lewis acid, whereas the ap form survives these conditions. The latter reacts in the presence of the stronger Lewis acid antimony pentachloride. This difference is apparently caused by a chloro group in proximity to the site where a cationic center develops during the reaction (Scheme 12).



Reaction catalyst — $SbCl_5$



$TiCl_4$

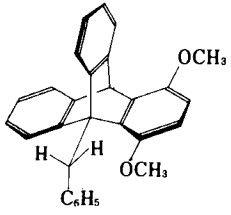
107 Scheme 12 **108**

B. Molecular Interactions

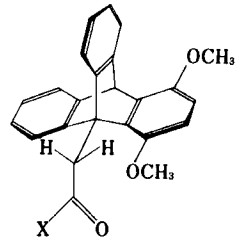
Another field where the chemistry of atropisomers can contribute is concerned with molecular interactions. Since atropisomers about an sp^2–sp^3 or sp^3–sp^3 bond

tend to be in a congested state, their functional groups may be positioned in close proximity. Thus very weak interactions, which are otherwise not detectable, may manifest themselves in such molecules. So far such manifestations have been confined to situations where molecular rotation is not frozen, but two groups can approach closely—for example, in conformational equilibria that are unusual from the steric point of view, and attributed to attractive interactions.

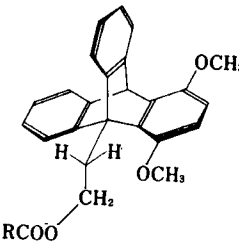
Suzuki and Ōki (178) inferred that there is an attractive interaction between the dimethoxybenzo and the phenyl group in the 9-benzyltriptycene derivatives (**128**) by observing the effect of changing the electron-accepting character of the benzyl group. The same group of workers postulated an attractive interaction between the carbonyl and methoxy groups in 1,4-dimethoxy-9-(substituted carbonylmethyl)triptycenes (**129**) (148), as well as between the acyloxymethyl and methoxy groups in 1,4-dimethoxy-9-(2-acyloxyethyl)triptycenes (**130**) (179). X-ray crystallographic data for compounds of this type, after separation into atropisomers, should give more reliable data for discussing such interactions.



128



129



130

Dunitz (180) has collected X-ray crystallographic data for carbonyl compounds that possess nucleophilic atoms in proximity to C=O, and has postulated that such molecules can be used as models for the incipient transition state (reaction coordinate) for the nucleophilic addition to carbonyl compounds. Atropisomeric compounds have the potential, by providing a variety of such data, for understanding the incipient transition states. For example, the interaction found in the 1,4-dimethoxy-9-(2-acyloxyethyl)triptycenes (**130**) can be viewed as a model for S_N2 type reactions where the acyloxy group is the leaving group and the methoxy is the nucleophile. In an extreme case of this sort, cyclization actually takes place. Such an example has been reported (181).

In conclusion, the chemistry of atropisomers holds a promising future in providing reactivity data for rotamers and information on molecular interactions that are otherwise not detectable. It is especially promising in that a variety of functional groups can be introduced into the 9-arylfluorene and 9-substituted triptycene systems and thus the electronic as well as steric effects of substituents can be examined. In the past, steric effects on reactivity were almost the sole

target of such investigations. The magnitude of these effects might be somewhat exaggerated because, in molecules that give stable atropisomers, the distances between functional groups are extraordinarily small. Yet this does not hamper the significance of atropisomer chemistry, which provides data for a better understanding of the properties of organic molecules in general and for a better knowledge of how to control the selectivity of chemical reactions.

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Static and Dynamic Stereochemistry of Push–Pull and Strained Ethylenes

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I. INTRODUCTION

The steric stability of the carbon–carbon double bond is one of the cornerstones of the old structural theory of organic chemistry. In simple ethylenes, cis–trans isomerization has a free-energy barrier of 62 to 65 kcal/mol (1–4). However, it has long been known that suitable substitution can lower this barrier considerably. The early work in this field was based on studies of the cis to trans isomerization of photochemically generated cis forms of 1,2-disubstituted ethylenes like stilbenes, β-substituted styrenes, and acrylic and cinnamic acid derivatives (Table 1). The lowest free-energy barrier reported in these classes of compounds is ca. 32 kcal/mol for *p*-nitro-*p'*-aminostilbene (10). As will be discussed later, the low energy of this barrier is often ascribed to an interaction between the donor and acceptor groups through the intervening π-electron system, a *push–pull* effect. Later work with more efficient donor and acceptor groups lowered the barriers into the energy region where NMR band shapes are affected by the isomerization process (the DNMR region) below +200°C, corresponding to barriers below ca. 25 kcal/mol, and even below the limit of ca. 22 kcal/mol,

Table 1
Torsional Barriers (cis→trans, kcal/mol) at the C=C Bond in A—CH=CH—B

A	B	E_a	log *A*	$\Delta G^{\ddagger a}$	Reference
D	D	65.0	~13	65.5 (723)	1
Me	Me	62.8	13.8	57.9 (723)	2
Cl	Cl	56.0	12.8	57.3 (723)	5
Me	CO_2Me	58	13.2	57.6 (723)	5
Me	CN	51	11.0	58.4 (723)	6
Ph	Ph	42.8	12.8	55.1 (723)	7
Ph	CN	46.0	11.6	51.1 (723)	8
Ph	CO_2Me	41.6	11.5	50.3 (723)	9
p-$MeOC_6H_4$	Ph	35.5	10.2	42.6 (561)	10
p-$O_2NC_6H_4$	Ph	34.0	10.2	41.1 (546)	10
p-$MeOC_6H_4$	*p*-$O_2NC_6H_4$	28.8	8.1	40.7 (524)	10
p-$H_2NC_6H_4$	*p*-$O_2NC_6H_4$	17.1	5	32.0 (411)	10

[a]Temperature (K) in parentheses.

where the isomerizations proceed at appreciable rates, even at room temperature.

Low torsional barriers in combination with strong steric interactions between donor and acceptor groups in push–pull ethylenes have in several cases been demonstrated to cause permanently twisted double bonds, in which a planar arrangement of substituents at the double bond may represent an energy maximum.

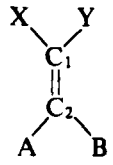
However, given a sufficiently strong steric effect, a permanent twist can be induced in a carbon–carbon double bond even without a push–pull effect. This is a field that has been the subject of much interest, as exemplified by the intense but still unsuccessful search for tetra-*tert*-butylethylene, and by the still very active studies of *trans*-cyclooctenes. Besides the synthetic challenge, such compounds present interesting chiroptical and other physical properties, and a knowledge of their heats of formation presents crucial tests for current force fields.

The interest in twisted double bonds has also generated a considerable activity in the theoretical field, and interesting stable twisted structures have been proposed, which, however, still await experimental confirmation.

II. PUSH–PULL ETHYLENES

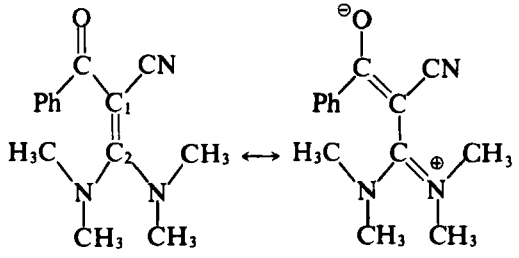
A. Definition, Structure, and General Conformational Properties

Push–pull or capto-dative ethylenes can be represented by the general formula **1** where A and/or B represent electron-donating groups and X and/or Y represent electron-accepting groups. Other substituents may be aryl or alkyl groups. The conformational properties of such compounds have been the subject of much



1

interest, mostly centered on the low torsional barriers of the $C_1{=}C_2$ bond, which are sometimes below the limit for the DNMR technique, ca. 5 kcal/mol for this type of compound. When the donor and acceptor groups have suitable structures, for example, acetyl and dimethylamino groups, they often show hindered rotations with substantial torsional barriers. These properties, low C=C barriers and high C—A and C—X barriers, are in general ascribed to electron delocalization, illustrated by the limiting structures **2a** and **2b**. In many cases, the



2a **2b**

barriers have been explained by high single-bond character of the $C_1{=}C_2$ bond and high double-bond character of the C—A and C—X bonds, respectively, due to considerable weight of such polar limiting structures as **2b**. However, this is an example of the often fallacious "ground state thinking," trying to explain an energy difference in terms of the properties of the ground state only. In fact, these molecules have quite stable ground states when strong steric effects are absent, and the low C=C barriers must be due primarily to the capacity of the X—C—Y part to stabilize a negative charge and of the A—C—B part to stabilize a positive charge in the 90° twisted transition state, as will be discussed in more detail in Sect. III.

In the following pages, the results of conformational studies of important classes of push–pull ethylenes will be reviewed, after which experimental and theoretical results bearing on the electronic structure of these compounds will be discussed.

Barriers to conformational changes ought to be discussed in terms of their activation enthalpies, $\Delta H^{\ddagger}$, which is the energy quantity most closely related to changes in internal energy. However, although $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ data are available from complete band-shape studies of a number of processes of interest to this review, they are of widely varying quality. For the majority of the compounds, only $\Delta G^{\ddagger}$ values obtained at the temperature of coalescence of symmetric or moderately biased NMR doublets ($\Delta G_c^{\ddagger}$) are available. Although such data may be quite reliable (11), the accumulating evidence for strongly negative $\Delta S^{\ddagger}$ values for rotations about push–pull substituted double bonds limits the validity of comparing $\Delta G^{\ddagger}$ values, even if they are obtained at the same or similar temperatures. However, there are indications that, at least in series of related compounds, $-\Delta S^{\ddagger}$ increases with $\Delta H^{\ddagger}$, and in such cases $\Delta G^{\ddagger}$ and $\Delta H^{\ddagger}$ values will fall in the same order, and a discussion of conjugation and steric effects in terms of $\Delta G^{\ddagger}$ will be acceptable.

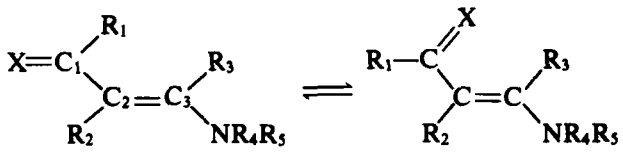
The literature on fast rotations around double bonds was reviewed up to 1972 in an earlier volume in this series (12), and the conformational properties of

systems with formal double bonds have been treated in a monograph on DNMR published in 1975 (13).

B. Review of Conformational Properties of Acyclic Push–Pull Ethylenes

1. Simple Enaminoketones and Their Thio Analogs

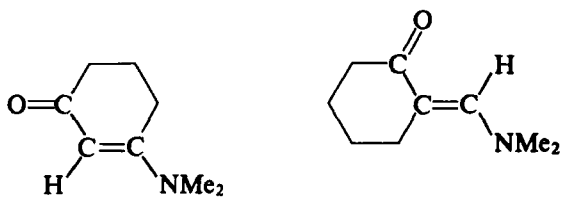
The title compounds (**3**, X = O or S) are vinylogous amides or thioamides in general readily available from the analogous β-dicarbonyl compounds. They



3a (*E*) **3b** (*Z*)

display hindered rotation of both the acyl (or thioacyl) and the amino group, and their stereochemistry has been extensively studied by spectroscopic methods.

Dabrowski et al. (14–19) and Filleux-Blanchard et al. (20,22) have found that the *E* form with respect to the C_1—C_2 bond dominates when $R_1 = R_2 = R_3 = H$, but that the *Z* form gradually gains when the size of R_1 increases, the $E \rightarrow Z$ barrier decreasing in the same series (Table 2), indicating increasing ground state strain and nonplanarity of the *E* form. As expected for vinylogous amides, the rotation of the amino group is also hindered (23,25), and the barrier has been shown to diminish with increasing size of R_1, that is, with increasing deviation of the acyl group in the *E* form from the plane. A comparison of the s-trans (**4**) and s-cis (**5**) forms held rigid by cyclization shows

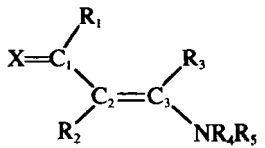


4 **5**

$\Delta G^{\ddagger}$ (C—N) = 12.0 kcal/mol $\Delta G^{\ddagger}$ (C—N) = 9.2 kcal/mol

the higher barrier in the s-trans (15), indicating a more efficient conjugation in the extended s-trans system.

Table 2
Free-Energy Barriers (kcal/mol) to Rotation in

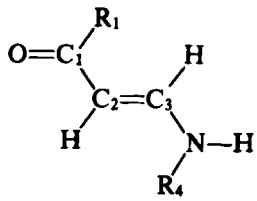


R_1	R_2	R_3	R_4/R_5	X	Solvent	$\Delta G^{\ddagger}$ (C_1—C_2)[a] $E \rightarrow Z$	$\Delta G^{\ddagger}$ (C_3—N)[a]	p_E[b]	Reference
H	H	H	Me/Me	O	CH_2=CCl_2	—	14.6 (292)	0.86	15
Me	H	H	Me/Me	O	$CDCl_3$	12.2 (255)[c]	—	0.40	23
					CH_2=CCl_2	11.5 (232)	—	0.31	14
i-Pr	H	H	Me/Me	O	CH_2=CCl_2	—	13.2 (264)	0.12	15
t-Bu	H	H	Me/Me	O	CH_2=CCl_2	—	13.1 (262)	0	15
H	H	Me	Me/Me	O	CH_2=CCl_2	—	12.2 (241)	100	15
Me	H	Me	Me/Me	O	CH_2=CCl_2	—	11.3 (221)	0	15
CH=CHMe	H	H	Me/Me	O	$CHCl_3$	—	14.3 (282)	—	20
Ph	H	H	Me/Me	O	CH_2Br_2	—	14.4 (281)	0	20
H	H	H	Me/Me	S	$CDCl_3$	—	17.1 (331)	0.05	17
Me	H	H	Me/Me	S	$CDCl_3$	16.0 (304)	16.4 (325)	0.36	17
Ph	H	H	Me/Me	S	CH_2Br_2	—	16.5 (317)	0	20
Ph	Ph	H	Me/Me	S	$CDCl_3$	13.0[d] (255)	13.7 (280)	0.64[e]	21
Ph	Ph	H	$(CH_2CH_2)O$	S	$CDCl_3$	<10.0 (<203)	11.7 (242)	—	21

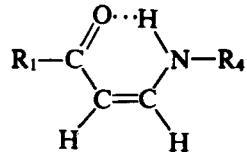
[a]Temperature (K) in parentheses.
[b]Fractional population.
[c]By ^{13}C NMe.
[d]*E* or *Z* not assigned.
[e]Major rotamer.

The torsional barrier of the amino group in thioamides is generally ca. 2 kcal/mol higher than in the corresponding amides (26), and this trend is also found in the enamino thioketones (17,23; Table 2). The increased conjugative interaction in the thioamides is reflected in the C_1—C_2 barriers, and the larger size of sulfur compared to oxygen affects the *E*/*Z* population ratio.

Simple *N*,*N*-disubstituted enaminoketones seem to exist in solution predominantly in the *E* form with respect to the double bond, as shown by the $^3J_{H-H}$ values. The situation is different with *N*-mono- or unsubstituted enaminoketones (**6**), in which the *Z* form is stablized by hydrogen bonding. The *E*–*Z* isomerization



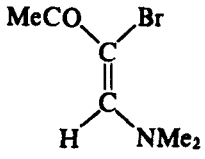
6a (*E*)



6b (*Z*)

in several such compounds with $R_4 = CH_3$ has been studied by stereomutation in different solvents (27). The rate of NH proton exchange was followed simultaneously using the N—CH_3 doublet. The two processes were found to have very similar free-energy barriers (ca. 20 kcal/mol), which indicates that the *E*–*Z* isomerization may not be a true double-bond rotation but may proceed via one of the possible tautomeric forms with a C_2—C_3 single bond, a mechanism proposed earlier by Huisgen et al. for β-aminoacrylates (28). For these compounds a lower limit to the barrier to uncatalyzed rotation was found to be 26.2 kcal/mol, but significantly lower barriers were observed in the presence of traces of acid (see Sect. III-3).

True double-bond rotations with low barriers have been proposed for **7** and **8** (19). However, the possibility for a C_1—C_2 rotation is not rigorously excluded,



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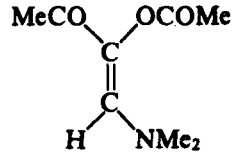
$\Delta G^{\ddagger} = 11.2$ kcal/mol



8

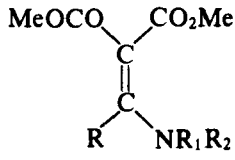
$\Delta G^{\ddagger} = 13.8$ kcal/mol

and the barriers are unexpectedly low considering that C_2 is substituted with one acceptor group but also with one, albeit weak, donor group.

The IR spectra of a large number of enaminoketones have been thoroughly studied, and the influence of conformation on the spectra has been discussed (29).

2. *Aminomethylene Compounds with Two Acceptor Groups*

In *N,N*-dialkylated members of this group (**1**, A = NR_1R_2, B = H or alkyl), several authors have observed fast thermal isomerizations at the double bond, using the DNMR technique. Most compounds of this type also display hindered rotation about the C—N bond with substantial barriers (see, e.g., ref. 30). Compounds of the general type **9** and **10** (R = H or Me) with a variety of



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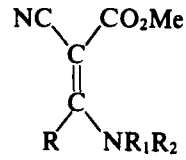


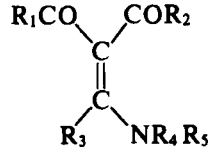
10

aliphatic and aromatic *N*-substituents show several cases of double-bond rotation with barriers in the range of 19 to < 9 kcal/mol, while NMe_2 torsional barriers are found in the range of 17.6 to < 9 kcal/mol (31–33). When R = Me, all barriers are lower than when R = H, indicating a considerable ground state strain in the former case. When R_1 (R_2) is aromatic, a decrease in the C—N and an increase in the C=C barrier is observed (Table 3). Interesting substituent effects are observed, the CN group being much more efficient than the CO_2Me group in increasing the C—N barrier, whereas the capacity for lowering the C=C barrier is in the reverse order, a result obviously not expected from simple bond order arguments.

One of the compounds from the previous study (**10**, R = R_1 = R_2 = Me) was subjected to a careful band-shape study over a wide temperature range (34). The CN barriers obtained in the two rotamers with respect to the C=C bond were quite different from those obtained by the coalescence approximation. It was also found that the activation entropy for the C=C rotation was 10 to 18 e.u. more negative than that for the C—N rotation, in agreement with results to be discussed later.

Further band-shape work (35) has been performed on malonic ester derivatives **9** (R = H; R_1, R_2 = $—(CH_2)_n—$, with *n* increasing from 2 to 5). The C=C barriers showed a steady decrease from $\Delta G^{\ddagger} > 23.2$ kcal/mol for $n = 2$ to 14.6 kcal/mol for $n = 5$, whereas the C—N barriers were less dependent on the ring size. An exception was the aziridine derivative, for which the C—N barrier was <7.3 kcal/mol.

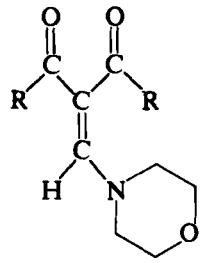
β,β-Diacylenamines (**11**) have continued to be the subject of considerable interest. Barriers to C=C and C—N rotation have been reported from systems where the carbonyl groups are held more or less rigidly in the plane by ring



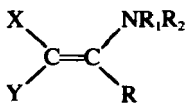
11

closure (36). Some of these compounds show remarkably high C—N barriers (Table 4), which can be ascribed to superior resonance interaction in the planar system. These barriers are in most cases higher in the compounds with 5-membered rings than in those with 6-membered rings, the reason probably being a larger ground state strain in the latter. The relatively high C=C barriers in **12** to **14** compared to that in **18** are explained by the better resonance stabilization of the ground state in the planar compounds. In the transition state the capacity for stabilizing a negative charge is similar, except for **12**, where the high C=C barrier is explained by the competing donor effect of the nitrogen atoms in the ring. In **13** this is diminished by a urea-type conjugation of the nitrogen atoms with the third carbonyl group. The remarkably high C—N barriers in **12** to **17** indicate a very efficient ground state conjugation in the cyclic systems. This work presents a nice analysis of the interplay of stabilizing conjugation and destabilizing steric interaction and their differential effects on the C=C and C—N barriers.

A large and interesting group of diacylenamines has been studied by NMR and IR spectroscopy (37). However, data have been recorded at room temperature only, and one of the conclusions seems questionable: the morpholino enamines **19** are assumed to exist entirely in the *EE* form. As will be discussed later (Sect.



19 (*EE*)

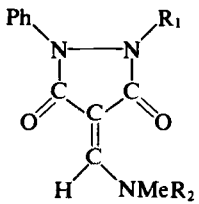
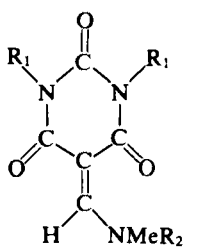
Table 3
Free-Energy Barriers (kcal/mol) for 

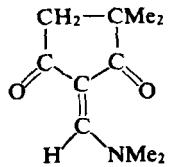
X	Y	R	R_1/R_2	Solvent	$\Delta G^{\ddagger}$ (C=C)[a] $E \rightarrow Z$	$\Delta G^{\ddagger}$ (C—N)[a]	p_E[b]	Reference
EtOCO	H	H	Me/Me	$CHCl_3$	—	13.9 (273)	1.0	25
MeOCO	MeOCO	H	Me/Me	CH_2Cl_2	15.6 (292)	13.3 (264)	—	32
MeOCO	MeOCO	Me	Me/Me	CH_2Cl_2	<9.1 (<178)	8.7 (176)	—	32
MeOCO	MeOCO	H	Me/Ph	CH_2Cl_2	19.4 (363)	—	—	32
MeOCO	MeOCO	H	$(CH_2)_2$	CH_2Cl_2	—	<7.3 (<143)	—	35
				C_4Cl_6	>23.2	—	—	35
MeOCO	MeOCO	H	$(CH_2)_3$	1-Chloronaphthalene	19.2 (298)	—	—	35
				CH_2Cl_2	—	14.4 (281)	—	35
MeOCO	MeOCO	H	$(CH_2)_4$	PhBr	17.5 (298)	—	—	35
				CH_2Cl_2	—	14.4 (293)	—	35
MeOCO	MeOCO	H	$(CH_2)_5$	CH_2Cl_2	14.6 (298)	12.2 (247)	—	35
MeOCO	MeOCO	H	Me/4-$NO_2C_6H_4$	$CHBr_3$	22.1 (410)	—	—	31

MeOCO	MeOCO	$(CH_2)_3$	/Me	$(CD_3)_2CO$	9.8 (192)	—	—	32
MeOCO	MeOCO	$(CH_2)_3$	/Ph	CH_2Cl_2	13.7 (278)	—	—	32
MeOCO	NC	H	Me/Me	PhBr	—	17.6 (329)	>0.99	33
NC	H	H	Me/Me	CCl_4	—	12.9 (298)	1.0	24
EtOCO	NC	H	Me/Me	$CDBr_3$	—	17.3 (326)	1.0	30
MeOCO	NC	Me	Me/Me	CH_2Cl_2	14.8 (248)	12.1 (238)	0.56	33
						14.8 (261)		
				CD_2Cl_2	14.8 (298)	10.8 (298)	0.56	34
						13.0 (298)		
MeOCO	NC	Me	Me/Ph	PhBr	18.3 (305)	—	0.69	33
MeOCO	NC	$(CH_2)_3$	/Ph	$CDCl_3$	18.6 (305)	—	0.95	33
NC	NC	H	Me/Me	$CDBr_3$	—	18.0 (333)	—	30
O_2N	H	H	Me/Me	$CDBr_3$	—	16.5 (325)	1.0	30
MeCO	MeCO	H	Me/Ph	CH_2Cl_2	13.9 (267)	—	—	31
MeCO	MeCO	H	Me/4-$NO_2C_6H_4$	CH_2Cl_2	16.9 (316)	—	—	31

[a]Temperature (K) in parentheses.
[b]Fractional population.

Table 4
Free Activation Energies (kcal/mol) for Rotations in Diacylenamines (36)

Compound		R_1	R_2	Solvent	$\Delta G^{\ddagger}$ (C=C)[a]	$\Delta G^{\ddagger}$ (C—N)[a]
	**a**	H	Me	Ph_2O	—	20.6 (402)
	b	Me	Me	Quinoline	17.8 (311)	—
				Ph_2O	—	20.9 (419)
	c	Ph	Me	Ph_2O	—	21.5 (433)
	d	Me	CH_2Ph	CD_2Cl_2	19.0 (345)	—
				Ph_2O	—	20.9 (416)
	e	2,4-$(NO_2)_2C_6H_3$	CH_2Ph	$CDCl_3$	16.7 (311)	23.6 (*E*, 317)
						23.2 (*Z*, 317)
12						
	**a**	Ph	Me	DMSO-d_6	—	20.3 (385)
	b	Ph	CH_2Ph	$CDCl_3$	—	22.3 (300)
	c	Me	CH_2Ph	$CDCl_3$	12.3 (230)	20.5 (265)
13						



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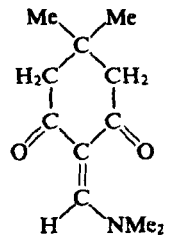

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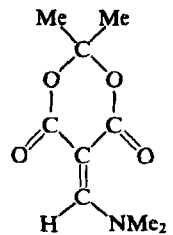
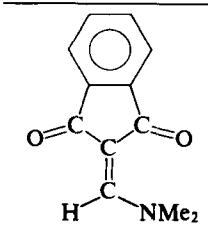
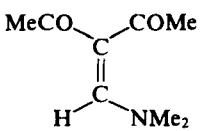


16

CD_2Cl_2	12.2 (228)	—
Ph_2O	—	22.1 (442)
Ph_2O	—	19.8 (383)
Ph_2O	—	20.5 (398)

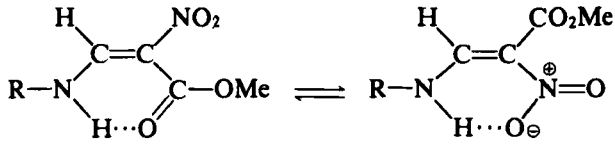
Table 4 (*Continued*)

Compound	R_1	R_2	Solvent	$\Delta G^{\ddagger}$ (C=C)[a]	$\Delta G^{\ddagger}$ (C—N)[a]
 **17**			Ph_2O	—	20.3 (408)
 **18**			CD_2Cl_2	10.2 (179)	12.7 (260)

[a]Temperature (K) in parentheses.

II-E), this is a high-energy form, and a mixture of *EZ* forms and possibly the *ZZ* form is more likely.

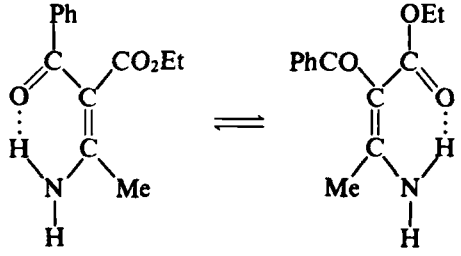
Bakhmutov and Burmistrov (38) have studied a number of secondary enamines with a nitro group and a carbomethoxy group as acceptors (**20**). These exist in



20a **20b**

two forms, both with strong hydrogen bonds. In solvents of very low basicity such as nitrobenzene, pure thermal rotation about the C=C bond was demonstrated by the kinetic order of unity with respect to **20** and by the persistence of the NH—CH coupling of 13 to 15 Hz up to 200°C. In pyridine, on the other hand, the kinetic order was 1.6, and the influence of X when R = *p*-XC_6H_4 indicated that formation of the anion of **20** was the rate-determining step. This was supported by the kinetic isotope effect of the NH group, k_H/k_D for the C=C rotation being 1.5 to 2 in the temperature region +20 to +40°C. The rate of NH exchange in pyridine solution was studied and the process was found to have a substantial negative activation entropy (−33 e.u.) and a kinetic order of 2, all indicating a bimolecular exchange mechanism. As for most acylenamines, the rotation is also subject to acid catalysis.

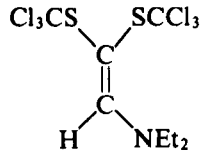
The C=C torsional barrier in a primary diacylenamine (**21**) has been found



21a **21b**

to be 18.7 ± 0.3 kcal/mol by stereomutation in $CDCl_3$ solution (39), but this is not necessarily a true thermal isomerization, since the absence of acid catalysis has not been demonstrated. However, the height of the barrier seems plausible for this combination of acceptors.

The somewhat unusual aminomethylene compound **22** has been described by Senning and Kelly (40). Its ^{1}H NMR spectrum shows a hindered rotation of the NEt_2 group with a barrier of ca. 14 kcal/mol, and an enantiomerization process

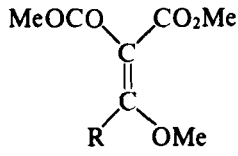


22

with a similar barrier. In the slow exchange limit the ethyl protons appear as an A_2X_3 and an ABX_3 system. It is not clear which are the chiral conformations that are involved in the second process, but the bulky substituents make a nonplanar NEt_2 group seem likely (see Sect. III-B-2). The results show that strongly inductively electron-attracting groups can be as effective as mesomeric acceptors in creating a relatively high C—N barrier.

3. Alkoxy- and Alkylthioalkylidene Compounds

Shvo (41) has studied a series of dimethyl 1-methoxyalkylidenemalonates (**23**) with R varying in the series H, Me, Et, *i*-Pr, *t*-Bu. When R = H, the ^{1}H NMR

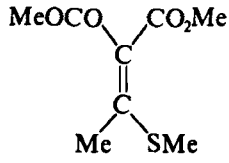


23

doublet of the ester methyl groups remains sharp at +206°C, giving a lower limit to the C=C barrier of 27.7 kcal/mol. However, increasing the size of R decreases the barrier from 25.7 kcal/mol for R = Me to 18.3 kcal/mol for R = *t*-Bu. The effect from R = H to R = Me is ascribed mainly to stabilization of R—$\overset{|}{C}^{\oplus}$—OMe in the transition state, whereas the larger substituents are assumed to lower the barrier further by increasing the ground state strain. However, as discussed for compounds **9**, Sect. II-B-2, the effect on both the C=C and the C—N barriers of going from R = H to R = Me clearly indicates that already Me makes a sizable contribution to the ground state strain, since R = Me can hardly stabilize the transition state for the C—N rotation. This interpretation is

supported by the X-ray structure of **21b** (39), in which the benzoyl group is twisted 48.5° out of the plane.

Shvo and Belsky (42) have also studied a methylthio analog of **23**, R = Me (**24**). Here the C=C barrier is above the DNMR region (>27.5), that is, at least

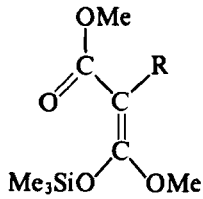


24

1.8 kcal higher than in the oxygen analog, indicating that CH_3S is less efficient than CH_3O in stabilizing the positive charge in this transition state.

4. Ketene Acetals, Ketene Mercaptals, and Ketene Aminals

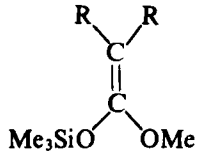
Few ketene acetals with electron-accepting substituents are known. Ainsworth et al. (43,44) have described a number of methyl trimethylsilyl acetals (**25**,



25

R = H, Me, Et, Ph, or CO_2Me) with interesting temperature-dependent NMR spectra. With R = CO_2Me, all OMe groups are equivalent on the NMR time scale down to −40°C, when a selective broadening is observed, though no splitting is reported. This indicates fast 1,5 shifts of the Me_3Si groups between the carbonyl oxygen atoms. When R = Ph, two isomers are observed at ambient temperature, and only the one in which CO_2Me and $OSiMe_3$ are cis undergoes fast Me_3Si exchange. The complete scrambling of the MeO groups in the first compound requires a C=C rotation that is fast on the NMR time scale down to −40°C, whereas the same rotation evidently is slow at ambient temperature in the phenyl analog. This corresponds to a C=C barrier that is lower than 12 kcal/mol when R = CO_2Me and higher than 16 kcal/mol when R = Ph.

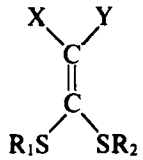
Of the more symmetrical ketene acetals (**26**, R = Me or Ph), the first shows a doublet for the C—Me protons up to at least + 140°C, and the second a singlet



26

for the phenyl protons unsplit at −60°C. The first observation clearly shows a high C=C barrier, whereas "accidental" equivalence is a more likely explanation for the phenyl proton singlet than a low barrier, since in general a phenyl group is far less efficient in lowering a C=C barrier than a CO_2Me group.

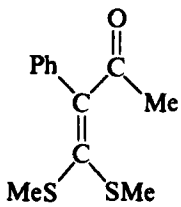
Ketene mercaptals (**27**) have rather high C=C barriers (Table 5), and only those with quite strongly electron-accepting groups fall within the region accessible to the DNMR method (45–49). As an example, the C=C barrier for **27**



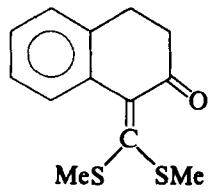
27

(X = NC, Y = CO_2Me, R_1 = R_2 = Me) at 24.8 kcal/mol is much higher than that for the dimethylaminoethylidene compound **10** (R = R_1 = R_2 = Me), which is 14.8 kcal/mol. This must be primarily ascribed to an inferior capacity of the MeS—C—SMe group to stabilize the positive charge in the transition state. However, steric effects also contribute to the high barriers. Models show that phenyl substituents must be twisted out of the plane by adjacent acceptor substituents larger than a cyano group, and the concomitant strain, which is not released in the transition state, must be barrier raising. A comparison between **28** and **29** bears this out (Table 5), even though an increased ground state strain in **29** may contribute to its lower barrier.

The capacity of *N*,*N*-dimethyliminium groups to act as electron acceptors has



28

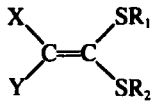


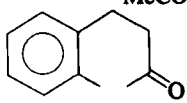
29

been studied by Filleux-Blanchard et al. (48). It can be seen (Table 5) that $Me_2\overset{+}{N}=CH$ is even more efficient than a nitro group in stabilizing a negative charge, an effect evidently related to the creation of a neutral enamine system in the transition state.

Some of these molecules also show fairly low (17.7 to 21.9 kcal/mol) barriers to rotation about the $\overset{+}{N}=C$ bond. This can be ascribed to the stabilized allylic cation appearing in the transition state. Although no further splitting occurs above $-110°C$, selective broadening of one of each of the NMe and SMe signals is observed, and ^3J (H_2—H_3) changes from 11.2 to 9.8 Hz in the temperature region -70 to $-110°C$. This is seen as the result of an equilibrium between rotamers

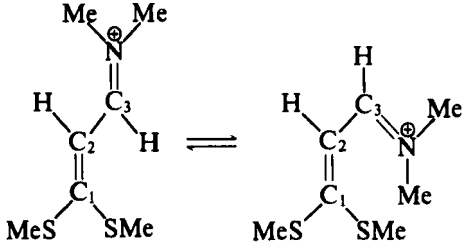
Table 5
Free-Energy Barriers to C=C Rotation in



X	Y	R_1/R_2	Solvent	$\Delta G^{\ddagger}$ (kcal/mol)[a]	Reference
MeCO	H	Me/Me	ODC[b]	>25 (>470)	45
Ph	NC	Me/Me	ODC	>25 (>470)	45
4-$NO_2C_6H_4$	NC	Me/Me	ODC	>25 (>470)	45
Ph	MeCO	Me/Me	ODC	>25 (>470)	45
		Me/Me	ODC	23.3 (440)	49
MeOCO	NC	Me/Me	ODC	24.8 (462)	45
MeOCO	NC	CH_2Ph/CH_2Ph	ODC	24.7 (455)	45
MeOCO	NC	Me/CH_2Ph	$CDCl_3$	22.4[c] (303)	45
			ODC	22.9[c] (303)	45
H_2NCO	NC	Me/Me	ODC	24.7 (455)	45
PhCO	NC	Me/Me	ODC	20.6 (398)	45
PhCO	EtOCO	Me/Me	ODC	19.4 (375)	45
PhCO	MeCO	Me/Me	ODC	18.0 (353)	45
NO_2	NC	Me/Me	ODC	19.1 (397)	46
NO_2	NC	CH_2Ph/CH_2Ph	ODC	19.8 (381)	46
NO_2	H	Me/CH_2Ph	ODC	28.3[c] (368)	47
$Me_2\overset{+}{N}=CH$	H	Me/Me	$C_2H_2Cl_4$	18.7 (352)	48
$Me_2\overset{+}{N}=CH$	Me	Me/Me	$C_2H_2Cl_4$	21.3 (388)	48
$Me_2\overset{+}{N}=CPh$	H	Me/Me	$C_2H_2Cl_4$	16.2 (324)	48
$Me_2\overset{+}{N}=CH$	Ph	Me/Me	$C_2H_2Cl_4$	17.0 (338)	48
$PhCH_2Me\overset{+}{N}=CH$	Ph	Me/Me	$C_2H_2Cl_4$	16.4 (328)	48

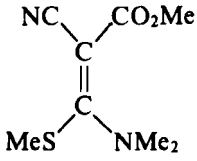
[a]Temperature (K) in parentheses.
[b]*o*-Dichlorobenzene.
[c]By stereomutation.

30a and **30b**, with the latter favored at lower temperature. This interpretation seems doubtful, since **30b** cannot have a planar conjugated system, and no other stabilizing effects are evident.



30a **30b**

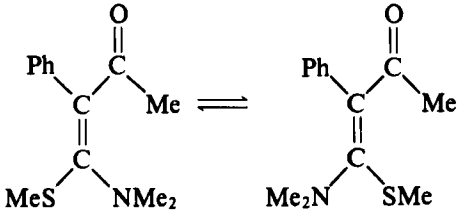
Systems with one amino group and one alkylthio group as donors, commonly known as ketene *N,S*-aminals, are sterically rather similar to the 1-ethylidenamino analogs like **9** and **10** (R = Me). However, comparison of the C=C barrier in **10**, where R = R_1 = R_2 = Me (14.8 kcal/mol; Table 3), with that of **31** (7.4 kcal/mol; Table 6) shows that the MeS group must be much more



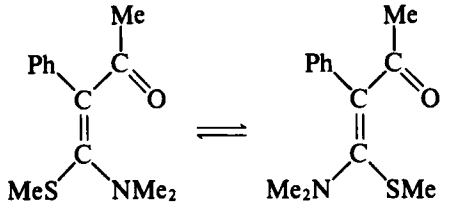
31

efficient than a Me group in stabilizing the transition state. In contradiction to this, Shvo and Belsky (42) concluded that these two groups should have rather similar effects. These authors, using the observed effect of R in $(MeOCO)_2C{=}CHNMeR$ when R = Me, Ph, and *p*-$C_6H_4NO_2$ (31,32), find that the C=C barrier in $(MeOCO)_2C{=}C(SMe)NMe_2$ must be as low as ca. 3.4 kcal/mol, but a similar derivation has not been made for **9** with R = R_1 = R_2 = Me.

Studies at low temperatures (50) reveal substantial barriers to rotation of the acceptor groups, not observed in other aminomethylene compounds with two acceptor groups, whereas the C—N barriers are similar in magnitude to those in the analogous ethylideneamino compounds. As an example, **32** at −124°C shows MeCO and MeS signals corresponding to all four possible rotamers (Scheme 1). At this temperature, only four broad NMe signals are seen, but the band-shape changes indicate that at least one of the rotamers has a C—N barrier of ca. 7 kcal/mol.

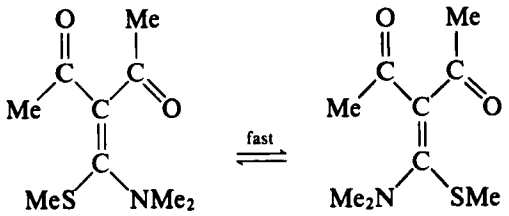


32a **32b**

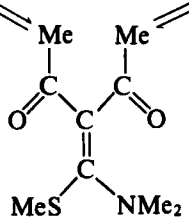


32c **32d**

Scheme 1

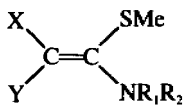


33a (*ZE*) **33b** (*EZ*)

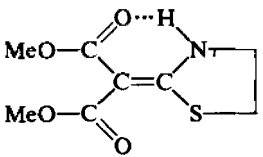
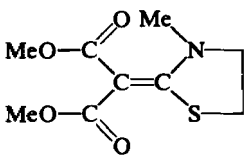


33c (*ZZ*)

Scheme 2

Table 6
Free-Energy Barriers to Bond Rotation (kcal/mol) in 

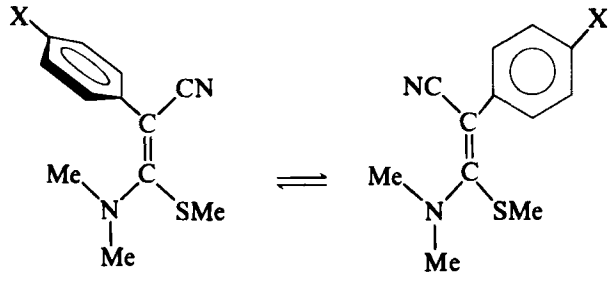
X	Y	R_1/R_2	Solvent	$\Delta G^{\ddagger}$ (C=C)[a,b]	$\Delta G^{\ddagger}$ (C—X)[a,c]	$\Delta G^{\ddagger}$ (C—N)[a,d]	p_{major}	Reference
Ph	NC	Me/Me	$CHCl_2F$	14.2 (315)	—	8.8 (184)	0.85 (*Z*)	50
4-$NO_2C_6H_4$	NC	Me/Me	$CHCl_2F$	8.9 (203)	7.7 (163)	10.0 (208)	0.83 (*Z*)	50
NC	NC	Me/Me	$CHCl_2F$	13.1[e] (258)	—	11.1 (225)	—	50
MeOCO	NC	Me/Me	$CHCl_2F$	7.4 (163)	<6[f] (<130)	10.4 (209)	0.88 (*Z*)	50
			CH_2Cl_2	—	—	11.0 (214)		42
PhCO	NC	Me/Me	$CHCl_2F$	<7[f] (<143)	<6[f] (<130)	11.5 (232)	—	50
Ph	MeCO	Me/Me	$CHCl_2F$	6.7 (153)	6.7 (153)	≤7 (153)	0.35[g]	50
MeCO	MeCO	Me/Me	$CHCl_2F$	<6 (130)	8.0 (168)	12.4 (231)	—	50
PhCO	MeCO	Me/Me	$CHCl_2F$	<6 (<130)	7.9 (163)	10.2 (203)	—	50
MeCO	MeOCO	Me/Me	$CHCl_2F$	<6 (<130)	—	11.7 (224)	—	50
MeOCO	MeOCO	Me/Me	$CHCl_2F$	<6 (<130)	7.3 (143)	10.2 (200)	—	50
			$(CD_3)_2CO$	—	—	8.9 (191)	—	42
MeOCO	MeOCO	H/Ph	CH_2Cl_2	12.0 (229)	—	—	—	42
MeOCO	MeOCO	Me/Ph	$(CD_3)_2CO$	<8.5 (<173)	—	—	—	42

MeOCO	MeOCO	Me/4-$NO_2C_6H_4$	$(CD_3)_2CO$	9.9 (201)	—	—	—	42
MeOCO	NC	Me/4-$NO_2C_6H_4$	CH_2Cl_2	13.2 (251)	—	—	—	42
NO_2	H	Me/Me	$CHCl_2F$	8.4 (174)	—	—	1.0 (*Z*)	47
			PhMe	22.3 (396)	—	—	—	42
			PhMe	<9.4 (<173)	—	—	—	42

[a]Temperature (K) in parentheses.
[b]Major to minor.
[c]Major to minor in major conformation.
[d]In major conformation.
[e]By ^{13}C NMR.
[f]Or one preferred rotamer.
[g]Major of four rotamers (see text).

The diacetyl compound **33** shows MeCO signals corresponding to one *EZ* and one *ZZ* form* with respect to the Ac—C bonds (Scheme 2) at −122°C, and both ^{1}H and ^{13}C NMR spectra are in agreement with a system in which **33a** and **33b** (the *EZ* forms) are in fast equilibrium by C=C rotation, although all other rotations are slow at this temperature.

The orientation of the MeS and Me_2N groups with respect to the acceptor groups is not always as one would expect from steric factors. Thus the *Z* forms **34a** and **35a** (Scheme 3) dominate strongly despite the fact that these rotamers must be more congested than *E* forms **34b** and **35b**. The reason may be a more



34a, X = H **34b**

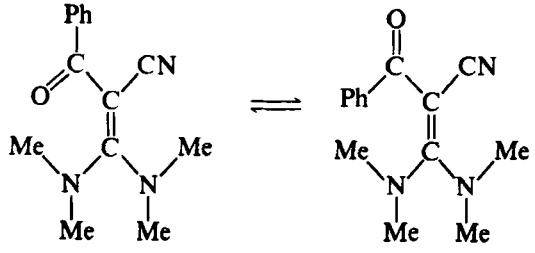
35a, X = O_2N **35b**

Scheme 3

efficient conjugation when the strongest donor (NMe_2) and the strongest acceptor (CN) are trans related. However, it may also simply be a case of better solvation of the *Z* forms, since they have the higher dipole moments, and they increase in population with increasing solvent polarity. Hindered rotation of the NMe_2 group above −130°C is only observed in **34a** and **35a**, not in the minor rotamers.

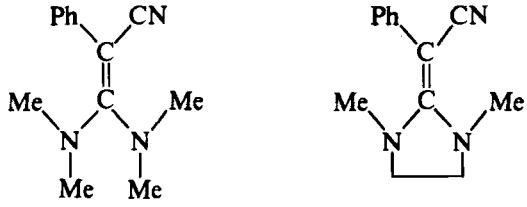
The 2,2-diaminoethylenes, *ketene aminals* (Table 7), appear in many respects similar to the analogous *N,S*-aminals. Several of them show hindered rotation about the C=C, C—N, and C—X bonds. In general, the two C—N barriers are different. In **36**, two rotamers are seen, **36a** being the major form in all solvents tried (51). The C—N barriers in **36b** are ca 2.5 kcal/mol higher than the corresponding barriers in **36a**. This is contrary to what would have been expected from steric factors alone (**36b** has the higher ground state energy). The difference seems to reflect the superior conjugation in s-trans enaminoketones compared to the s-cis analogs discussed in connection with compounds **4** and **5**.

*The *E/Z* nomenclature is here extended to apply not only to the C=C double bond but also to the bond linking the C=C and C=O groups, which has some double bond character.



36a 36b

The most striking and unexpected difference between *N,S*-aminals and *N,N*-aminals is that in pairs with the same combination of acceptor groups, the aminal in general has the higher C=C barrier. This means that the combination Me_2N, SMe seems to be superior to two NMe_2 groups in stabilizing a positive charge in the transition state. Although this argument neglects possible effects in the ground state, it seems reasonable to assume that the high C=C barriers in the aminals are due to a twist of the NMe_2 groups out of the plane, enforced by their mutual steric interaction and their interaction with the acceptor groups. The situation with respect to the former interaction is similar to that in tetramethylurea and tetramethylthiourea. For these, an electron diffraction study (52) has shown both a considerable deviation from planarity (with conserved C_2 symmetry) and slightly pyramidal NMe_2 groups. The importance of planarity for low C=C barriers in aminals is readily demonstrated by a study of cyclic compounds. While **38** shows decoalescence at -83°C, corresponding to a C=C barrier of

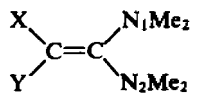


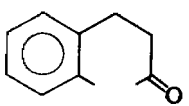
37 $\Delta G^{\ddagger}_{190} = 19.3$ kcal/mol

38 $\Delta G^{\ddagger}_{190} = 9.5$ kcal/mol

9.5 kcal/mol (53), a $\Delta G^{\ddagger}$ of 19.3 kcal/mol can be calculated for **37** at the same temperature, using $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values from a complete band-shape study (51). Both strong ground state strain and improved stabilization of the transition state contribute to the low barrier in **38**. When better acceptor groups than Ph and CN are employed, systems result that are permanently twisted about the double bond. They will be discussed in Sect. II-E.

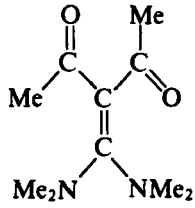
The torsional barriers of the acceptor groups are mostly higher in the aminals

Table 7
Free-Energy Barriers (kcal/mol) to Rotation in 

X	Y	Solvent	$\Delta G^{\ddagger}$ (C=C)[a,b]	$\Delta G^{\ddagger}$ (C—X/C—Y)[a,b]		$\Delta G^{\ddagger}$ (C—N_1/C—N_2)[a]	Reference
MeOCO	NC	PhF	15.2 (266)	—		14.2 (*E*), 13.7 (*Z*) (266)	51
PhCO	NC	PhF + $CDCl_3$ (3 : 1)	15.4 (299)	13.6 (253)	**36a**	11.0 (*E*), 10.9 (*Z*) (210)	51
					36b	13.7 (*E*), 13.5 (*Z*) (253)	
NC	NC	$CDCl_3$	—	—		10.3 (203)	51
Ph	NC	ODC	20.6 (380)	—		—	51
		PhF	—	—		11.3 (*E*), 11.8 (*Z*) (221)	
Ph	MeCO	$CDCl_3$ + CS_2 (1 : 1)	9.8 (201)	12.9 (231)		15.2 (295)	51
		ODC	—	—		17.1 (324)	51
		$CDCl_3$ + CS_2 (1 : 1)	9.5 (191)	—		—	
PhCO	MeCO	$CDCl_3$ + CS_2 (1 : 1)	9.4 (193)	—		16.4 (318)	51
MeCO	MeCO	CH_2Cl_2 + CS_2 (1 : 1)	<8 (<150)	10.2 (208)[c]		15.0 (279)	51
MeCO	MeOCO	CH_2Cl_2 + pyridine (1 : 1)	<8 (<150)	—		15.5 (283)	51
MeOCO	MeOCO	$CDCl_3$ + CS_2 (1 : 1)	<8 (<150)	8.1 (157)[c]		15.2 (276)	51
NO_2	H	$CHCl_2F$ + PhF (1 : 1)	10.7 (202)	—		11.8 (202), <10 (<190)	47

[a]Temperature (K) in parentheses.
[b]Major to minor.
[c]*EZ* to *ZE*.

than in the corresponding *N,S*-aminals, and the conformational behavior is also different. Thus, in the diacetyl derivative **39**, only the *EZ* form is seen, which

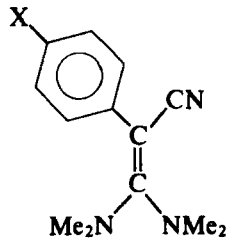


39

undergoes slow degenerate exchange below $-65°C$, while the C=C rotation remains fast even at $-135°C$.

The C—N barriers are also in most cases higher in the aminals than in the *N,S*-aminals with the same set of acceptor groups, a result not expected from simple conjugation arguments. This difference is even more surprising when one considers that the transition state to rotation of one of the amino groups in aminals receives an extra stabilization because the other amino group can rotate into coplanarity with the double bond–acceptor group system.

Kessler (54) has studied a series of aminals with *p*-substituted phenyl groups as acceptors (**40**), obtaining $\Delta G^{\ddagger}$ at coalescence for the C=C, both C—N, and



40

the C—Ar rotations (Table 8). Rate constants at 25°C were calculated with different assumed $\Delta S^{\ddagger}$ values, and reasonably linear log k -σ_p^- correlations were obtained in all cases. It is interesting to note that the C=C rotation shows a greater substituent sensitivity (with opposite sign) than the C—N and C—Ar rotations. This can be ascribed to the dipolar character of the transition state, in which furthermore a planar Ar—C—CN system is possible. Kessler also observed a somewhat greater substituent sensitivity for the C—N bond that is trans to the aromatic ring, possibly reflecting a closer approach to ground state coplanarity of this amino group with the C=CAr(CN) system.

Table 8
Free-Energy Barriers (kcal/mol) to Rotation for **40** (54)

X	$\Delta G^{\ddagger}$ (C=C)[a,b]	$\Delta G^{\ddagger}$ (C—N)E[a,c]	$\Delta G^{\ddagger}$ (C—N)Z[a,c]	$\Delta G^{\ddagger}$ (C—Ar)[a,c]
H	21.0 (411)	12.3 (242)	11.6 (229)	—
F	21.1 (412)	11.8 (234)	11.2 (220)	—
Cl	20.1 (394)	12.3 (242)	11.8 (231)	—
Br	20.2 (395)	12.4 (245)	12.0 (236)	—
CO_2Me	18.2 (356)	13.0 (255)	12.6 (246)	10.2 (209)
COMe	17.9 (350)	13.2 (260)	12.9 (251)	10.3 (213)
CN	17.6 (345)	13.1 (258)	13.1 (255)	10.1 (209)
NO_2	16.2 (318)	13.8 (270)	13.9 (270)	10.9 (225)

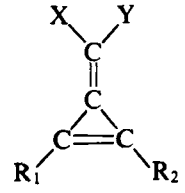
[a]Temperature (K) in parentheses.
[b]In 1,2,4-trichlorobenzene.
[c]In $CDCl_3$.

C. Systems with Aromatic Transition States

With push–pull ethylenes in which the donor part is a cyclic conjugated system with $4n + 2$ π electrons and/or the acceptor part is one with $4n$ π electrons, the possibility exists for aromatic stabilization of the transition state to C=C rotation. Several such systems with both carbocylic and heterocyclic ring components have been studied.

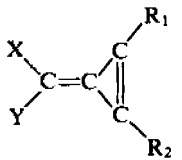
1. Triafulvenes

Triafulvene compounds (**41**) with acceptor groups for X and Y have been studied notably by Eicher et al. (55,56), who found C=C barriers from 14 kcal/mol upward (Table 9). The barrier-lowering effect of the acceptor groups seems to fall in the same order as for ketene mercaptals and aminals, but the capacity of the cyclopropenium ring to stabilize the transition state seems to be less than that of the $(MeS)_2C$ group in ketene mercaptals. The barrier is quite sensitive



41a, $R_1 = R_2 = Ph$, X = Y = CN
b, $R_1 = R_2 = Me$, X = Y = CN
c, $R_1 = R_2 = p\text{-}MeC_6H_4$, X = Y = CF_3
d, $R_1 = R_2 = Ph$, X = CN, Y = CO_2Me

Table 9
Free-Energy Barriers to Rotation for



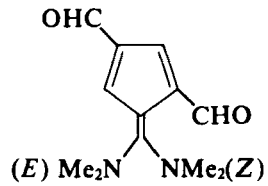
R_1	R_2	X	Y	Solvent	$\Delta G^{\ddagger}$ (kcal/mol)[a,b]	Reference
Me	Ph	MeCO	MeCO	$PhNO_2$	19.0 (360)	55
Me	Ph	MeCO	PhCO	$PhNO_2$	22.6 (403)	55
Me	Ph	$PhCH_2CO$	PhCO	$PhNO_2$	22.6 (404)	55
Me	Ph	CHO	PhCO	$PhNO_2$	21.8 (421)	55
Me	Ph	PhNHCO	PhCO	$PhNO_2$	>23.7 (>453)	55
4-MeC_6H_4	4-MeC_6H_4	MeCO	PhCO	1-Chloronaphthalene	19.7 (371)	55
4-$MeOC_6H_4$	4-$MeOC_6H_4$	MeCO	PhCO	1-Chloronaphthalene	19.0 (354)	55
4-*t*-BuC_6H_4	4-*t*-BuC_6H_4	MeCO	PhCO	1-Chloronaphthalene	20.7 (383)	55
4-*t*-BuC_6H_4	4-*t*-BuC_6H_4	MeCO	PhCO	$PhNO_2$	18.5 (343)	55
4-*t*-BuC_6H_4	4-*t*-BuC_6H_4	PhNHCO	PhCO	$PhNO_2$	20.9 (382)	55
Ph	*t*-Bu	NC	EtOCO	[c]	28.9[d] (370)	56
Ph	Me	PhCO	EtOCO	[c]	22.4[d] (323)	56

[a]Temperature (K) in parentheses.
[b]Major to minor.
[c]Solvent not given.
[d]By stereomutation.

to substituents that can stabilize the cyclopropenium ring, especially phenyl groups with donor substituents in the para position.

2. *Pentafulvenes and Triapentafulvalenes (Calicenes)*

The cyclopentadiene ring is an obvious candidate for an acceptor component, and fulvenes with donor groups in the 6-position have been studied by several groups (30,57–60). The C=C barrier in simple 6-aminofulvenes is ca. 20 kcal/mol (57,58; Table 10). One would expect this barrier to be lowered by acceptor substituents in the cyclopentadiene ring. However, although several mono- and diformyl derivatives have been described, with one exception all of them have unsymmetrical donor and acceptor pairs, and the existence in each case of one strongly favored rotamer may explain their simple, temperature-independent ^{1}H NMR spectra (apart from the NMe_2 resonance). This, however, is not the case with the 6,6-bisdimethylaminofulvene **42** (59), which shows two doublets for



42

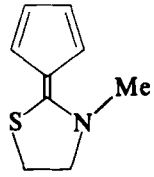
the NMe_2 groups at low temperature with $t_c = -5°C$ and $+75°C$ respectively. However, the doublet appearing above $+75°C$ remains unchanged up to 150°C, indicating a C=C barrier above 22 kcal/mol. This result is quite unexpected and incompatible with data discussed subsequently.

The C—N barriers, on the other hand, 13.9 kcal/mol for the encumbered *Z* Me_2N group and 18.4 kcal/mol for the *E* group, appear quite normal.

Comparison of C=C barriers in Table 10 with those in Tables 3 and 4 shows that the cyclopentadiene ring has a moderate capacity for stabilizing a dipolar transition state, being slightly less efficient than two CO_2R groups or one CN and one CO_2R group.

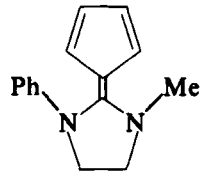
As with other ketene aminals, inclusion of the donor groups in 5- or 6-membered rings (**43** to **45**) lowers the C=C barriers (60). The data for **44** and **45** are difficult to reconcile with a high C=C barrier for **42**.

The high dipole moments of triapentafulvalenes **46**—6.3 D for the hexaphenyl derivative (61), 5.4 to 5.9 D estimated for the parent compound (62)—have been seen as an indication for an aromatic ground state. This contention has been



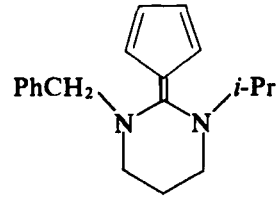
43

$\Delta G^{\ddagger}_{362}$ = 18.0 kcal/mol
(in toluene-d_8)



44

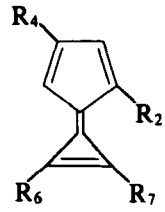
$\Delta G^{\ddagger}_{200}$ = 9.8 kcal/mol
(in $CHCl_2F$)



45

$\Delta G^{\ddagger} < 7$ kcal mol

disputed (63), but it seems safe to assume that the lowest transition state to rotation about the C=C bond is dipolar and stabilized by the cyclopropenium and cyclopentadienide ion resonances. In harmony with this, Kende et al. (64) found barriers in the range 18.0 to 19.4 kcal/mol for **46a** in a variety of solvents. Prinzbach et al. (62) reported data for **46b**, which can be interpreted in terms



46

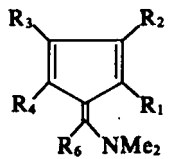
a, R_2 = CHO, R_4 = H,
$R_6 = R_7$ = Pr
b, $R_2 = R_4$ = *t*-Bu
$R_6 = R_7$ = Me

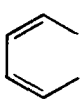
of a C=C rotation with $\Delta G^{\ddagger}$ ca. 17 kcal/mol. In the first of these compounds, the barrier is certainly lowered by the formyl group and in the second by ground state strain, but the barrier in the parent compound is not likely to exceed 30 kcal/mol.

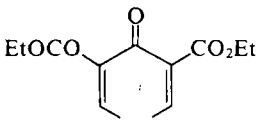
3. *Quinone Methides*

Six-membered rings can only act as acceptors in push–pull systems in combination with electron sinks, such as C=O, C=NR, or $C{=}\overset{+}{N}R_2$, in ortho or para positions. A simple and important system utilizing this kind of acceptor is the

Table 10
Free-Energy Barriers (kcal/mol) to Rotation in 6-Dimethylaminofulvenes

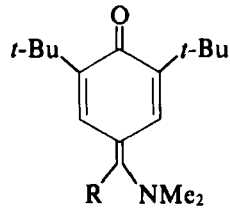


R_1	R_2	R_3	R_4	R_6	Solvent	$\Delta G^{\ddagger}$ (C=C)[a]	$\Delta G^{\ddagger}$ (C—N)[a]	Reference
H	H	H	H	H	Me_2CO-d_6	—	13.4 (257)	30
					$MeCONMe_2$	21.9 (423)	—	57[b]
					$CDCl_3$–C_6F_6 (1 : 3)	—	13.5 (273)	58
					Me_2SO	22.1 (421)		58
H	H	H	H	Me	$CDCl_3$	17.5 (330)	10.7 (208)	58
					Me_2SO	16.4 (311)	—	58
H	H	H	H	Ph	Me_2SO	19.2 (373)	—	58
					$CDCl_3$	—	11.8 (239)	58
H	H			H	Me_2CO-d_6	—	10.4 (218)	30

CHO	H	H	H	H	Cyclohexanone		—	17.0 (322)	30
H	CHO	CHO	H	H	Cyclohexanone		—	20.2 (379)	30
H			H	H	Pyridine		—	20.6 (381)	58
					$CHCl_2CCl_3$		—	19.6 (369)	58
CHO	CHO			H	$CDCl_3$		—	12.6 (273)	58
H	H	H	H	NMe_2	$CDCl_3$		—	<11 (<213)	59
CHO	H	CHO	H	NMe_2	$CDCl_3$		—	13.9[c] (264); 18.4[d] (348)	59
					Quinoline	>22	(>423)	—	

[a]Temperature (K) in parentheses.
[b]The E_a values given in this reference are in fact $\Delta G_c^{\ddagger}$ values.
[c]Z.
[d]E.

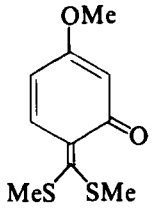
quinone methide **47a** (65), which shows a fairly low barrier to C=C rotation (Table 11). It appears that the *p*-quinone system, which becomes a fully aromatic



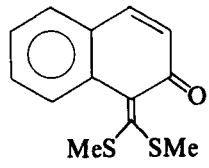
47a, R = H
b, R = MeS

phenolate ion in the transition state, is more efficient than the cyclopentadienide system in lowering the C=C barrier, and even slightly more efficient than the malonate moiety.

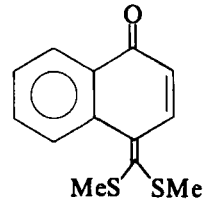
Some quinone methides with two MeS groups or one MeS and one Me_2N group as donors (**47b**, **48** to **50**) show quite low barriers (49). In the naphthoquinone methides a ground state destabilizing peri effect must be at work, but



48



49



50

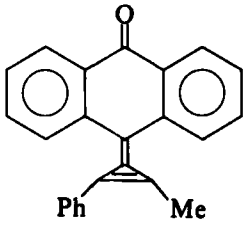
Table 11
Free-Energy Barriers (kcal/mol) to Rotation in Quinone Methides

Compound	Solvent	$\Delta G^{\ddagger}$ (C=C)[a]	$\Delta G^{\ddagger}$ (C—N)[a]	Reference
47a	Nitrobenzene-d_5	14.5 (291)	—	65
	Pyridine-d_5-CD_2Cl_2	—	12.4 (227)	
47b	CS_2	8.4 (176)	9.3 (193)	49
48	CS_2	13.7 (259)	—	49
49	CS_2	7.8 (160)	—	49
50	CS_2	8.2 (170)	—	49
51	1-Chloronaphthalene	21.1 (385)	—	55
52	CH_2Cl_2	<11 (<213)	—	55

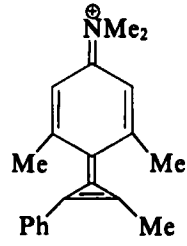
[a]Temperature (K) in parentheses.

49 has the lowest C=C barrier reported for any ketene mercaptal, indicating a higher transition state stability for the *o*- than for the *p*-quinonoid system.

Eicher and Pelz (55) have investigated some triafulvenes of the anthrone (**51**) and quinoniminium (**52**) methide types. The quinoniminium group appears to



51

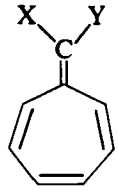


52

be the best acceptor combination so far reported, far superior to the second best, the 2,4-pentanedione moiety (Table 9). This is probably related to the fact that no charge separation is required in the transition state of **52**, and it can be compared with the low C=C barriers in the ketene mercaptals with a $Me_2\overset{+}{N}{=}CR$ group as acceptor (Table 5).

4. Larger Carbocyclic Systems

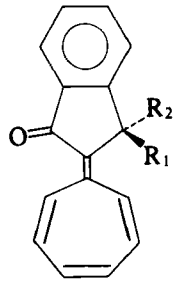
Stable *heptafulvenes* (**53**) with strong acceptor groups in the exocyclic position



53

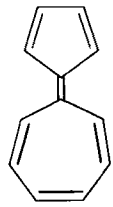
have been known for some time (66) and low C=C barriers could be expected for them.

Bertelli et al. (67) have studied three 2-cycloheptatrienylidenindanones (**54a,b,c**), which can be regarded as heptafulvenes. In **54a** and **b** the C=C barrier was too high to be measured by ^1H NMR, but in **54c** ground state strain brought the barrier down to 19.3 kcal/mol. Using an estimate for this strain obtained from another reaction, the authors proposed a barrier of 21.9 kcal/mol for **54a**. Pentaheptafulvalenes (sesquifulvalenes) (**55**) should behave similarly to the triapen-



54a, $R_1 = R_2 = H$
b, $R_1 = H$, $R_2 = Me$
c, $R_1 = R_2 = Me$

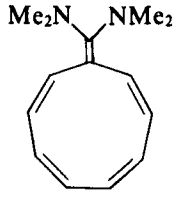
tafulvalenes, but work by Prinzbach et al. (62,68) shows that simple derivatives are quite labile, and that the ground state polarity is rather low. No dynamic studies seem to have been reported. With larger ring systems, the problem with



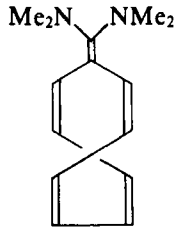
55

planarity becomes critical. Two nonafulvene systems with donor groups on the exocyclic carbon atom have been reported, and their properties indicate some push–pull character.

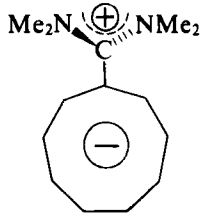
Hafner and Tappe (69) have studied the 10,10-bis(dimethylamino) derivative **56**. According to the UV spectrum, it exists in solution in an equilibrium between



56



57

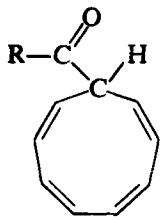


58

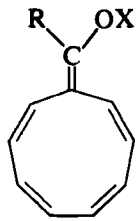
two forms, one with λ_{max} 330 nm, favored by nonpolar solvents, the other with λ_{max} 403 nm and favored by polar solvents and low temperature. In CD_2Cl_2 solution, the UV spectrum indicates substantial proportions of both forms at ambient temperature. The NMR spectrum shows a singlet for the 12 NMe protons and a multiplet in the range δ 5.3 to 6.4 for the ring protons. With decreasing temperature, the NMe resonance broadens and splits at −53°C into a doublet, corresponding to a rotational barrier of 11.2 kcal/mol. Simultaneously, the ring proton resonances move to lower field and form a narrow multiplet around δ 7.4. The NMe resonance also moves gradually to lower field with decreasing temperature. Results of 220 MHz ^{1}H NMR studies and analysis of the HH-coupling constants reveal that the conformation in nonpolar solvents (**57**) is nonplanar, with torsional angles in the range of 60° for the single bonds in the ring system, whereas the conformation occurring in polar solvents at low temperature (**56**) has a nearly planar 9-membered ring with torsional angles less than 30° (70).

A similar explanation has been proposed by Boche *et al.* (71), who point out that the $\overset{+}{C}(NMe_2)_2$ part has to be twisted out of the plane of the ring. In such a case the $\overset{+}{C}(NMe_2)_2$ part simulates an amidinium ion, in which a high C—N barrier can be expected. $\Delta G^{\ddagger}$ for the *N,N,N',N'*-tetramethylformamidinium ion is 15.4 kcal/mol (72), but the observed barrier should depend on a rate constant that is a population-weighted mean of the rate constants for C—N rotation in **57** and **58**.

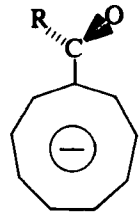
Another interesting cyclononatetraene system has been studied by Boche (71,73,74). Treatment of all-*cis*-9-acetyl- or -9-benzoyl-cyclonona-1,3,5,7-tetraene (**59a** or **b**) in tetrahydrofuran (THF) with $KN(SiMe_3)_2$ at −78°C gave potassium salts with ^{1}H and ^{13}C NMR spectra indicating acyl-[9]-annulene anion structures (**61**). When the corresponding reaction was performed with $LiN(SiMe_3)_2$ as a base, a completely different result was obtained. The NMR spectra at room temperature were very similar to those of the corresponding nonafulvenes **60**



59a, R = Me
b, R = Ph
c, R = MeO
d, R = O^-



60a to **d** as **59**

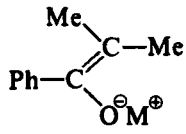


61a to **d** as **59**

(X = $SiMe_3$), and like these, the Li salts underwent rapid valence isomerization at +50°C to dihydroindene derivatives. However, when dipolar aprotic solvents were added to THF solutions of the Li salts, the spectra changed to those of **61**. To explain the different spectra of the K and Li salts, the former are described as solvent-separated ion pairs with the negative charge delocalized in the 9-membered ring (**61**), and the latter as contact-ion pairs with the negative charge localized on the oxygen atom (**60**, X = Li).

The Na salts in THF showed an intermediate behavior, and their spectra revealed an interesting temperature dependence. At +25°C the spectra were very similar to those of the Li salts, but at −52°C they had changed to the appearance of the spectra of the K salts. The spectra indicate a fast equilibrium **60** (X = Na) ⇌ **61** with the latter favored by decreasing temperature. Analysis of the temperature dependence of individual chemical shifts allowed the evaluation of $\Delta H°$, −6.9 kcal/mol, and $\Delta S°$, −30 e.u., for this equilibrium (i.e., the contact-ion pairs are favored by entropy but disfavored by enthalpy). A similar effect may explain the temperature dependence of the NMR spectrum of **56**.

In the nonafulvenes **60** (X = $SiMe_3$), the rotation around the exocyclic double bond is slow below +50°, whereas it is fast in the contact-ion pairs **60** (X = Li). This is probably due to fast equilibration via a small proportion of **61**. In contrast, ordinary enolates like **62** show slow rotation about the C=C bond also at +200°C (75).

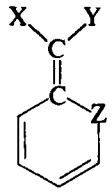


62

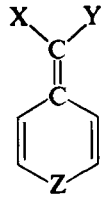
The Li salts of **59c** and **d**, in which R has a greater donor capacity, exist solely as solvent-separated ion pairs.

5. *Heteroanalogs of Heptafulvenes*

Typical heterocyclic donors are 2- or 4-heteracyclohexadienes (**63**) with Z = O,

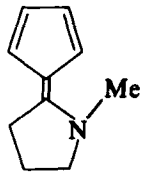


63a



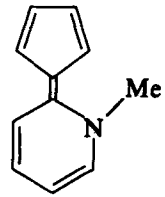
63b

S, or NR. In the transition state to C=C rotation, pyrylium, thiopyrylium, or pyridinium ions are formed, which should cause a considerable lowering of the C=C barriers compared to those in systems lacking this delocalization possibility. This is clearly demonstrated by the fulvenes **64** and **65** (57). The barrier



64

$\Delta G^{\ddagger}_{373}$ = 19.6 kcal/mol



65

$\Delta G^{\ddagger}_{223}$ = 11.3 kcal/mol

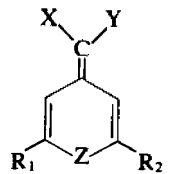
difference, ca. 8 kcal/mol, is much smaller than the resonance energy of the pyridinium ion, since a pyridinium cyclopentadienide limiting structure is also of importance in the planar initial state of **65**.

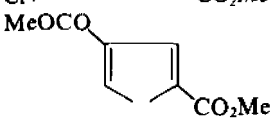
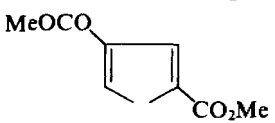
Barriers for a collection of compounds of type **63b** are given in Table 12. The barrier-lowering effect of the heteroatom Z is seen to increase in the series O < S < NR, and possible explanations will be discussed in Sect. III-B-1. A wide range of combinations of acceptor groups has been employed, and the order of the barrier-lowering effect is found to be NO_2 > MeCO > MeOCO > CN. However, the first two entries in Table 12 are seen to diverge from this order, the compound with X, Y = MeOCO, CO_2Me having a barrier ca. 3 kcal/mol higher than the one with NC, CO_2Me (76). The normal order is found in other dihydropyridines and also in pyrans and thiopyrans, and the reason for the aforementioned anomaly remains obscure.

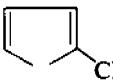
Most of the data in Table 12 come from the work of Shvo et al. (78). Careful band-shape analysis and solvent-effect studies permitted evaluation of the rate constants and $\Delta G^{\ddagger}$ values at 298 K, which renders the discussion of substituent effects more meaningful than usual. The authors obtained reasonably linear Hammett plots when correlating log k_{298} with σ_R^- (79) for X and Y, holding one of these substituents constant. They also found that the dihydropyridine system may act as an unusually efficient donor, giving a $\Delta G^{\ddagger}$ of 17.6 kcal/mol with X, Y = H, CN, the only barrier below 25 kcal/mol reported for any donor-substituted cyanoethylene. However, with other acceptor combinations the dihydropyridine moiety is not so outstanding, and this illustrates the difficulty of measuring donor and/or acceptor effects by rotational barriers alone (*vide infra*).

A number of 2-thiopyran derivatives with one carbonyl group as acceptor (**66**, **67**; Table 13) has been studied by Kretschmer et al. (80). The conformations with respect to the C_1—C_2 and C_2=C_3 bonds (*ZZ*, *ZE*, *EZ*, or *EE*)* were analyzed with lanthanide shift reagents. With compounds **66** (R_1 = H, R_2 = Ph, and

Table 12
Free-Energy Barriers (kcal/mol) to Rotation in



X	Y	Z	R_1	R_2	Solvent	$\Delta G^{\ddagger}$ (C=C)[b]	Reference
MeOCO	CO_2Me	NBu	Me	Ph	HMPT	23.0 (298)	76
CN	CO_2Me	NBu	Me	Me	HMPT	20.1 (298)	76
CN	CO_2Me	NMe	Me	Ph	HMPT	20.0 (298)	76
CN	CO_2Me	O	Me	Me	HMPT	>27	76
CN	CO_2Me	S	Me	Me	HMPT	>27	76
		O	Me	Me	$CDCl_3$	16.5 (339)	77
		S	Me	Me	$CDCl_3$	13.8 (280)	77

		S	Me	Me	$CDCl_3$	19.0 (384)	77
NO_2	CO_2Me	O	Me	Me	HMPT-d_{18}	17.2 (298)	78
CN	COMe	O	Me	Me	HMPT-d_{18}	>22.1	78
NO_2	COMe	O	Me	Me	$CDCl_3$	14.5 (298)	78
					CD_3CN	13.8 (298)	78
NO_2	CN	O	Me	Me	C_4Cl_6	>23.2	78
MeOCO	COMe	O	Me	Me	Me_2CO-d_6	15.8 (298)	78
NO_2	H	O	Me	Me	Me_2CO-d_6	>22.2	78
CN	CO_2Me	NBu	Me	Me	Me_2CO-d_6	16.0 (298)	78
NO_2	CO_2Me	NBu	Me	Me	Me_2CO-d_6	<8.7 (<183)	78
CN	COMe	NBu	Me	Me	$CDCl_3$	15.6 (298)	78
					CD_3CN	14.7 (298)	78
NO_2	COMe	NBu	Me	Me	Me_2CO-d_6	<8.7 (<183)	78
NO_2	COMe	NBu	Me	Me	CD_3CN	13.0 (298)	78
CN	H	NBu	Me	Me	CD_3NO_2	17.6 (298)	78
NO_2	H	NBu	Me	Me	Me_2CO-d_6	14.4 (298)	78
MeCO	H	NBu	Me	Me	Me_2CO-d_6	14.7 (298)	78
NO_2	CO_2Me	S	Me	Me	$CDCl_3$	15.1 (298)	78
CN	COMe	S	Me	Me	Me_2CO-d_6	16.7 (298)	78
NO_2	COMe	S	Me	Me	Me_2CO-d_6	11.6 (298)	78
CN	NO_2	S	Me	Me	Me_2CO-d_6	14.5 (298)	78
NO_2	H	S	Me	Me	Me_2CO-d_6	>17.4	78

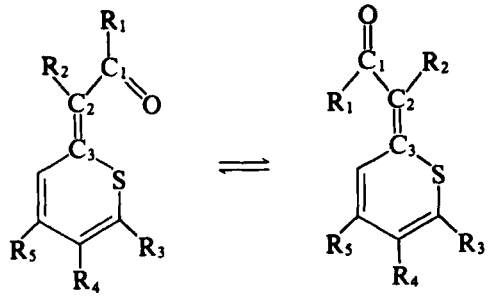
[a]HMPT = hexamethylphosphoric triamide.
[b]Temperature (K) in parentheses.

Table 13

Free-Energy Barriers (kcal/mol) to Rotation in Compounds **66** and **67** (80)

66	R_1	R_2	R_3	R_4	R_5	Solvent	p_{EE}[a]	$\Delta G^{\ddagger}$ (C_2═C_3, $EE \rightarrow ZZ$)
	H	Me	Me	Me	H	Me_2SO-d_6	0.61	18.9
	H	Me	Ph	Ph	H	Me_2SO-d_6	0.61	24.7
	H	Me	Ph	4-MeC_6H_4	H	Me_2SO-d_6	0.91	>25.5
	H	Me	Ph	H	Ph	Me_2SO-d_6	0.63	22.0
	H	Me	4-$MeOC_6H_4$	H	H	Me_2SO-d_6	0.68	21.5
	H	Me	4-$MeOC_6H_4$	4-$MeOC_6H_4$	H	$C_6D_5NO_2$	0.67	>25.5
67	n	R_1	R_2	R_3		Solvent	p_E[a]	$\Delta G^{\ddagger}$ (C_1—C_2, $E \rightarrow Z$)
	2	Ph	Ph	H		$CDCl_3/CS_2$	0.18	12.1
	2	Ph	H	Ph		$CDCl_3/CS_2$	0.19	12.0
	3	Ph	Ph	H		$CDCl_3/CS_2$	0.25	10.7
	3	4-MeC_6H_4	Ph	H		$CDCl_3/CS_2$	0.25	10.8
	3	—$(CH_2)_4$—		H		$CDCl_3/CS_2$	0.22	10.6
	4	Ph	Ph	H		$CDCl_3/CS_2$	—	<10.2
	4	—$(CH_2)_5$—		H		$CDCl_3/CS_2$	0.31	10.3

[a]Fractional population.

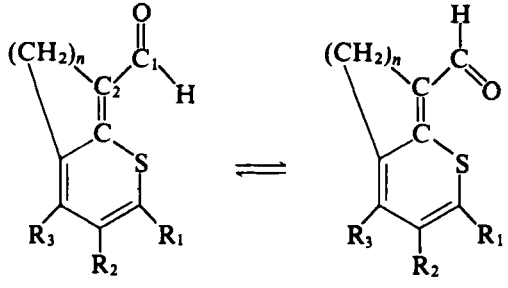


(*ZZ*) (*EE*)

66

R_1 = R_2 = Me), only the *ZZ* form could be observed, but with R_1 = H, R_2 = Me, a 2 : 1 ratio of *EE* and *ZZ* forms was found. Signal broadenings without observable splitting in the temperature range of −39 to −64°C indicated equilibria with low concentrations of the *ZE* and *EZ* forms, respectively, and with barriers to aldehyde group rotation (major → minor) in the range of 10 to 12 kcal/mol.

When the C_2=C_3 bond was fixed by ring closure in the *Z* conformation as in **67**, both *E* and *Z* forms with respect to the C_1—C_2 bond could be observed,



(*E*) (*Z*)

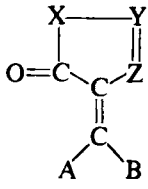
67

the barrier decreasing with increasing ring size, possibly because of increasing departure from planarity.

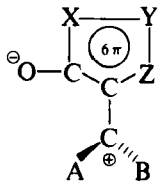
6. Heteroanalogs of Quinone Methides

Aza analogs of cyclopentadiene and cyclononatetraene rings could act as acceptor parts in push–pull systems, and possibly be more powerful than their carbocyclic analogs, but no stereochemical studies of such systems seem to have been reported. The remaining group of systems with potentially aromatic acceptors, the quinone methides, have a number of counterparts in heterocyclic chemistry.

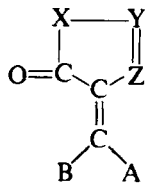
Five-membered ring compounds of the type **68**, where A and B represent donor groups, have been studied in some instances. Berg (81) found C=C barriers in



68a



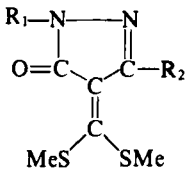
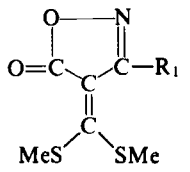
Transition state



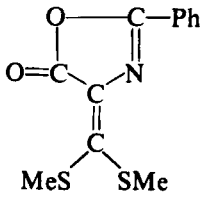
68b

4-bis(methylthio)methylene-pyrazolones (**69**) and -isoxazolones (**70**) to be accessible by NMR band-shape analysis (Table 14), whereas barriers above 25 kcal/mol were found for oxazolone (**71**) and thiazolone (**72** to **74**) analogs. However, as pointed out previously, this cannot be taken as a measure of the tendency of the respective ring systems to adopt an aromatic electronic structure,

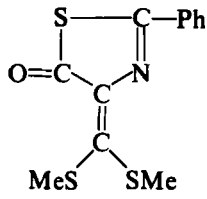
Table 14
Free-Energy Barriers (kcal/mol) to Rotation in Heteroanalogs of Quinone Methides (81)

Compound		R_1	R_2	Solvent	$\Delta G^{\ddagger}$ (C=C)[a]
					
	a	Me	Me	ODC	21.5 (403)
	b	Ph	Me	ODC	18.8 (358)
	c	Me	Ph	ODC	18.1 (366)
	d	Ph	Ph	ODC	16.2 (328)
69					
					
	a	Me	—	ODC	18.8 (347)
	b	Ph	—	ODC	16.5 (331)
70					

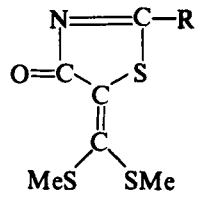
[a]Temperature (K) in parentheses.



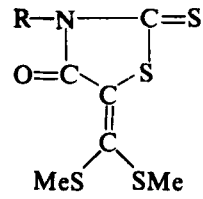
71



72



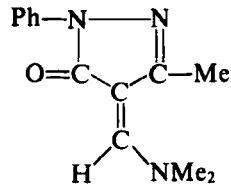
73a, R = Ph
b, R = NMe_2



74a, R = Me
b, R = Ph

since ground state stabilization plays an important role in determining the C=C barrier.

A 4-methylenepyrazolone with one dimethylamino group as donor (**75**) has been described by Mannschreck et al. (36), but it exists in one preferred con-



75

formation, and only the C—N barrier (18.7 kcal/mol in diphenyl ether at 381 K) has been determined. This value is significantly lower than that for the corresponding barrier in the analog **12** (Table 4) with two carbonyl groups.

D. Push–Pull Dienes

The stereochemistry of the interesting group of compounds known as push–pull dienes has not been much studied, although a fair number are available. The earliest studies stem from the interest in the influence of the number of intervening double bonds in vinylogous amides (**76**) on the barrier to C—N rotation. It was

$$RCO—(CH{=}CH)_n—NMe_2$$

76

shown by Radeglia (82) and by Martin et al. (83) that the barrier drops with an increasing number of double bonds (Table 15). Radeglia also observed that the

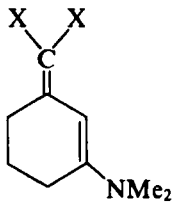
Table 15
Free-Energy Barriers (kcal/mol) to Rotation in **76** (R = H)

n	Solvent	$\Delta G^{\ddagger}$ (C—N)[a]	Reference
0	Neat	20.8	83
	$CDCl_3$	19.5	82
1	CH_2Br_2	15.6 (305)	83
	$CDCl_3$	14.7	82
2	CH_2Br_2	13.0 (253)	83
	$CDCl_3$	12.3	82

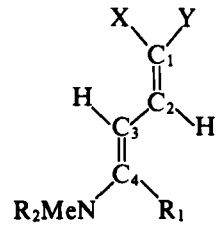
[a]Temperature (K) in parentheses.

barriers increase with increasing solvent polarity. Dahlqvist and Forsén (84) studied the C—N rotation in the cyclic dienes **77a** and **b** by the complete band-shape method and obtained $\Delta G^{\ddagger}_{298}$'s of 15.3 and 11.4 kcal/mol, respectively, in CD_2Cl_2, with remarkably positive $\Delta S^{\ddagger}$ values (16 ± 3 e.u. for **77a**).

Prokof'ev et al. (85) studied a number of push–pull butadienes **78** and observed



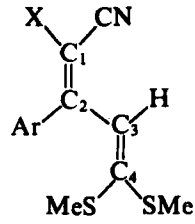
77a, X = CN
b, X = CO_2Et



78

hindered rotation about both the C_1=C_2 bond and the C_4—N bond (Table 16). The relative effects of the acceptor groups X and Y are similar to those previously observed. Strong effects of solvent polarity and also of concentration were observed, the C_1=C_2 barrier decreasing and the C—N barrier increasing with increasing concentration and solvent polarity. The rotation about the C_2—C_3 bond must also be hindered, but no effects of this process on the NMe spectra are reported.

Michalik et al. (86) have studied some similar systems (**79**). In these, the SMe proton resonances appear as symmetrical doublets at ambient temperature, which undergo coalescence in the temperature region of 151 to 180°C, corresponding to barriers to rotation about the C_3=C_4 bond of 21.6 to 23.3 kcal/mol. In comparable systems (i.e., with Ar = *p*-ClC_6H_4), the dicyano compound **79a** has a $\Delta G^{\ddagger}$ of 21.9 kcal/mol; the corresponding cyano ester **79b**, 22.3 kcal/mol. Thus the cyano group acts as a more efficient acceptor than the ester group, an



79a, X = CN
b, X = CO_2Et

anomaly similar to the one discussed in Sect. II-C-5. In the case of **79** this may be explained in terms of deviation of the ester group from coplanarity. No effects of rotation about the C_1=C_2 or C_2—C_3 bonds on the NMR spectrum were mentioned in this work.

E. Twisted Push–Pull Ethylenes

The change in potential energy accompanying torsion about the C_1=C_2 bond in a push–pull ethylene has an important component which depends on the overlap between the p_z orbitals on C_1 and C_2, and which we may call E_π, which has maxima at torsion angles of 90° and 270°. In many of the molecules discussed

Table 16
Free-Energy Barriers to Rotation (kcal/mol) in **78** (85)

X	Y	R_1	R_2	Solvent	$\Delta G^\ddagger$ (C_1=C_2)[a]	$\Delta G^\ddagger$ (C—N)[a]
MeOCO	CO_2Me	H	Me	CD_3OD	21.7 (398)	14.6 (287)
H_2NCO	CO_2Me	H	Me	CD_3OD	21.1 (392)	14.9 (291)
MeCO	CO_2Me	H	Me	CD_3OD	16.4 (306)	15.3 (299)
				CD_3OD + $CDCl_3$ (1 : 9 v/v)	20.7 (380)	15.0 (292)
				CH_3CN	21.2 (389)	14.9 (291)
MeCO	COMe	H	Me	CD_3OD	13.0 (246)	15.1 (296)
				$CDCl_3$	22.1 (415)	14.5 (284)
NO_2	CO_2Me	H	Me	CD_3OD + $CDCl_3$ (1 : 9 v/v)	16.1 (300)	16.9 (328)
				CH_3CN	16.6 (312)	17.2 (332)
MeCO	CO_2Me	H	Ph	CD_3OD	20.0 (364)	<12.3 (<243)
MeCO	CO_2Me	Me	Me	CD_3OD + $CDCl_3$ (1 : 9 v/v)	15.9 (296)	13.2 (249)
MeCO	CO_2Me	Ph	Me	CD_3OD	16.4 (326)	13.8 (279)
NO_2	CO_2Me	Ph	Me	$CDCl_3$	19.3 (374)	15.3 (306)

[a]Temperature (K) in parentheses.

in the previous sections, the torsional energy must also have a component of steric repulsion, E_s, with maxima at torsion angles of approximately 0° and 180°. The barriers at 90° and 270° are referred to as the π barriers, and those at 0° and 180° as steric barriers, although both evidently have important components of both E_π and E_s. Depending on the relations between these two components in the planar and in the 90° twisted states, three different cases may arise, as depicted in Figures 1–3.

Case 1. E_π (90°) $\gg E_s$ (0°) (Fig. 1). This is a "normal" push–pull system, and a donor group A has different environments in the energy minima near 0° and near 180°, provided that the acceptor groups X and Y are different. The energy required to pass across the π barrier can be measured by monitoring the band shape of the A resonance when the preexponential lifetimes are intermediate on the NMR time scale.

Case 2. E_π (90°) $\ll E_s$ (0°) (Fig. 2). In this case the π barrier between the two minima near 45° and near 135° is too low to be measured, and the molecules are considerably twisted about the $C_1{=}C_2$ bond in the ground state. Each donor group has only one site, but prochiral nuclei in such a group are diastereotopic when X $\neq$ Y and the passage across the steric barrier is slow (Fig. 4). Passage across the steric barrier exchanges these nuclei, and a study of the related band-shape changes allows a determination of the barrier to passage from the left minimum to the enantiomeric one on the right via a planar state.

Case 3. E_π (90°) $\approx E_s$ (0°). Now the minima are found near 45° and 135° twist angles, and appreciable maxima exist both near 0° (180°) and 90° (270°). At slow exchange, a donor group A has two sites corresponding to the above minima, and prochiral nuclei in A are diastereotopic in both sites. The exchange system can thus be depicted as a four-site case, and a complete analysis can give both the steric barrier and the π barrier.

The detailed shapes of these curves depend on many factors, and reliable theoretical calculations are probably not yet feasible. However, I believe that the foregoing very simplified curves, where E_π is represented by $0.5\ V_0\ [1 + \cos 2(\theta + 90°)]$ and E_s by Gaussians, give useful pictures of the situations that may be encountered.

It is also clear that the delineation of these three cases is based on the lower limit to measurability of torsional barriers. In practice, it is difficult to go below 7 kcal/mol with push–pull ethylenes, since these rather polar compounds tend to aggregate at low temperatures and give very broad bands below -120 to -130°C. As will be discussed later, several compounds that show a Case 1 type of NMR spectrum in solution are shown by X-ray crystallography to be twisted

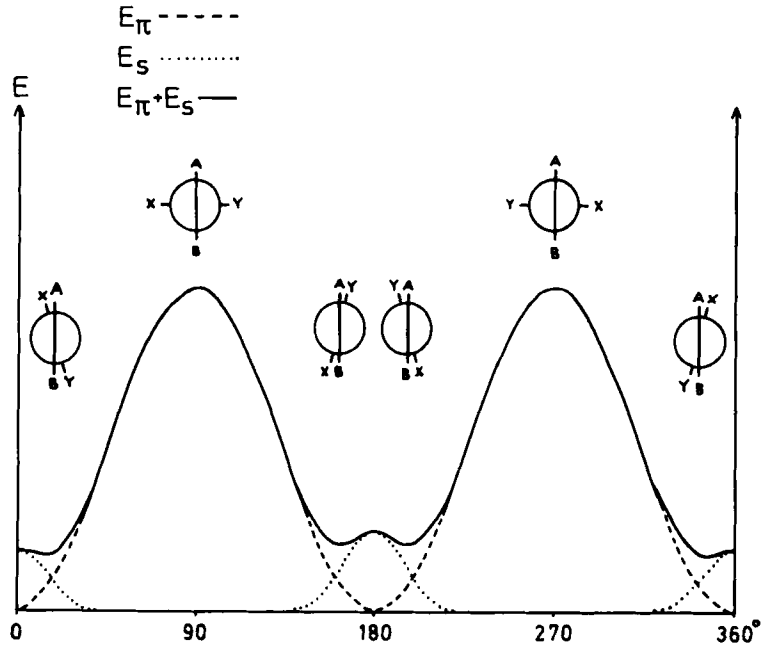


Figure 1. Potential energy curves for XYC = CAB when E_π (90°) $\gg$ E_s (0°) (Case 1).

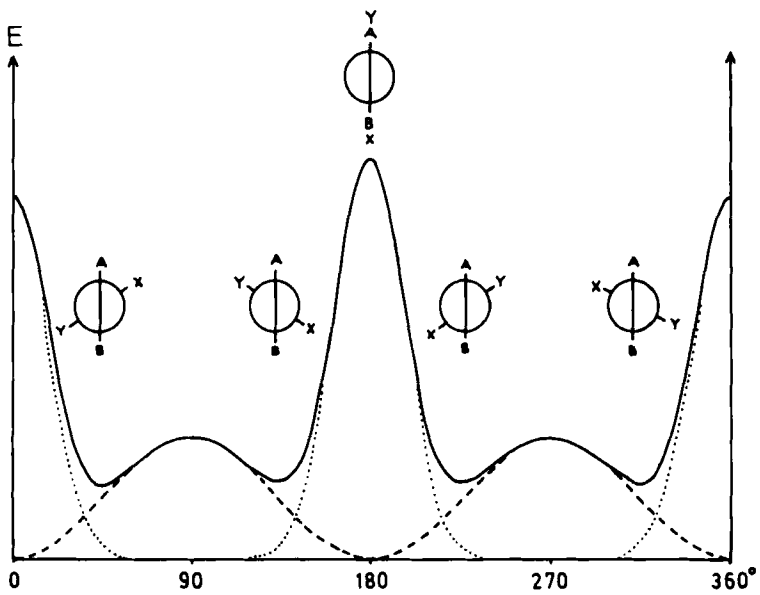


Figure 2. Potential energy curves for XYC = CAB when E_π (90°) $\ll$ E_s (0°) (Case 2).

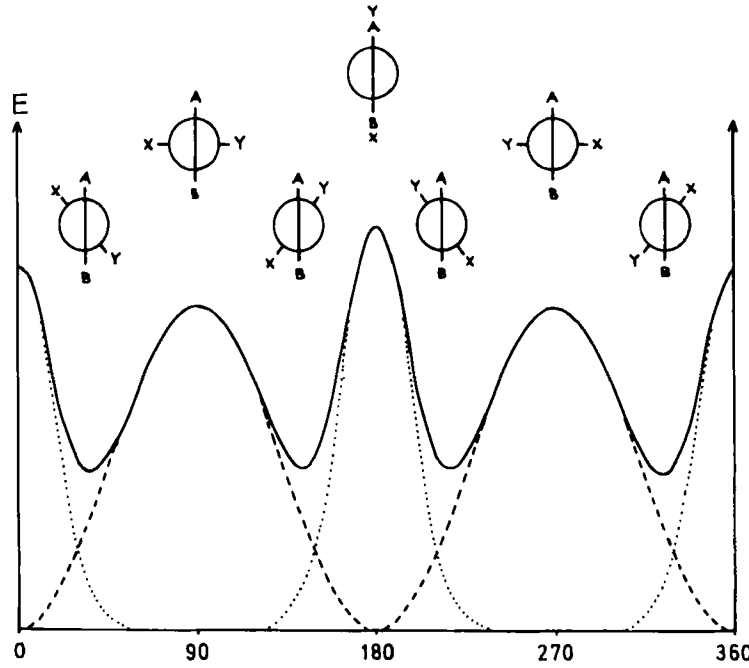


Figure 3. Potential energy curves for XYC = CAB when E_π (90°) ≈ E_s (0°) (Case 3).

in the solid state and may well be so in solution also, although the steric barriers are too low to affect the NMR spectrum.

The requirements for Case 2, a low π barrier and a high steric barrier, could be expected to be fulfilled by some of the 2,2-bis(dimethylamino)ethylenes discussed in Sect. II-B-4, but NMR spectra show that they belong to Case 1, probably because E_s (0°) is diminished by the out-of-plane twist of the dimethylamino groups. However, when this twist is prevented by cyclization, and when X and Y are good acceptors, representatives for Case 2 result.

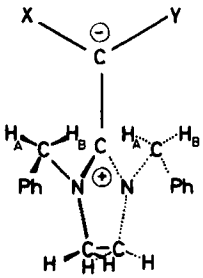
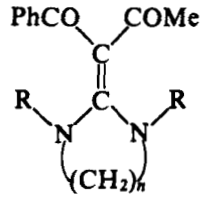


Figure 4. Case 2 push–pull ethylene with prochiral substituents.

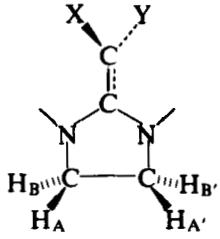
An early example is **80a** (87), the NMe resonance of which appears as a singlet at and slightly below ambient temperature, whereas the NCH_2 resonance



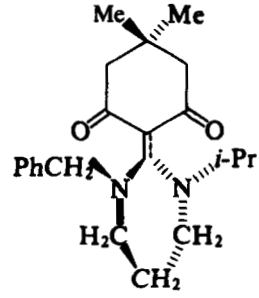
80a, R = Me, $n = 2$
b, R = CH_2Ph, $n = 2$
c, R = CH_2Ph, $n = 3$
d, R = Me, $n = 3$

appears as an AA'BB' system. Analysis of this system showed that the distribution of magnetic environments is as required by a Case 2 system (**81**, 88). In **80b**, the prochiral benzylic protons give an AB spectrum, and from the coalescence of this at higher temperatures, a steric barrier of 16.5 kcal/mol can be obtained.

Prochiral nuclei in the acceptor part can also be used as probes for Case 2 systems, if the donor part is unsymmetrical. An example is given by the dimedone derivative **82**, in which the Me groups on the ring have a chemical shift difference



81

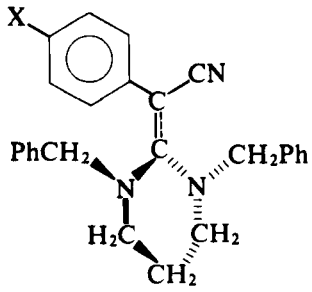


82

of 0.078 ppm. The resulting doublet is unchanged at 192°C, indicating a steric barrier >25 kcal/mol (88).

To obtain a Case 3 system, a high steric and a high π barrier are required. The steric barrier may be increased simply by increasing the size of the donor ring, as shown by comparison of $\Delta G^{\ddagger}$ for **80b** and **80c**, 16.5 and 22.0 kcal/mol, respectively (88). The π barrier is increased by weaker acceptor groups, and X,

Y = Ph, CN is a suitable combination. In agreement with expectations, the NMR spectrum of the benzylic protons in **83a** at −130°C consists of two still



83a, X = H
b, X = NO_2
c, X = NH_2

strongly exchange-broadened AB spectra, which change with increasing temperature into one AB spectrum at −90°C (Fig. 5) (53). The steric barrier (10.7 kcal/mol) was evaluated using the band shape of this single AB system above −90°C, and the π barrier (7.2 ± 0.2 kcal/mol) was obtained either by simulating the low-temperature ^1H spectrum or by using the ^{13}C resonances of the benzylic ^{13}C atoms. Most of these resonances are strongly broadened by the aforementioned aggregation, but the quaternary carbons, being less affected by this effect, give sharp signals at slow exchange, and these can be used for band-shape analysis (88).

It is evident that the steric barrier has an important component of π-electron energy, since it is strongly affected by the para substituent in the phenyl ring. In **83b** the steric barrier is higher than in **83a**, and the π barrier is too low to be measured (only one AB spectrum from the benzylic protons at −130°C), whereas in **83c** the two barriers have changed in the opposite direction (Table 17). This can be explained by the hypothesis, supported by model studies and crude strain energy calculations, that the phenyl ring has to be perpendicular to the double-bond system when the latter passes the planar state. The price in π-electron stabilization energy to be paid for this is lower when X = H than when X = NO_2, and still lower when X = NH_2.

Returning to the Case 2 systems, one may expect that the large twist of the double bond should have strong effects on the electron distribution. A considerable fraction of the π-electron density originally in the double bond must be delocalized into the acceptor part of the molecule. The effect of this delocalization has been studied in some twisted 1,1-diacetylethylenes (**84**), in which the partial negative charge makes the acceptor part Ac—C_1—Ac similar to an acetylacetonate anion (89). In this anion as well as in **84**, four rotamers (one degenerate

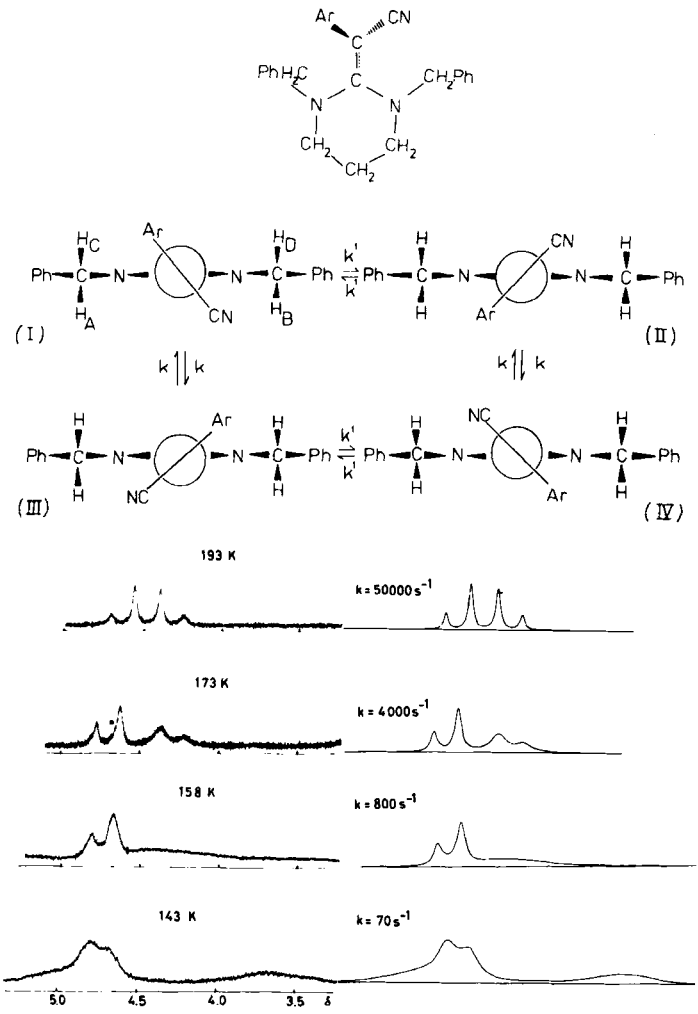
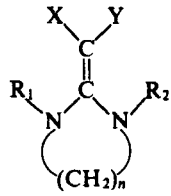


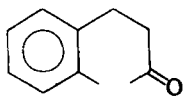
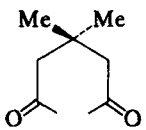
Figure 5. Exchange diagram and experimental and theoretical 100 MHz ^{1}H NMR spectra (solvent $CHCl_2F$) for **83a** (53).

pair) with respect to the carbonyl groups are possible (Scheme 4). The ^{1}H NMR spectra of **83a** to **d** under conditions of slow exchange show two forms, one with diastereotopic and the other with homotopic COMe protons. The first must be the degenerate *EZ–ZE* pair, whereas the second may be *EE* or *ZZ*. The *EE* form is less likely because of the strong repulsion to be expected between parallel dipoles, and it was shown by the effect of solvent polarity and in particular by the ASIS (aromatic solvent-induced shift) effect that the symmetric form is indeed *ZZ*. However, it could be shown by band-shape analysis that the $EZ \rightleftharpoons ZE$

exchange in Scheme 4 in some cases goes via the (unobservable) *EE* form as well as (predominantly) via the *ZZ* form; that is, the *EZ* → *EE* barrier is only slightly higher than the *EZ* → *ZZ* barrier, although the *EE* form is considerably higher in energy than the *ZZ* form.

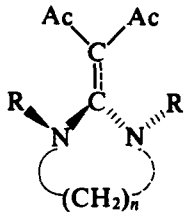
Table 17
Free-Energy Barriers (kcal/mol) to Rotation through the Perpendicular ($\Delta G_\pi^\ddagger$) and the Planar ($\Delta G_s^\ddagger$) Transition States[a] in



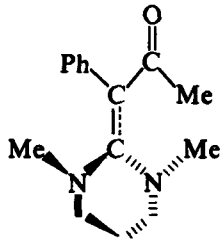
X	Y	R_1	R_2	*n*	Solvent	$\Delta G_\pi^{\ddagger\,b}$	$\Delta G_s^{\ddagger\,b}$
PhCO	COMe	$PhCH_2$	CH_2Ph	2	ODC	—	16.5 (349)
PhCO	COMe	$PhCH_2$	CH_2Ph	3	ODC	—	22.0 (424)
PhCO	COMe	*i*-Pr	*i*-Pr	2	ODC	—	18.0 (348)
PhCO	COMe	*i*-Pr	*i*-Pr	3	ODC	—	23.8 (424)
PhCO	COMe	$PhCH_2$	*i*-Pr	3	ODC	—	23.1 (412)
		$PhCH_2$	CH_2Ph	3	ODC	—	23.2 (441)
		$PhCH_2$	*i*-Pr	3	ODC	—	>25 (>465)
Ph	CN	$PhCH_2$	CH_2Ph	3	$CHCl_2F$	7.0 (158) 7.3[c] (146)	10.7 (219)
Ph	CN	Me	Me	3	$CHCl_2F$	7.4 (148)	—
Ph	CN	*i*-Pr	*i*-Pr	3	$CHCl_2F$	—	11.2 (220)
Ph	CN	$PhCH_2$	*i*-Pr	3	$CHCl_2F$	—	11.4 (230)
4-$NO_2C_6H_4$	CN	$PhCH_2$	CH_2Ph	3	$CHCl_2F$	—	13.9 (270)
4-$NH_2C_6H_4$	CN	$PhCH_2$	CH_2Ph	3	$CHCl_2F$	8.3[c] (165)	9.7 (203)

[a]Case 2 and 3 systems, (88).
[b]Temperature (K) in parentheses.
[c]By ^{13}C NMR.

The barriers to acetyl group rotation in **84a** to **d** are at least as high as in the acetylacetonate anion* (Table 18), indicating a considerable delocalization of negative charge into Ac—C_1—Ac. As mentioned later (Table 19), the twist angle in **84a** is 73°.

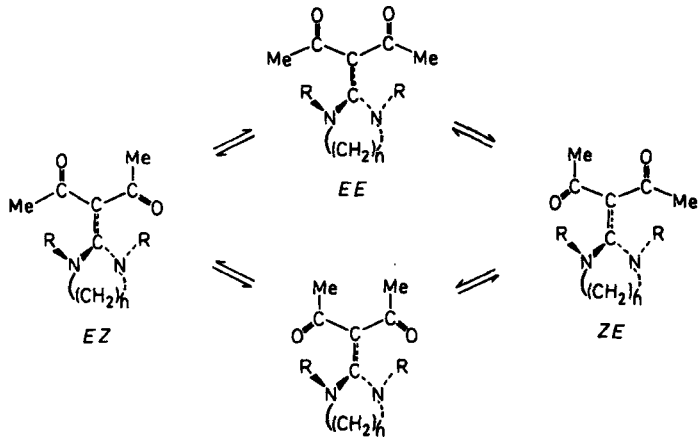


84a, R = Me, n = 2
b, R = Me, n = 3
c, R = CH_2Ph, n = 2
d, R = CH_2Ph, n = 3



84e (major form)

In **84e**, with only one acetyl group, the barrier is even higher, probably because the negative charge is mostly localized on the C_1—Ac part, making the loss of π-electron stabilization on rotation of the acetyl group even larger than in **84a** to **d**.



Scheme 4

*The barrier to *EE* to *ZZ* exchange in this ion has been found by E. A. Noe and M. Raban (*J. Am. Chem. Soc.* **1974**, *96*, 6184) to be 12.9 kcal/mol in pyridine-d_5 solution.

III. GROUND STATE AND TRANSITION STATE PROPERTIES

As mentioned in Sect. II-A, it has been a common practice to explain the low torsional barriers in push–pull ethylenes by assumed low double-bond orders of the C_1=C_2bonds. However, this approach is questionable, for several reasons. The underlying assumption is that a proportionality exists between V_0 in the twofold torsional barrier [1] and the π-bond order p_π. This is a useful approximation for small changes in p_π and in torsional angle θ (90), but not for large changes. In our case a change in barrier from 65.5 to 15 kcal/mol should, if the aforementioned hypothesis were valid, correspond to a change in p_π from 1.0 to 0.23, assuming V_0 to be zero for the C(sp^2)—C(sp^2) bond without conjugation. In the following section, available information will be used to show that polar limiting structures like **2b** are less important than structures with a double bond between C_1 and C_2, and that a more fruitful approach to the torsional barriers is to discuss the ground states and the transition states separately.

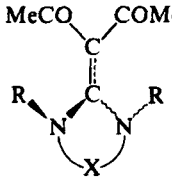
$$V = 0.5\, V_0\, [1 + \cos 2(\theta + 90)] \qquad [1]$$

A. Ground State Properties

1. Geometries

It is generally accepted that linear relationships [2] exist between bond lengths and π-bond orders. (R_s and R_d are single- and double-bond lengths.) This has been demonstrated for C(sp^2)—C(sp^2) bonds (91), which are 150.5 pm at p_π = 0 (92) and 133.7 pm at p_π = 1.0 (93). A p_π value of 0.25 for a push–pull ethylene should correspond to a bond length of 146.3 pm. The crystal structures of a large number of push–pull ethylenes, both planar and twisted, have been determined, and C_1=C_2 bond lengths between 133.0 and 146.6 pm have been observed (Table 19). However, for planar systems the bond lengths fall in the narrower range of 133.0 to 142.2 pm, with the majority below 140.0. Unfortunately, many of the systems studied are too symmetric for their torsional barriers to be determined by the NMR technique, but it is still possible to discern a rough correlation between bond lengths and known or expected torsional barriers. Compounds **85** to **87** and **41a** and **41b** probably have $\Delta G^{\ddagger} \geq 25$ kcal/mol, and **88**, **89a**, and **89b** probably ≥20 kcal/mol. Compound **90** is known to have $\Delta G^{\ddagger}_{300}$ = 19.1 kcal/mol in *o*-dichlorobenzene (102), and **9** (R = H, R_1 = R_2 = Me) has $\Delta G^{\ddagger}_{292}$ = 15.6 kcal/mol (32). An isomer of **91** (Table 12) has $\Delta G^{\ddagger}_{384}$ = 19.0 kcal/mol, and the barrier in **91** is probably rather similar. The barrier in **92** could be estimated based on that in **65** (11.3 kcal/mol) with a correction of a few kilocalories per mole for the ground state strain in the latter (cf. **97**), and **93a**

Table 18
Free-Energy Barriers (kcal/mol) to Acetyl Group Rotations[a] (89) in



X	R	$\Delta G^{\ddagger}$ ($EZ \rightarrow ZZ$)[b]	$\Delta G^{\ddagger}$ ($EZ \rightarrow EE$)[b]
$(CH_2)_2$	Me	12.3 (241)	13.4 (241)
$(CH_2)_3$	Me	13.4 (238)	[c]
$CH_2CMe_2CH_2$	Me	13.6 (247)	13.8 (247)
$(CH_2)_2$	CH_2Ph	12.4 (239)	>14 (239)
$(CH_2)_3$	CH_2Ph	13.6 (258)	>15 (258)

[a]Solvent $CHCl_2F$.
[b]Temperature (K) in parentheses.
[c]Unobservable due to signal overlap.

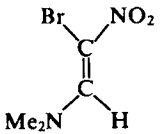
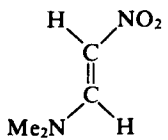
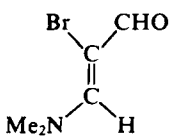
has $\Delta G^{\ddagger}_{423} = 21.9$ kcal/mol. The barrier in **94a** is 13.1 kcal/mol, and that in **96** is probably lower (cf. **44**, **45**). Most of the remaining compounds in Table 19 are examples of Case 2, and observed barriers would have been steric, that is, with the planar state as transition state.

$$R_i = R_s - p_{\pi,i}(R_s - R_d) \qquad [2]$$

Thus, it seems as if a barrier of ca. 20 kcal/mol corresponds to a bond length of ca. 138 pm (i.e., p_π is not less than 0.75), considerably more than required by "the ground state model." HMO-type calculations on a close analog of **90** gave $p_\pi = 0.76$ (45), and CNDO/2 calculations on several ketene mercaptals and aminals have given p_π values between 0.80 and 0.70 (113). Shvo et al. (114) performed INDO calculations on **9**, R = H, $R_1 = R_2$ = Me, and on **9**, R = H, R_1, R_2 = CH_2CH_2, and they obtained $p_\pi = 0.787$ and 0.802, respectively. In ref. 45, a crude linear relation was observed between $\Delta G^{\ddagger}$ and p_π, which may seem to support the "ground state model." However, it more likely reflects the fact that π-electron delocalization in the ground state and stabilization of the positive and negative charges in the dipolar transition state are to a first approximation favored by the same types of substituents.

The heptafulvene **103** seems to deviate from this scheme, since it has R(C_1=C_2) = 142.2 pm and probably $\Delta G^{\ddagger} \geq 25$ kcal/mol (cf. **54**). It is a planar molecule, and it is also unusual in its response to steric effects. While all other systems in Table 19 avoid undue steric interactions between donors and acceptors

Table 19
Bond Lengths R (pm) and Twist Angles about $C_1{=}C_2$ (θ) from X-ray Crystallographic Studies

Compound	R ($C_1{=}C_2$)	R (C_1—X)	R (C_2—N)	θ	Reference
 **85**	133.0	141.0	137.0	0	94
 **86**	134.5	139.4	139.4	0	95
 **87**	135.0	142.0	132.0	0	94
41a	136.7	142.4	—	0	96
41b	136.7	141.6	—	0	97

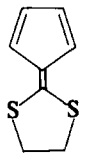
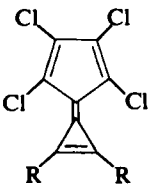
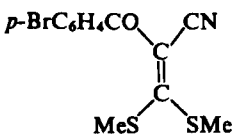
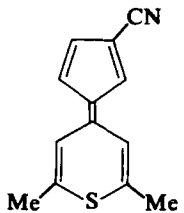
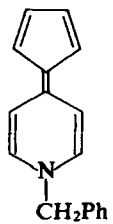
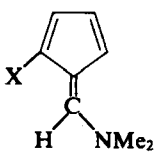
41c		135.7	146.1	—	7.1	98
 **88**		136.9	—	—	0	99
 **89**	**a**, R = Ph	136.5	—	—	0	100
	b, R = Me	137.0	—	—	0	101
 **90**		136.9	142.7 (C—CN) 149.0 (C—CO)	— —	15.2	102
9, R = H, R_1 = R_2 = Me		138.0	143.3 (planar) 148.7 (twisted 68°)	133.7	0	103

Table 19 (*Continued*)

Compound	R (C_1=C_2)	R (C_1—X)	R(C_2—N)	θ	Reference
 **91**	138.0	—	—	0	104
 **92**	138.8	—	—	0	105
 **93**	**a**, X = H **b**, X = CHO	138.7 139.1	— —	133.1 130.9	0 0	106 106

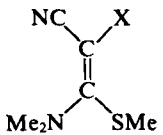
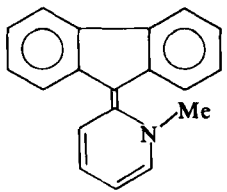
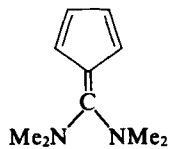
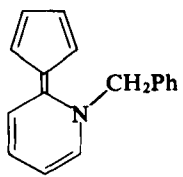
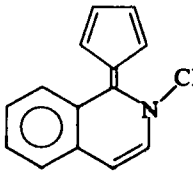
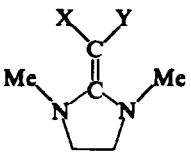
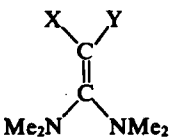
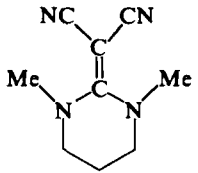
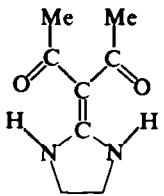
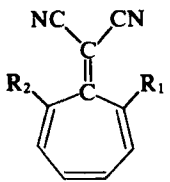
 **94**	**a**, X = CN	139.0	142.2	131.3	26	107
	b, X = COPh	141.4	142.3 (C—CN) 144.6 (C—CO)	131.8	38.3	108
 **95**		140.0	—	—	35.7	109
 **96**		140.7	—	135.5 (32° twisted)	29	110
 **97**		141.0	—	138.4	18.6	105

Table 19 (*Continued*)

Compound		R (C_1=C_2)	R (C_1—X)	R(C_2—N)	θ	Reference
 **98**	$CH_2C_6H_3Cl_2$-(2,6)	141.2	—	138.4	31.2	105
32		141.2	—	—	33.5	107
 **99**	**a**, X = Y = CN	140.7	141.8	135.2	20	107
	b, X = CN Y = COC_6H_4Br-4	144.8	142.3 (C—CO) 141.0 (C—CN)	132.8	41.1	102
	c, X = COMe Y = CO_2Me	146.6	142.6 [(*Z*)—Ac] 142.4 [(*E*)—CO_2Me]	135.2	63	107
84a		146.6	140.9 [(*Z*)—Ac] 143.3 [(*E*)—Ac]	132.1	73	107
 **100**	**a**, X = Y = CN	140.6	141.2	134.8	29	107

 **101**		142.9	140.4	134.1	32	107
 **102**		144.2	145.0	133.0	5	107
 **103**	**a**, $R_1 = R_2 = H$	142.2	145.0	—	0	111a
	b, $R_1 = R_2 = Me$	136.7	141.7	—	0	111b
	c, $R_1 = H$, $R_2 = i$-Pr	136.7	143.8	—	0	112

by rotation about the $C_1{=}C_2$ bond, the heptafulvenes **103b** and **c** retain nearly planar double bonds with only slight pyramidality at C_1 in the ring. Instead, the rings assume deep boat shapes, and the structures are similar to those of the unsubstituted heptafulvene (115).

One could expect a similar bond length-barrier relation to hold for the rotations of dimethylamino and acetyl groups, but here the data are much less convincing. In a pair like **93a** and **b** with $\Delta G^{\ddagger}$ (C—N) = 13.4 and 17.0 kcal/mol, respectively (Table 10), the C—N bond lengths fall in the correct order, but otherwise no correlation is observed.

2. *Dipole Moments*

The separation of formal charges in a polar limiting structure like **2b** creates a dipole moment of ca. 20 D. Therefore, if such structures were of great importance, quite high dipole moments should be expected for push–pull ethylenes. Data for a reasonable number of mostly symmetrical and rather rigid compounds are known (Table 20). Several high dipole moments are observed, though not in the vicinity of those required for a complete transfer of the double-bond π

Table 20
Dipole Moments for Push–Pull Ethylenes

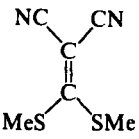
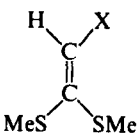
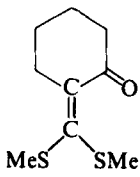
Compound		μ_{exp} (D)	μ_{calc} (D)	Reference
 **104**		6.16	1.05 (*EE*) 3.59 (*EZ*) 7.13 (*ZZ*)	116
 **105**	**a**, X = COMe	4.13		116
	b, X = NO_2	5.64		47
 **106**		2.99		116

Table 20 (*Continued*)

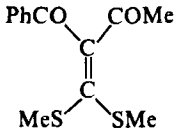
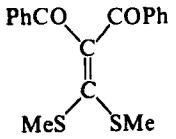
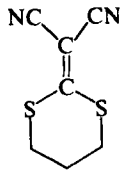
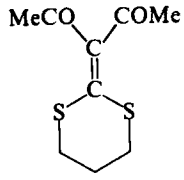
Compound	μ_{exp} (D)	μ_{calc} (D)	Reference
28	2.99		116
29	3.17		116
 **107**	3.94		116
 **108**	3.76		116
 **109**	7.54	7.13	116
 **110**	4.13	0.84 (*ZZ*) 5.28 (*EZ*) 8.33 (*EE*)	116
99a	7.93	7.86	116
99d, X = H, Y = NO_2	7.39		47
100a	7.84	6.32	116
100b, X = H, Y = NO_2	7.64		47
101	8.02	7.60	116
41a	7.9	8.88[a]	117
41d	5.9		118
41c	7.42		119
88	3.75		120
96	5.4		121

Table 20 (*Continued*)

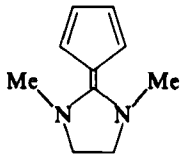
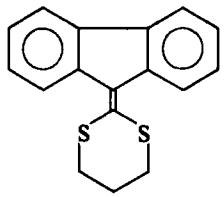
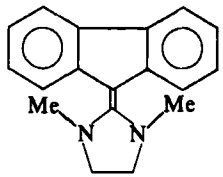
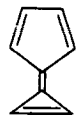
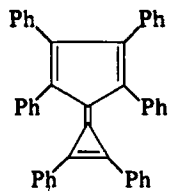
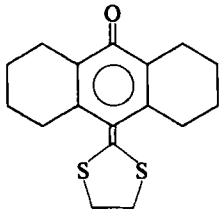
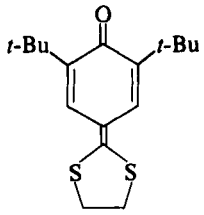
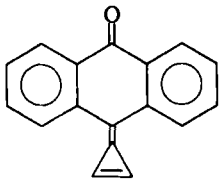
Compound	μ_{exp} (D)	μ_{calc} (D)	Reference
 **111**		6.15[b]	60
 **112**	2.74		116
 **113**	5.91		116
 **114**		5.7[c]	122
89c, R = Pr	7.56		123
89a	7.97		124
	8.10		125
 **115**	6.3		125
		6.04[d]	122

Table 20 (*Continued*)

Compound	μ_{exp} (D)	μ_{calc} (D)	Reference
 **116**	4.80		126
 **117**	6.36		126
 **118**	9.4		127
53a, X = Y = CN	7.49		128
b, X = CN, Y = CO_2Et	4.40		128
80a	6.54		116

[a]Calculated for the 2-methyl-3-phenyl analog by the CNDO/2 method (96).
[b]Calculated by the CNDO/2 method.
[c]Calculated by the PPP method.
[d]Calculated by a modified HMO method.

electrons to the acceptor part. The dipole moment is a global property of the molecule, and no experimental separation of π and σ contributions is possible. However, several dipole moments have been calculated by the CNDO/2 method, and reasonable agreement with experiment is found for such rigid compounds as **99a**, **101**, and **109**. Based on this agreement, one can undertake a separation, which shows that in **99a** ca. 0.5 π electrons have been transferred from the donor to the acceptor side, whereas in **109**, with less efficient donor groups, the

π polarization amounts to only 0.13 electrons (Fig. 6). A σ polarization is also observed, which seems to be governed both by the electronegativities (core charges) of the respective atoms and by their π charges (116). In **110**, the magnitude of the dipole moments supports the earlier conclusion that 1,1-diacetylethylenes prefer the *ZZ* and *EZ* to the *EE* conformation. Similarly, the *ZZ* form of **104** must be important in benzene solution.

The dipole moment calculated for **111** is somewhat higher than for **96**, as expected. The total π charge in the cyclopentadiene ring is calculated to be 0.54 electrons. A somewhat smaller polarization, 0.40 π electrons, is calculated for 7,8-diphenylcalicene (124), and 0.34 π electrons for hexaphenylcalicene **115**, (122) by the PPP (Pariser–Parr–Pople) method. Thus it seems as if the π polarization roughly follows the same trend as the bond lengths and the C=C torsional barriers.

The effect of the twist about the C=C bond in **113** is unexpectedly weak. Comparison between **88** and **112** shows that dibenzoannelation lowers the moment by ca. 1 D. Therefore, for a planar **113**, a moment of ca. 5.2 D should

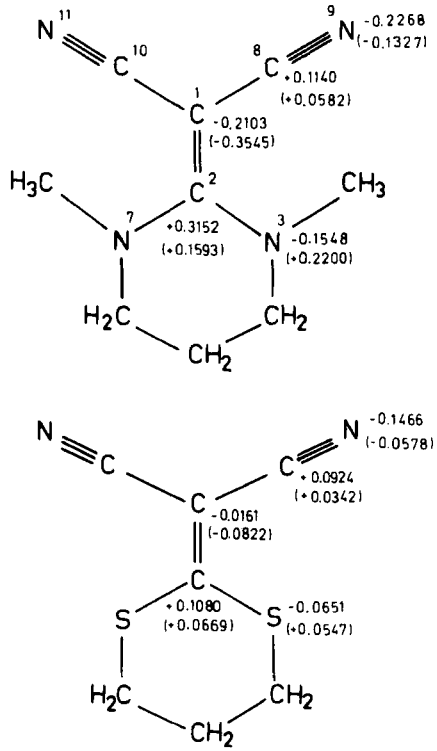


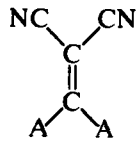
Figure 6. CNDO/2 electron densities (π-electron densities in parentheses) for **101** (top) and **109** (bottom).

be expected, not much lower than the observed 5.9 D. As will be discussed in Sect. III-B-3, the calculated dipole moments for perpendicularly twisted push–pull ethylenes are on the order of 10 to 12 D.

Summing up, we find that most push–pull ethylenes are comparatively strongly polarized, but that even the largest π polarizations found by combined use of dipole moments and CNDO/2 calculations do not allow the molecules to be pictured with a dominant weight for the dipolar limiting structures.

3. *Ultraviolet Photoelectron Spectra (UPS)*

Accepting the approximate validity of Koopmans' theorem (129), UPS can be said to give information about the energies of the occupied orbitals in the ground state. Two UPS studies of push–pull ethylenes have been reported (130,131). In ref. 130, the ionization potentials (IPs) of **119** are discussed, where A denotes



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MeS, MeSe, Me_2N, or cyclic systems containing these donor atoms. Two sharp bands are seen below 11 eV, of which that with the lowest IP is ascribed to ionization from the highest occupied π orbital, π_1, which has a large contribution from the symmetric combination of the donor p_z orbitals, and that with the second lowest to ionization from the antisymmetric combination of these orbitals (n_-). Both IPs decrease with decreasing ionization potential of A (Table 21), that is, in the series S < Se < N.

In ref. 131, the effect on the UPS of twist about the C=C bond was studied, using compounds of the type **84** and planar analogs. In the UPS of the diacetyl compounds, four bands appear with IP below 11 eV, ascribed to π_1, the antisymmetric and symmetric combinations of the C=O lone pairs [$n(O)_-$ and $n(O)_+$], and $n(N)_-$. The splitting of $n(O)_-$ and $n(O)_+$ occurs entirely by through-bond interaction, and it is calculated to be 1.6, 0.9, and 0.4 eV in the *EE*, *EZ*, and *ZZ* form, respectively. In **84a** and **b** it is 0.62 and 0.64 eV, and in **120** it is 0.38 eV, indicating a dominance of the *EZ* form in the diacetyl compounds in the gas phase.

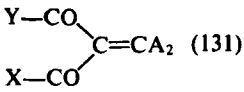
Comparison of the spectra of **84a** and **84b** shows that IP (π_1) decreases with increasing twist angle. This is in agreement with CNDO/2 calculations, which also indicate that this orbital becomes increasingly localized on the acceptor part

Table 21

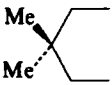
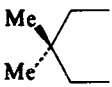
Ionization Potentials (eV) and Assignments[a] from UPS

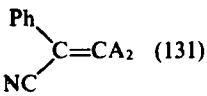
$(NC)_2C{=}CA_2$ (130)

A_2	π_1	$n(A)_-$
$(SMe)_2$	9.16	9.89
SCH_2S	9.08	10.50
$S(CH_2)_2S$	8.88	9.94
$S(CH_2)_3S$	9.11	10.03
$(SeMe)_2$	8.85	9.39
$Se(CH_2)_2Se$	8.82	9.54
$(NMe_2)_2$	8.21	9.17
$MeN(CH_2)_2NMe$	8.20	9.51
$MeN(CH_2)_3NMe$	8.11	9.33



(131)

X/Y	A_2	π_1	$n(O)_-$	$n(O)_+$	$n(A)_-$
Me/Me	$(SMe)_2$	8.50	9.16	9.85	9.16
Me/Me	$S(CH_2)_2S$	8.28	8.9 (sh)[b]	9.63	9.16
Me/Me	$S(CH_2)_3S$	8.15	8.9 (sh)[b]	9.62	9.17
Me/Me	$(NMe_2)_2$	7.61	8.3 (sh)[b]	9.04	8.47
Me/Me	$MeN(CH_2)_2NMe$	7.32	7.95	8.57	8.92
Me/Me	$MeN(CH_2)_3NMe$	7.13	7.80	8.44	8.90
	$S(CH_2)_2S$	8.32	8.61	8.98	9.22
	$MeN(CH_2)_2NMe$	7.48	7.96	8.34	8.79

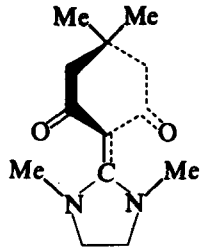


(131)

A_2	π_1	$n(N)_-$
$(NMe_2)_2$	7.20	8.50
$MeN(CH_2)_2NMe$	7.10	9.01
$MeN(CH_2)_3NMe$	6.85	9.0 (sh)[b]

[a]By band shapes and CNDO/2 calculations.

[b]Shoulder.



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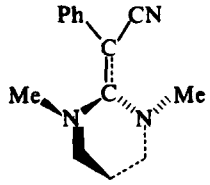
of the molecule, to become in the perpendicular state the HOMO of the carbanion system. Similar effects were observed in the UPS of **38** and **121**.



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B. The Transition State

The activation data presented in Sect. II are based on a large body of mostly rather precisely determined rate constants. However, their value for an estimation of the electronic effects of substituents is limited, partly because they were obtained in different solvents and at different temperatures, and partly because many of them to a varying extent depend on steric factors. Still, by a judicious choice of compounds it is possible to discuss the general trends in substituent effects.

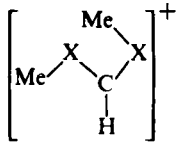
The low C=C barriers in push–pull ethylenes compared to the 65.5 kcal/mol in ethylene show that the effects of delocalization on the π-electron energy in the transition state must be much greater than the effects in the ground state—that is, the important substituent effects on the barriers must occur in the transition state. Besides, an effect that improves delocalization in the ground state would be barrier raising, if it were not accompanied by an at least equal stabilization of the transition state.

1. Substituent Effects on the C=C Barriers

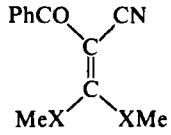
The most important combinations of *donor groups* that have been studied are R, OMe; R_2N, H; R_2N, Me; Me_3SiO, OMe; $(MeS)_2$; MeS, NMe_2; $(Me_2N)_2$;

$RN(CH_2)_nNR$; and the various potentially aromatic cyclic donor systems. Unfortunately, barriers are not known for ethylenes, where all these donor combinations are joined to one single acceptor combination, and comparisons of donor capacity have to be made in indirect ways. Thus, the following series of increasing donor capacity may be obtained: H, OMe < cyclopropene < $(MeS)_2$ < H, NMe_2 < Me_3SiO, OMe < $(Me_2N)_2$ < MeS, NMe_2 < $RN(CH_2)_n$-NR < *N*-alkyl-2-dihydropyridine, with the cycloheptatriene system somewhere in the middle of the series. However, we have observed in Sect. II that the apparent donor capacity also depends on the acceptor groups, and the order given may in places be reversed between different acceptor group combinations.

The order implies that Me_2SiO, OMe is more effective in stabilizing a carbocation than $(MeS)_2$. This is opposed to the expected greater stabilizing effect of one RS compared to one RO group in $RX\overset{+}{C}H_2$ (132), but it is in agreement with the observation that the rotational barrier in the dimethoxymethyl cation **122a** (133) is a few kilocalories per mole higher than that in the dithio analog **122b** (134). It may also be mentioned that although $\Delta G^{\ddagger}$ for **123a** is 20.6 kcal/mol, it is >25 kcal/mol for the diseleno analog **123b** (135), despite the fact that



122a, X = O
b, X = S



123a, X = S
b, X = Se

MeSe appears as a better donor than MeS in the UPS (Table 21). The order observed between **23**, R = Me and **24** also implies that $MeO-\overset{|}{\underset{+}{C}}-Me$ is relatively more stable than $MeS-\overset{|}{\underset{+}{C}}-Me$ On the other hand, sulfur acts as a distinctly better donor than oxygen in the heteroanalogs of heptafulvenes **63b** (Table 12). The variation in relative donor capacity of O and S as expressed in the barriers may in general be explained by differential stabilization of the ground and transition states.

Attempts have been made to correlate the effects of *acceptor groups* on the C=C barriers by Hammett substituent constants. Since the important interaction is concerned with the delocalization of a negative charge, the σ_p^- scale should be more appropriate than the normal σ scale (136). However, in the σ_p^- scale, CN is more efficient than COMe, which is contrary to experience, and therefore Shvo et al. preferred the $\sigma_R^- = \sigma_p^- - \sigma_I$ scale (78; see also Sect. II-C-5). Similarly, in a series of ketene mercaptals, a reasonable correlation was found

between $\Delta H^{\ddagger}$ and $\Sigma\sigma_R^-$ (46). Thus, the order of acceptor capacity is $H < CN < CONR_2 < CO_2R < COR < NO_2$, the same order as has been found for the acidifying effect in carbon acids (137). The cyclopentadiene ring seems to be a little less effective than two CO_2Me groups.

One system with $(SCCl_3)_2$ as the acceptor has been studied. In **22**, the NMR spectra can be interpreted in terms of a Case 3 system (Sect. II-E) with the steric barrier and the C—N barrier both being ca. 14 kcal/mol, and the π barrier considerably higher. The C—N rotation and the passage past the steric barrier may in that case be correlated. This problem could probably be solved by a combined ^1H and ^{13}C NMR study.

In **41c**, the high dipole moment, 7.42 D compared with 2.79 D for 1,1-diphenyl-2,2-bis(trifluoromethyl)ethylene, indicates a strong ground state polarization, but no barrier data are available (98,119).

2. *Substituent Effects on the C—N Barriers*

An inspection of HC—NMe_2 barriers in Tables 2 to 4 shows $\Delta G^{\ddagger}$ values from 8.7 to 22.3 kcal/mol. Seen apart from the gain in energy due to pyramidalization in the transition state (nearly the same for all systems) and from possible steric effects, these barriers represent the energies of interaction between the planar NMe_2 groups and the remainder of the conjugated system. The interaction energy ΔE can be obtained by second-order perturbation theory as [3], where H_{ij} is the Hamiltonian matrix element between the p_z (N) orbital and the LUMO of the remainder of the conjugated system, and $\delta\epsilon_{ij}$ is the energy difference between these orbitals. The LUMO energy and its distribution are determined by the interaction between the acceptor orbitals and the ethylenic orbitals (138). The LUMO energy depends among other things on the energy of the LUMO of the acceptor, which explains why C=S is more barrier raising than C=O (139). The LUMO is also lowered by strongly electronegative acceptors. Therefore, ΔE is determined both by inductive and mesomeric effects of the acceptors. In the systems XCH=CHNMe_2, the effect of X increases in the series $CN < COMe < CO_2Me < COCHOPh < NO_2$. The barriers—for X = NO_2, 16.5; CHO, 14.7; CO_2Me, 13.9; MeCO, 13.3; and CN, 12.9 kcal/mol—correlate badly with all σ scales, but least badly with σ_R^-. With two acceptors, steric effects become important except with the 1,1-dicyano compound, and ground state strain combined with the possibility for coplanarity in the transition state contribute to lowering the barriers. A case in point is the pairs **9** and **10** (R = H, $R_1 = R_2$ = Me) with C—N barriers 13.7 and 17.6 kcal/mol. It seems here as if CN should be more efficient than CO_2Me in raising the C—N barrier, in contradiction to the effects in the simpler series. The reason is probably found in the conformations. In **10**, the NMe_2 group is trans to the CO_2Me group, and no steric interference occurs (33). In **9**, the cis CO_2Me group is forced out of

coplanarity by 68° (103; Table 19), which raises the ground state energy, whereas the transition state is stabilized by the return of the cis CO_2Me group to the double-bond plane. However, the electronic interaction between the substituents must also be of importance for the LUMO energy, since the dicyano analog of **9** and **10** has about the same C—N barrier as **9**, 17.7 kcal/mol in $CHCl_2CHCl_2$ (24) and 18.0 kcal/mol in $CDBr_3$ (30). With two donors and two acceptors, the situation may be even more complex. In the ketene aminals (Table 7; 51) the C—N barriers increase in the series X, Y = $(CN)_2$, 10.3; CN, CO_2Me, 13.7; $(COMe)_2$, 15.0; $(CO_2Me)_2$, 15.2.

$$\Delta E = \frac{2H_{ij}^2}{\delta\epsilon_{ij}} \qquad [3]$$

3. *Solvent Effects and Activation Entropies*

In the first DNMR studies of push–pull ethylenes, a strong effect of solvent polarity on the C=C barriers was noted. Thus Kende et al. (64) found $\Delta G^{\ddagger} = 18.0$ kcal/mol for **46a** in *N*,*N*-dimethylformamide (dielectric constant $\epsilon = 38$) and 19.4 kcal/mol in Ph_2O ($\epsilon = 4$). Similar observations have been made by many other workers, and they have been seen as a strong support for a zwitterionic transition state. Kessler et al. (140) observed reasonably linear correlations between $\Delta G_c^{\ddagger}$ for two ketene aminals and the solvent polarity parameter E_T (141) with variations in $\Delta G_c^{\ddagger}$ of ca. 2.5 kcal/mol over E_T values between 25 and 46. Similarly, Shvo et al. (78) found linear correlations between log k_{298} and the polarity parameter Z (141) for three compounds from Table 12.

A more quantitative treatment has been tried (60), using the reaction field model (142). According to this, a dipolar solute molecule (dipole moment μD) in a polar or polarizable solvent creates a reaction field R, the value of which at the site of the molecule is given by [4]. K is a constant (14.40×10^6), and a is the radius of the cavity, assumed spherical, which contains the solute molecule. The stabilizing interaction, ΔE (kcal/mol) is obtained from [5], and a from [6] when the density ρ of the solute is known. The solvent effect on the rotational barrier, $\delta\Delta E$, is obtained from [7] when the dipole moments of the ground state (μ_{gs}) and the transition state (μ_{ts}) are known. They can be obtained by CNDO/2 calculations, and it is in general found that μ_{ts} is ca. twice as large as μ_{gs} (10 to 12 D). When this treatment was performed for **43**, $\delta\Delta E$ was calculated to ca. 4 kcal/mol in toluene and twice as large in acetonitrile. The observables are $\Delta G_{362}^{\ddagger}$ (C_7D_8) = 18.0 and $\Delta G_{299}^{\ddagger}$ (CD_3CN) = 15.0 kcal/mol. Thus the calculated stabilization seems to be of the right order of magnitude, but the comparisons should have been made with the $\Delta H^{\ddagger}$ values, which requires $\Delta S^{\ddagger}$ for the two solvents to be known. Unfortunately, these data are not available, since the ^1H NMR spectrum of **43** is not suitable for a precise band-shape analysis.

$$R = \frac{K(\epsilon - 1)\mu}{(2\epsilon + 1)a^3} \quad [4]$$

$$\Delta E = R \cdot \mu = \frac{K(\epsilon - 1)\mu^2}{(2\epsilon + 1)a^3} \quad [5]$$

$$4\pi a^3/3 = M/N\rho \quad [6]$$

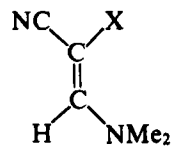
$$\delta\Delta E = \Delta E \text{ (transition state)} - \Delta E \text{ (ground state)} \quad [7]$$

Besides the effect of solvent polarity, the C=C rotation in many push–pull ethylenes is sensitive to acid catalysis (143). This is probably explained by protonation of the acceptor groups, for example, the oxygen atoms in C=O groups (16), which increases their acceptor capacity. Small amounts of acids in halogenated solvents, or acidic impurities, may have drastic effects on the barriers, and it is advisable to add a small quantity of a base such as 2,4-lutidine to obtain reliable rate constants (81). Basic catalysis is also possible, but it has only been observed in compounds containing secondary amino groups (38).

The transition state to C—N rotation is less polar than the ground state, and therefore barriers to this rotation are increased by increased solvent polarity (20,83). For similar reasons, the barriers to passage through the planar state in Case 2 push–pull ethylenes increase moderately with increasing solvent polarity (143).

One should expect the *activation entropy* ($\Delta S^{\ddagger}$) to C=C rotation in Case 1 push–pull ethylenes to be negative, since the increase in polarity in the transition state should increase the order in the solvated structure. The effect should increase with increasing difference in polarity between ground and transition states, and also with increasing solvent polarity. These expectations have been completely borne out by experiments (78,140,143), as Table 22 shows. Contrary to what is generally found for conformational processes (144), $\Delta S^{\ddagger}$ values ≤ -20 e.u. are frequently found for C=C rotation in push–pull systems.

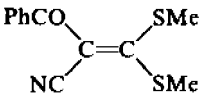
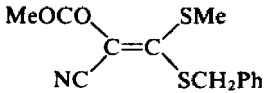
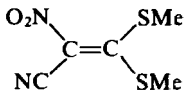
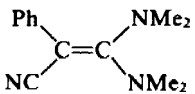
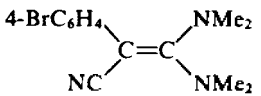
In Case 2 systems, the ground state is more polar than the transition state to C=C rotation, and positive $\Delta S^{\ddagger}$ values would be expected, as is indeed observed (Table 22). The situation is similar for the C—N rotations, and here a positive value (16 ± 3 e.u.) was found for **77a** (84). However, Hobson and Reeves found values near zero (2.7 ± 1.1 and −3.9 ± 2.0 e.u.) for **124a** and **b** (24).

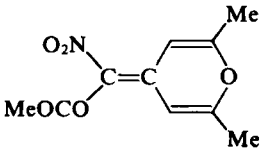
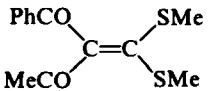
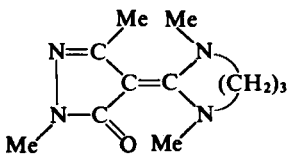


124a, X = H
b, X = CN

Table 22

Activation Enthalpies ($\Delta H^{\ddagger}$, kcal/mol) and Entropies ($\Delta S^{\ddagger}$, cal/mol K) for Rotations Through Perpendicular (π) and Planar (S) Transition states (TS) in Case 1 and Case 2 Push–Pull Ethylenes

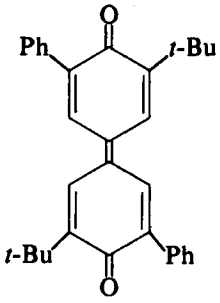
Compound	TS	Solvent	Z^a	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	Ref.
	π	ODC		13.8 ± 0.6	−17.3 ± 1.4	45
	π	$CDCl_3$	63.2	15.0 ± 0.9	−24.0 ± 2.9[b]	45
	π	ODC		13.1 ± 0.1	−15.1 ± 0.5	46
	π	ODC		18.1 ± 0.2	−6.6 ± 0.4	51
	π	C_6D_5Br	59.0	15.1 ± 0.7	−12.3 ± 1.6	140

	π	HMPT-d_{18}	62.8	10.5 ± 0.3	−21.7 ± 1.0	78
		CD_3CN	71.3	7.3 ± 0.3	−27.4 ± 0.1	78
	π	ODC		11.9 ± 0.4	−18.1 ± 0.9	143
80b	S	ODC		19.2 ± 0.7	+ 7.7 ± 2.0	143
80c	S	ODC		26.4 ± 1.2	+10.2 ± 2.7	143
69a	π	ODC		16.2 ± 0.9	−10.6 ± 2.4	143
69c	π	ODC		13.3 ± 0.6	−14.8 ± 1.4	143
	S	ODC		25.7 ± 0.9	+ 6.6 ± 2.0	143

[a]From ref. 141.
[b]By stereomutation.

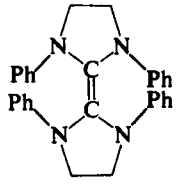
IV. STRAINED ETHYLENES WITHOUT PUSH–PULL EFFECT

In symmetric overcrowded or otherwise strained ethylenes, the strain may be partially released by rotation around the C=C bond or by other deformations, and the barrier to *E–Z* isomerization may be lowered compared to that of ethylene by ground state strain and by delocalization of the double-bond π electrons into unsaturated substituents, forming a diradical transition state. The importance of the delocalization effect is illustrated by the low barrier ($\Delta G^{\ddagger}_{310}$ = 23.2 kcal/mol) in the diphenoquinone **125** (145), in which the ground state strain must be rather low.

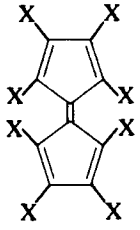


125

Two common routes for release of strain in symmetric ethylenes may be described as *folding* and *twisting*. Which of them will give the lowest energy to a particular system depends on several factors, but it seems as if twisting is favored when good delocalization possibilities exist for the diradical state, whereas folding may permit a better conservation of the π conjugation across the double bond. Folding can be illustrated by 1,1′,3,3′-tetraphenylbis(imidazol-2-ylidene), **126** (146), shown in Fig. 7*a*. Here the strain is released by slight pyramidalization at the ethylenic carbon atoms, keeping the imidazolidine rings essentially in two



126



127a, X = Cl
b, X = Br

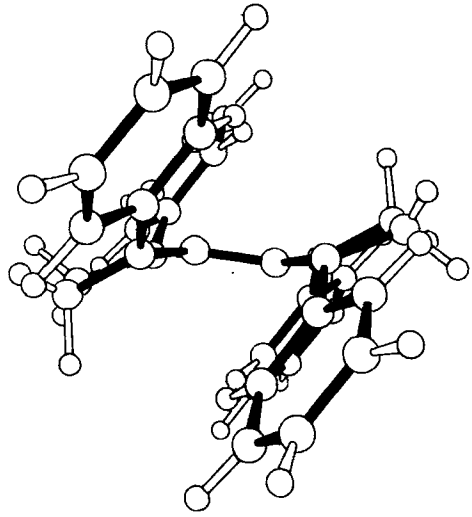


Figure 7a. Molecular stereochemistry of **126** (146).

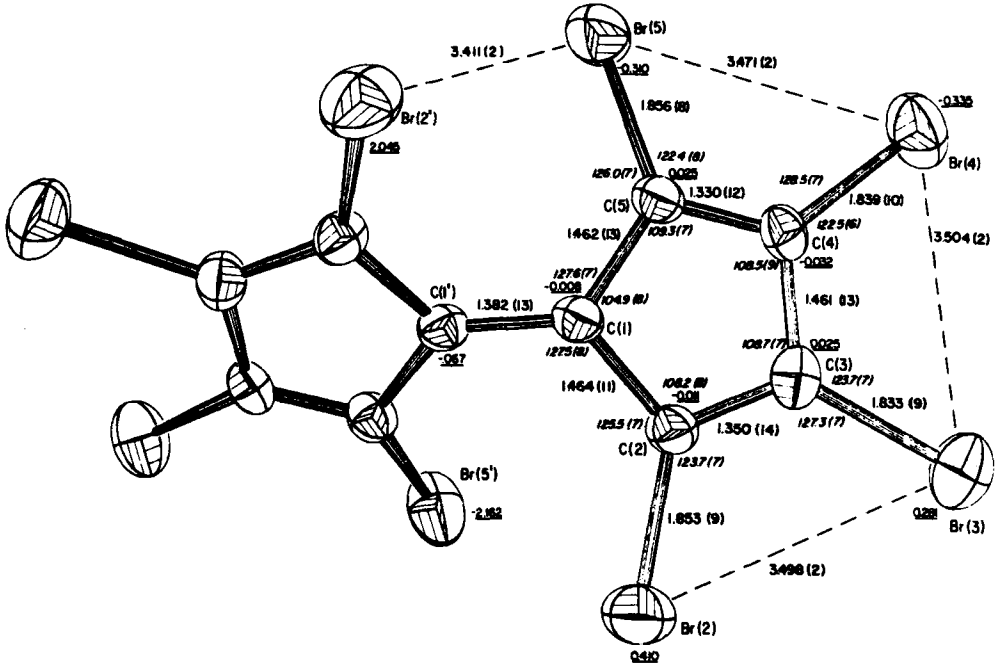
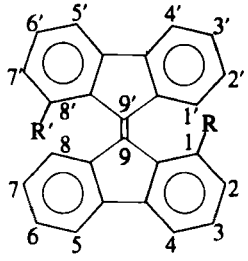


Figure 7b. Molecular stereochemistry of **127b** (148).

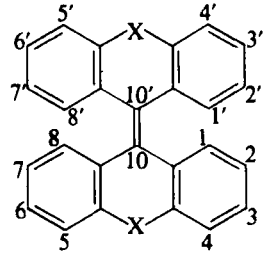
parallel planes, and by bending the phenyl rings away from the opposite half of the molecule. In this way the phenyl rings are moved out of interfering distance with a moderate distortion of the double bond. On the other hand, octachloro- and octabromopentafulvalene, **127a** and **b** (147,148) shown in Fig. 7*b*, have planar cyclopentadiene rings, which are twisted by 34.5° and 37.1°, respectively at the inter-ring double bond.

A. Bistricyclic Ethylenes

Some members of this class of overcrowded ethylenes have been the subjects of intense interest over several decades because of their thermochromic and photochromic properties, which are related to the formation on heating or irradiation of more or less labile isomers, which absorb light at much longer wavelength than the stable forms. Some molecules of this class have come into the spotlight because of their interesting static and dynamic stereochemistry. The most studied systems are the bifluorenylidenes (**128**), the dixanthylenes (**129a**), biacridylidenes (**129b**) and bianthronylidenes (**129c**). X-ray crystallographic structure determinations have given significantly different results for the two groups **128** and **129**. The bifluorenylidenes **128a** and **b** have nearly planar fluorene groups, which are twisted by ca. 42° and 52° about the 9,9′ double bond (149). Bixanthylidene, **129a** (150), and bianthrone, **129c** (151), on the



128a, R = R′ = H
b, R = R′ = CO_2i-Pr
c, R = R′ = CO_2Me
d, R = CO_2Me, R′ = CO_2i-Pr
e, R = R′ = Me



129a, X = O
b, X = NR
c, X = CO

other hand, adopt an anti-folded structure (Fig. 8). The 10,10′ carbon atoms are slightly pyramidalized in opposite directions, and the benzene rings are folded away from the opposite half of the molecule, forming angles of ca. 40° with the mean ethylenic plane. This increases the C_1 to C_1' distance to 299 and 290 pm, respectively.

Ollis et al. (152) studied the variable temperature ^{1}H NMR of **128b** to **d**. At

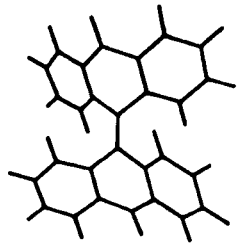


Figure 8. Structure A for **129**.

ambient temperature the spectra showed the presence of *E* and *Z* forms, and anisochrony of the methyl groups in each isopropyl group was interpreted as a consequence of a twisted or folded conformation, with a preference for the latter conformation based on an earlier incomplete X-ray structure determination (153). With increasing temperature, exchange between *E* and *Z* and enantiomerization become rapid and cause coalescence of the NMR spectra. By simulation of the exchange-broadened spectra, rate constants could be derived, from which a $\Delta G^{\ddagger}$ of 20 to 21 kcal/mol for the two exchange processes was calculated. Assuming the same conformation in solution as in the crystal, the NMR spectra can be interpreted as for a Case 3 twisted ethylene, with almost equal steric and π electronic barriers. The detailed interconversion pathways can be based, with some modifications, on those proposed in ref. 152 (Fig. 9), using folded structures as intermediates. Ollis et al. proposed that the low barriers are partly to be rationalized by high ground state strain, and this hypothesis is strengthened by the observation by Agranat et al. (154) that the barrier to *E*–*Z* isomerization is higher than 25.6 kcal/mol (T_c > 220°C) in 2,2′-difluoro-**128**, whereas it is 19 kcal/mol in the 1,1′-dimethyl analog **128e**. In the difluoro compound the steric congestion must be similar to that in **128a**, whereas the ground state strain

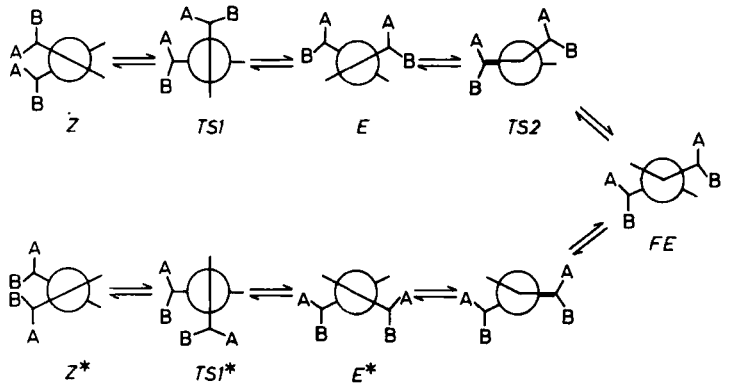


Figure 9. Possible pathways for *E* → *Z* exchange and for enantiomerization in **128**.

in **128e** may be even greater than in **128b** to **d**, since, at least in cyclohexanes, a methyl group is sterically more demanding than an ester group (155).

It is also interesting to study the results of empirical strain energy calculations performed by Lenoir and Lemmen (156) on **128a**, (*E*)- and (*Z*)-**128e**, and 1,1′,8,8′-tetramethyl-**128**, using the Allinger MMPI program (157,158). The torsion angle between the fluorene planes was calculated to 42.9° for **128a** and 58.4° for the tetramethyl derivative. The calculated strain energies were, in the foregoing order, 52.72, 58.25, 57.24, and 63.76 kcal/mol, and the energy of the folded **128a** was computed to be 7.8 kcal/mol higher than that of the twisted form. The lower energy calculated for the *Z* than for the *E* form is not quite as expected, since both for **128b** and **128e** the *E* forms are found to dominate in solution (152,154), and for **128b** also in the crystal (149).*

The hypothesis that **128** is twisted in solution and that the transition state to *E–Z* isomerization has perpendicular fluorene groups was supported by a study of 2,3,2′,3′-dibenzo-annelated **128** (159). In this, the steric situation around the double bond is similar to that in **128a**, but an improved stabilization of the diradical perpendicular transition state should lead to a lower barrier to *E–Z* isomerization, as is found ($\Delta G^{\ddagger}_{453}$ = 23.5 kcal/mol). A close approach of the 1 and 1′ (8 and 8′) positions in **128** is indicated by a through-space ^{1}H–^{19}F coupling of 7 Hz in (*E*)-1,1′-difluoro-**128** (160). In this compound the barrier to *E–Z* exchange is >25.6 kcal, because of the small contribution of the fluorine atoms to the ground state strain.

The stereochemistry of compounds **129a** to **c** with 6-membered central rings has been thoroughly studied by Agranat et al. (161–167). The folded structure (the *A* form, Fig. 8) found in the crystalline state of dixanthylen and bianthronylidene was shown to be the most stable conformation in solution for all compounds **129**. This conclusion is based on the observed strong shielding of the 1,1′,8,8′ protons, which in the folded form are close to the hexagonal axes of the opposing benzene rings, whereas in the twisted structure (the *B* form) they are in a deshielded region. The assignment is supported by empirical strain energy calculations (168), which give the *A* form as the most stable with the *B* form as second.

The conformational behavior was conveniently studied by placing "tag" substituents in the 2,2′-positions. The substituted compounds exist in *E* and *Z* forms, and when the tags are of moderate size (Me, CF_3, Et), the populations of the two forms are very similar. On the other hand, with 1,1′-substituents larger than F, only the *E* form is observed. The *E* and *Z* forms interconvert with lifetimes that are generally accessible on the NMR time scale. $\Delta G^{\ddagger}$ values of ca. 18 kcal/mol were obtained for **129a**, and of 20 to 22 kcal/mol for **129b** and **c**. Benzo-annelation raises the *E–Z* barrier (161,166), indicating that passage of

*According to a private communication by Dr. Lenoir, two columns in Table 3 of Ref. 156 were accidentally transposed, and the above-mentioned *E* and *Z* form energies should be exchanged.

the perpendicular twisted state is not the rate-determining step. Instead, the size of the substituents in the 2,2′-positions plays a role, raising the barrier by 1 kcal/mol from Me to *t*-Bu. This points to a rate-determining step involving an "edge-passage." More detailed information was obtained by using *i*-Pr groups as 2,2′-substituents (163,164). The Me groups in each *i*-Pr group are diastereotopic in both the *E* and the *Z* form, though only the latter is chiral (165). The probable preferred routes leading to *E*–*Z* interchange and to exchange between the Me sites in each of the *E* and *Z* forms are depicted in Figure 10. In this scheme, passage of two substituted edges, probably a high-energy process, is avoided.

Unfortunately, the chemical shift differences between the four methyl sites in the 2,2′-diisopropyl derivatives are very small (0.11 to 0.12 ppm in the *Z* form, 0.01 to 0.03 ppm in the *E* form), and no detailed band-shape analysis is possible. However, additional information was obtained by a study of the thermochromic forms of several bianthronylidenes (167). These species are now regarded as having the *B* form (*TWZ* and *TWE* in Fig. 10), which is also seen as identical to a colored species formed on photolysis of the *A* form (168,169). Because of its strong absorption at 650 to 730 nm (ϵ_{max} = 15,500) where the *A* form is transparent, the equilibrium concentration of the *B* form could be measured as a function of the temperature, and ΔH° ($A \rightleftharpoons B$) could be obtained from the slope of a plot of log *K* versus $1/T$. Note that K = [(*TWE*) + (*TWZ*)]/

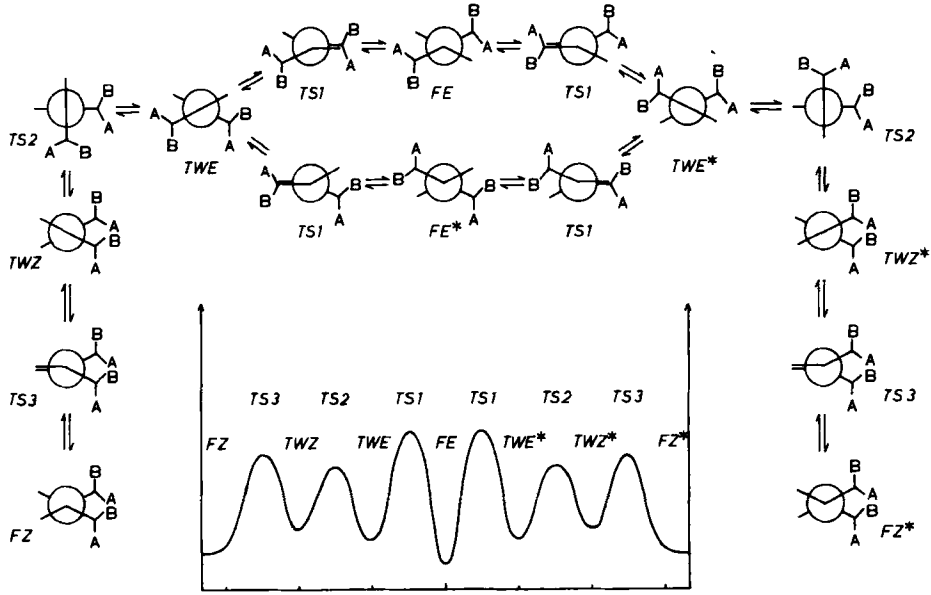


Figure 10. Pathways and potential energy curves for $E \rightarrow Z$ exchange and for enantiomerization in **129**.

[(*FE*) + (*FZ*)] is a function of several equilibria depicted in Figure 10.

An excess of the twisted form (*B*) was prepared from the photostable 2,2′-bis(trifluoromethyl)-**129c** by laser flash photolysis, and its decay to the folded form (*A*) was followed photometrically. From the rate constants at four temperatures, $\Delta H^{\ddagger}$ ($B \rightarrow A$) = 16.1 ± 0.7 kcal/mol was obtained. For this compound, ΔH° ($A \rightleftharpoons B$) = 4.2 kcal/mol had been found, and the sum of these two values agrees well with $\Delta G^{\ddagger}$ ($E \rightarrow Z$) = 21.5 ± 0.3 kcal/mol obtained by band-shape analysis, which probably corresponds to a $\Delta H^{\ddagger}$ value of 20 to 21 kcal/mol, assuming $\Delta S^{\ddagger}$ to be −2 to −5 e.u.

B. *trans*-Cyclooctene and Analogs

trans-Cyclooctene has been known for nearly 30 years, and as a highly strained dissymmetric compound with a simple chromophore it has played a role as a test case for theoretical calculations of rotatory strengths (170). Opinions have varied on whether it should be regarded as a dissymmetrically perturbed symmetric chromophore (171,172) or whether it is inherently dissymmetric (173). Electron diffraction studies by Gavin and Wang (174) indicated that the double bond is significantly twisted, with a C_8—C_1=C_2—C_3 dihedral angle of 157° and with the ring in a distorted chair conformation (Fig. 11*a*). The twisted double-bond was confirmed in an electron diffraction study by Traetteberg (175), but she found that the crown (twist) conformation of the ring (Fig. 11*b*) with a C=C dihedral angle of 136° fit the observed intensity function better than did the distorted chair form. This conclusion is supported by empirical force-field calculations by two groups, using different force fields (90, 176), which gave the twist form as the more stable one, 2.43 and 3.54 kcal/mol respectively below the distorted chair form. In the twist form (Fig. 11*b*), the olefinic carbon atoms assume slightly pyramidal structures with the hydrogen atoms bent inward, toward the ring, thereby counterbalancing the effect of the twist on the π overlap.

The location of hydrogen atoms by electron diffraction suffers from some uncertainty, and in order to confirm the state of hybridization of the olefinic carbons, Traetteberg et al. (177) undertook a combined electron diffraction and strain energy calculation study of 1-methyl-*trans*-cyclooctene. Calculations, us-

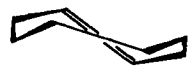


Figure 11a. Distorted chair form of *trans*-cyclooctene.

Figure 11b. Twist form of *trans*-cyclooctene.

ing the Allinger MM2 force field (178), were also performed for *trans*-cyclooctene and the not yet available 1,2-dimethyl-*trans*-cyclooctene. The experimental data show a larger twist (dihedral angle 130.3°) in the 1-methyl derivative, and a stronger pyramidalization of the C_1 atom but a weaker one of the C_2 atom, both compared to *trans*-cyclooctene. The strain energy calculations gave results in qualitative agreement with this, and they predict an increasing twist in the series *trans*-cyclooctene, 1-methyl-*trans*-cyclooctene, and 1,2-dimethyl-*trans*-cyclooctene.

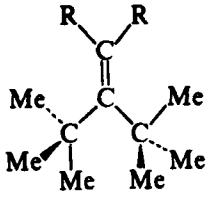
Ermer (179) describes more extended force-field calculations, following a reasonable reaction coordinate from the twist to the distorted chair form. The barrier ($\Delta H^{\ddagger}$) between these is found to be 7.21 kcal/mol, implying that the interconversion is fast except at very low temperatures.

Trans-cycloheptene is much less stable than *trans*-cyclooctene and is not isolable at ambient temperature. Its high internal strain is manifested by its ready isomerization to the cis form. Its energy in excess for the cis form has been calculated to be 20.3 kcal/mol, and the C_7—C_1=C_2—C_3 dihedral angle has been calculated as 125° (90). A trans-to-cis free-energy barrier of 19.4 kcal/mol has been measured for the photochemically generated trans form ($\Delta H^{\ddagger}_{270} = 18.2 \pm 1.2$ kcal/mol; $\Delta S^{\ddagger}_{270} = -4.4 \pm 4.4$ cal/mol K (180). *trans*-Cyclohept-2-enone has about the same stability as *trans*-cycloheptene (181) but 1-phenyl-*trans*-cycloheptene has $\Delta G^{\ddagger}$ (trans → cis) 20.9 kcal/mol (182).

trans-Cyclohexene is as expected even less stable, and a species formed by flash photolysis of *cis*-cyclohexene and claimed to be the trans form isomerizes to *cis*-cyclohexene with a barrier of 7 kcal/mol (183).

C. Tetrasubstituted Twisted Ethylenes

Tetrasubstituted twisted ethylenes have become of much interest, partly because of the advent of new synthetic methods (184,185) suitable for the preparation of highly strained olefins. However, the most interesting target, tetra-*tert*-butylethylene (**130a**) eludes investigators. It has been the object of several force-field calculations with somewhat varying outcomes. Ermer and Lifson (176,186) cal-

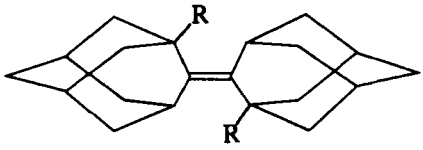


130a, R = *t*-Bu
b, R = Ph

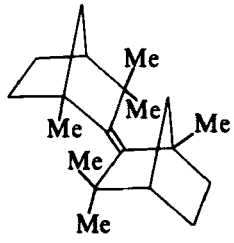
culated a torsional angle of 75°, and Lenoir et al. (187) and Burkert (188), using the Allinger MMI force field (157,158), independently arrived at a torsional angle of only 45° and a bond length of 137.7 pm, with no out-of-plane distortion of the *t*-Bu groups. The total strain energy was calculated at 100.5 kcal/mol. Favini et al. (189), using the Schleyer–Andose–Mislow force field (190), found a torsional angle of 45.5°, a bond length of 136.0 pm, and a strain energy of 89.6 kcal/mol. However, the authors (189) found another energy minimum with a torsional angle of only 13°, 4 kcal higher and separated from the most stable conformer by a remarkably high energy barrier. If this is correct, it might show up as a negative thermochromism of **130a**. The authors also point out that hydrocarbons with higher strain energies are known, such as bicyclo[1,1,1]pentane (97.2 kcal/mol), cubane (166.9 kcal/mol), and basketane (119.4 kcal/mol), and that therefore the prospects for preparing **130a** are not entirely dim.

Favini et al. (189) also report calculations on 1,1-diphenyl-2,2-di-*tert*-butylethylene (**130b**), which has been shown by X-ray crystallography to be twisted by 24° and has R(C=C) 136 pm (191). The calculated twist and bond length, 19.8° and 135.7 pm, as well as most other structural details, agree well with the experimental data.

Some polycyclic analogs of **130a** have been prepared and subjected to X-ray crystallographic studies. Particularly interesting are the biadamantylidenes (**131**) and *syn*-difenchylidene (**132**). While **131a** has a planar double bond and R(C=C)



131a, R = H
b, R = Et

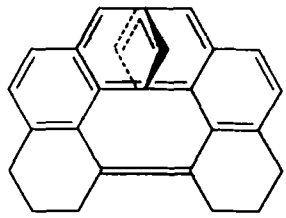


132 (*E*)

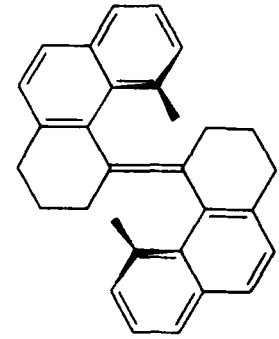
133.6 pm (192), **131b** is twisted 12° and has R(C=C) 135.8 pm (193), well reproduced by force-field calculations.

The extent of substitution of the carbon atoms α to the C=C bond is the same in **132** as in **130a**, but some nonbonded interactions are removed by ring closure in **132**, and the C=C torsion angle is only 11.8° with R(C=C) 134.9 pm (194) in good agreement with calculations (187). The strain energies in **131b** and **132** were calculated to be 41.58 and 60.67 kcal/mol, respectively.

Feringa and Wynberg (195) have prepared two chiral twisted ethylenes, *cis*- and *trans*-1,1′,2,2′,3,3′-hexahydrobiphenanthrylidene (**133** and **134**). They could be resolved (**133** only partly) by HPLC on alumina impregnated with TAPA [α-(2,4,5,7-tetranitrofluorenylideneaminooxy)propionic acid] (196), and UV, ORD, and CD spectra are reported. A slow cis–trans isomerization is mentioned but



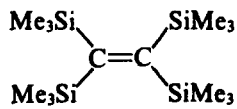
133



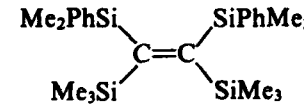
134

no rate data are given.

Two interesting analogs of **130a** have been reported by Sakurai et al.: tetrakis (trimethylsilyl)ethylene, **135** (197), and 1,2-bis(dimethylphenylsilyl)-1,2-bis(trimethylsilyl)ethylene, **136**, (198). The latter is formed predominantly in



135



136 (*Z*)

the *Z* conformation, and this is thermally transferred to a 40:60 *E*–*Z* equilibrium mixture. From the rate constant at 68°C, $\Delta G^{\ddagger}$ = 30 kcal/mol could be calculated. Under irradiation a 60:40 *E*–*Z* steady state was observed. An X-ray crystallographic study of **135** (199) gave a C=C torsional angle of 29.5° and R(C=C) 136.8 pm. The C(sp^2)—Si bonds are strongly elongated, 191.5 pm compared to 184 to 187 pm in unstrained systems. Structure **135** shows thermochromic behavior with an isosbestic point at ca. 385 nm, which may be explained by a thermally increased population of a more twisted, higher-lying conformation. The existence of a thermally accessible triplet state is indicated by the formation of a radical, identified by its ESR spectrum as $(Me_3Si)_2CH—\dot{C}(SiMe_3)_2$, on heating of **135**, neat or in decaline solution, to 150°C (198).

V. *AB INITIO* CALCULATIONS

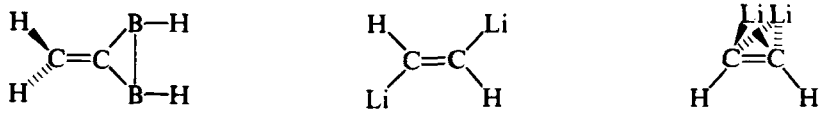
A. Dilithioethylenes and Analogs

In 1976, Schleyer et al. (200) reported that *ab initio* calculations on 1,1-dilithioethylene (**137**) both on the STO-3G and the 4-31G levels gave the result that both energy and C=C bond length are remarkably insensitive to the angle of

137

twist about the C=C bond, and that the perpendicularly twisted form is slightly more stable. Furthermore, the energies of the planar and twisted triplets were found to be so much lower than those of the corresponding singlets that a ground state triplet was proposed, though the methods of calculation are known to artificially favor triplet states. This result was supported by Laidig and Schaefer (201), who improved the calculations by extending the basis set and taking electron correlation explicitly into account. They predicted the twisted triplet state to be the ground state, with the planar triplet, the twisted singlet, and the planar singlet respectively 1.4, 10.5, and 12.5 kcal/mol higher in energy. The preparation of 1,1-dilithio-2-methylpropene has been described (202), but no experimental confirmation of the foregoing computational results has been reported. Calculations on similar olefinic systems containing electron-deficient substituents (e.g., **138**) have been performed, and analogous results (though with singlet ground states) were reported (203).

Extensive calculations have also been performed on 1,2-dilithioethylene, for which the stable isomers are predicted to be the planar trans form **139** and a doubly bridged form **140**, both in the singlet state (204).

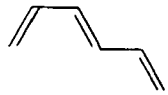


138 **139** **140**

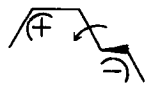
B. The Sudden-Polarization Effect

The sudden-polarization effect falls somewhat outside the scope of this chapter, since it is confined to electronically excited states. However, since it may have

important stereoelectronic consequences, a brief account is appropriate. Salem et al. (205) observed in *ab initio* calculation on *s-cis-s-trans*-hexatriene (**141**) that the charge distribution in the excited singlet state Z_1 changed drastically on rotation about the 3,4 double bond. When the twist angle approached 90°, a strong polarization set in (**142**), corresponding to a maximal charge transport of



141



142

ca. 0.8 electrons and leading to a zwitterionic instead of the expected diradical Z_1 state. The charge separation peaked very strongly at 90°, falling practically to zero 2° outside this angle, which is the basis for the name *sudden polarization*. Calculations on a number of similar systems including ethylene have given similar results. A slight dissymmetry of the twisted double bond is required, such as the s-cis and s-trans bonds in **141**, and for a single double bond a minor pyramidalization of one carbon atom or unequal substituents is sufficient. Brooks and Schaefer (206) obtained similar results in a multiconfigurational SCF calculation on twisted ethylene, which shows that the effect is not an artifact of the more limited approach used in the earlier calculations. The effect awaits experimental confirmation. It is evident that such strong polarizations of normally nonpolar systems should have important effects on the outcome of photochemical reactions. Salem has proposed that the visual process may be triggered by a twist and polarization of the excited *N*-retinylidene molecule (207).

VI. CONCLUSION

The data presented in this chapter summarize the important developments during the last 15 years in our knowledge of the steric stability of the double bond. It is now possible, based on a large body of experimental results, to predict polarization, rotational barriers, and bond lengths of double bonds in typical push–pull ethylenes with reasonable accuracy. For systems without push–pull effects, the power of empirical strain energy calculations to give precise information on conformations and on energies of conformational changes in complex strained molecules has been amply demonstrated.

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I wish to thank Professor G. Boche, Marburg; Professor K. Hafner, Darmstadt; Dr. E. Kleinpeter, and Dr. G. Kretschmer, Leipzig; Professor H. Sakurai, Sendai;

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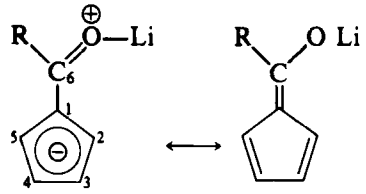
NOTE ADDED IN PROOF

After the manuscript for this chapter had been submitted, the following publications have come to the author's attention.

Boche et al. (208) have studied the temperature-dependent ^{13}CNMR spectra of the Li-enolates of the three acylcyclopentadienes **143a** to **c** in tetrahydrofuran-d_8. While the spectrum of **143a** indicated slow rotation about the 1–6 bond below



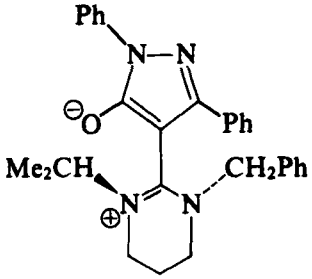
143a, R = Me
b, R = tBu
c, R = OMe

55°C, at which temperature decomposition occurred, the spectra of **143b** and **143c** indicated fast rotation at ambient temperature. Decoalescence of the ^{13}C signals occurred at moderately low temperature, corresponding to free energy barriers of 12.4 and 13.0 kcal/mol, respectively. The lower barrier in **143b** than in **143a** is explained by ground-state strain, and in **143c** the rotation is facilitated by the donor effect of the methoxy group. Unlike the nonafulvene analogs **60**, X = Li, **143a** to **c** show almost identical NMR spectra after addition of HMPT.

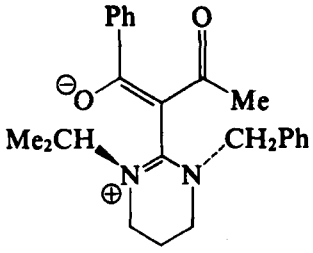
Thus, the enolates **143b** and **c** (and probably also **143a**) are intermediate in behavior between true enolates like **62** and the acyl-[9]annulene anions **61** (in solvent separated ion pairs). This order is well documented by MNDO calculations.

Resolution of two chiral twisted push–pull ethylenes, **144** and **145**, has been performed by chromatography on triacetylcellulose (209). The barriers obtained by thermal racemization in ethanol agree well with those found by NMR band-shape technique, taking the positive $\Delta S^{\ddagger}$ and the difference in solvent into account (Tables 17 and 22).

The electrochemical reduction and oxidation reactions of bistricyclic ethylenes



144
$\Delta G^{\ddagger}_{342.7} = 26.2$ kcal/mol



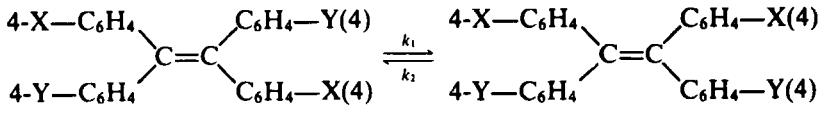
145
$\Delta G^{\ddagger}_{330.9} = 25.6$ kcal/mol

have evoked considerable interest. It has been found that the radical ions and di-ions derived from biacridylidenes and bianthronylidenes prefer a twisted conformation analogous to the *B* form. On reduction of the cationic forms or on oxidation of the anionic forms, the neutral compounds are initially formed in the *B* conformation, and the rate of transformation $B \rightarrow A$ and the $A \rightleftharpoons B$ equilibrium can be studied. Olsen and Evans (210) and Hammerich and Parker (211) have studied the bianthronylidene system **129c**. The first group worked at 21 ± 1°C and obtained $k_{B \rightarrow A} = 2.2$ sec^{-1} and $k_{A \rightarrow B} = 8.1 \times 10^{-3}$ sec^{-1}, corresponding to $\Delta G^{\ddagger} = 16.7$ kcal/mol ($B \rightarrow A$) and 20.0 kcal/mol ($A \rightarrow B$). Hammerich and Parker worked over a temperature interval and found the Arrhenius activation parameters $E_a = 15.3$ and 18.1 kcal/mol for $B \rightarrow A$ and $A \rightarrow B$, respectively, with $\log A = 11.7$ for both processes. This corresponds to $\Delta S^{\ddagger} = -7$ e.u., in good agreement with the data for the racemization of a series of optically active biphenyls (212).

Ahlberg, Hammerich, and Parker (213) also studied the 10,10′-dimethylbiacridylidene system (**129b**, R = Me) and found E_a ($B \rightarrow A$) = 16.4 kcal/mol.

Neta and Evans (214) studied the anion radicals of some bianthronylidenes. The anion radical was prepared in the $A^{\cdot}$ form by pulse radiolysis in 2-propanol, and its conversion to $B^{\cdot}$ was followed by fast spectrophotometric technique. The rate was determined at 21°C for **129c**, its 3,3′-dimethyl, 3,3′-dimethoxy, and 1,1′-dimethyl analogs, and free energy barriers of 10.6, 10.6, 11.5, and 13.1 kcal/mole, respectively, were found, which were considerably lower than that for the $B \rightarrow A$ conversion in the neutral molecules.

Leigh and Arnold (215) have studied the rates of thermal $E \rightleftharpoons Z$ isomerization in *p*-substituted tetraphenylethylenes (**146a** to **d**). From their rate data, $\Delta G^{\ddagger}_{479}$ ($Z \rightarrow E$) can be calculated to be 37.6, 37.3, and 37.1 kcal/mol for **146a**, **146b**, and **146c**, respectively, and 36.1 kcal/mol for **146d**. The $\log(k_1 + k_2)$ values for the three first compounds correlate well with $\sigma^{\cdot}$ constants designed to reproduce stabilization of benzyl radicals, but the point for **146d** lies well off the line, indicating an extra stabilization of the diradical transition state. This effect

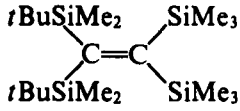


E *Z*

146a, X = H, Y = Me
b, X = H, Y = MeO
c, X = H, Y = CN
d, X = MeO, Y = CN

is rationalized by the authors with reference to the so-called merostabilization (216) or capto-dative stabilization (217), proposed by several groups to explain the unusual stability of radicals carrying both donor and acceptor substituents.

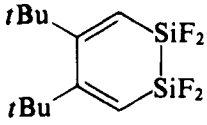
Sakurai et al. (218) obtained the highly strained ethylene **147** as an unexpected



147

product in the reaction between 1,2-bis(bromodimethylsilyl)-1.2-bis-(trimethylsilyl)ethylene and *t*BuLi. An X-ray crystallographic study gave an R(C=C) value of 137.0 pm and a dihedral angle of 49.6° between the two (strictly planar) C(sp^2) planes. This is the most strongly twisted system studied so far outside the group of push–pull systems.

The possible role of the silicon atom in stabilizing twisted C=C bonds is further illustrated by an X-ray crystallographic study of **148** (219), which displays one C=C bond of 134.5 pm with a twist of 24° and one of 138.8 pm with a twist of 17°.

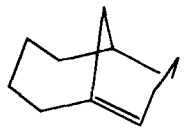


148

Maier and Schleyer (220) have studied the problem of the stability of bridge-head double bonds in bi- and polycyclic systems. They define an olefinic strain (OS) as the difference in strain energy between the olefin and its parent saturated

hydrocarbon, both in their most stable conformation. The authors have calculated the energies of a large number of structures, using the Allinger MM1 force field, and after comparison with experimental data they come to the prediction that bridgehead olefins should be isolable when OS $\leq$ 17 kcal/mol, observable when 17 kcal/mol $\leq$ OS $\leq$ 21 kcal/mol, and unstable (although in many instances possible to trap in chemical reactions) when OS $\geq$ 21 kcal/mol. The rules apply to bridgehead olefins with twisted double bonds but in general not to "zero-bridge olefins," for example **149**, which may be isolable even when OS > 20 kcal/mol. In some highly strained systems, the olefin is found to be "hyper-stable" with OS < 0. Only a borderline case (**150**) with OS = −1.5 kcal/mol

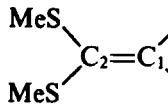
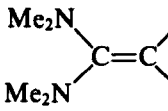
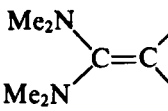
149



150

is known, but others with OS as low as −13 kcal/mole are predicted. The rule suggested by Wiseman (221) according to which an observable bridgehead olefin should have the trans double-bond element in an eight-membered or larger ring is shown to be a necessary though not always sufficient condition.

The X-ray crystallography group in Bangalore has continued to study push–pull ethylenes, and three new structures are now available (222).

	$R(C_1=C_2)$, pm	$R(C_1—X)$, pm	$R(C_2—N)$/ $(C_2—S)$, pm	$\theta°$
	137.6	141.6(C_1—CN) 143.0(C—NO_2)	172.9	12.8
	141.2	143.5(C_1—COMe) 149.1(C_1—Ph)	135.7	34.8
	146.1	144.3(C_1—CO_2Me) 141.3(C_1—COMe)	133.6	58.6

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On Factoring Chirality and Stereoisomerism

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I. PREFACE

The topic of factorization has been discussed by us in several publications (1–3). At first we sought definitions for the three main classes of chirality that had been distinguished by Cahn, Ingold, and Prelog (4) in formulating the Sequence Rule. When one of the authors of the Sequence Rule proposed a fundamental change (5) and thereby challenged relationships that appeared to be generally

accepted, these conflicting views were investigated and the traditional ones found to be valid (3). In this chapter an effort will be made to gather this scattered material into a coherent account and to reexamine the principles of steric classification. The system that has evolved modifies our own earlier proposals and, in contrast to that introduced by Cahn et al., is not limited to classes of stereoisomerism that are chiral in three dimensions. The defining aspects of our primary categories are not symmetry properties (4,5) but bonding relationships that may be to a point, line, or plane. As a result, chiral planes are exemplified by different compounds under the two systems. Emphasis will be on their important differences rather than on details, especially if they were covered before.

II. INTRODUCTION

The impossibility of effecting congruence between a structure and its mirror image has been termed *chirality* (6). It is an all-pervasive property, as it affects all parts of a chiral structure. In chemistry, for example, the relationships of any atom to all others of the same molecule cannot be precisely matched by those of any atom of the enantiomer. As the chirality of the molecule can be deduced most simply and conclusively from a symmetry analysis of the whole, nothing further might seem to be required for a full understanding of the chiral differences in the reactions of molecules with chiral reagents. This holistic view is rather close to the picture revealed to us by Pasteur when he deduced the chiral structure of optically active molecules. His extraordinary insight received an eloquent tribute from Sir Robert Robinson (7) during the centennial honoring van't Hoff and Le Bel. However, it seems that the latter were not given their due when Pasteur was credited also with having had a "clear understanding of internal compensation as in *meso*-tartaric acid." He could indeed distinguish between the racemic mixture of the tartaric acids and the isomer with the achiral structure by noting the chiral or achiral habit of the crystals, but his picture of a meso structure no longer seems appropriate. As a salt of racemic malic acid happened to form achiral crystals, Pasteur mistook the acid for an analog of *meso*-tartaric acid and characterized it as follows: "It is natural malic acid untwisted, if I may so express myself. The natural acid is a spiral stair as regards the arrangement of its atoms, this acid is the same stair made of the same steps, but straight in place of being spiral" (7). The inapt image of the straight stair shows that we must look beyond the achiral facade of the whole if we are to perceive the localized and opposing chiralities of *meso*-tartaric acid. Manifestations of such localized chirality have been reported for a closely related meso compound, erythritol. Its two primary carbinol groups, which are linked to two asymmetric carbon atoms with inverse configurations, are attacked selectively by phosphorylating enzymes. Depending on the sources of these kinases, they yield either (2*R*)- or (2*S*)-erythritol 1-phosphate (8).

The dissection of a molecular model into those components that are deemed to be essential for the understanding of the stereochemistry of the whole may be termed *factorization* (9). The first and most important step toward this goal was taken by van't Hoff and Le Bel when they introduced the concept of the asymmetric carbon atom (10a,11a) and discussed the achiral stereoisomerism of the olefins (10b,11b). We need such factorization not only for the enumeration and description of possible stereoisomers, important as these objectives are, but also, as we have seen, for the understanding of stereoselective reactions. More subtle differences also giving rise to differences in reactivity with chiral reagents, but referable to products of a different factorization, will be taken up in Sect. IX.

III. FACTORING CHIRALITY AS RELATED TO SYMMETRY ELEMENTS OR POINT GROUPS

When the existence of chiral structures containing no asymmetric atoms was reported, their chirality was termed *molecular* (12). This failure to look for the partial structure responsible for the chirality defeats the purpose of factorization. When Kuhn (13) introduced the term *atropisomerism* (isomerism caused by the restriction of "free" rotation of single bonds) to characterize the chiral isomerism of the biphenyls (14) and the cis–trans isomerism of certain terphenyls, he regarded the isomerism of the biphenyls merely as a special case of molecular asymmetry. The same position was taken by Lüttringhaus and Gralheer (15), who found another subclass of atropisomerism in the so-called *ansa* (Latin for "handle") compounds, which are characterized by an aromatic ring with a bridge limited in its orientation to one face of the ring (**4**, Fig. 1). Evidently, the concept of atropisomerism did not signify the localization of chirality in a partial structure and it left the chirality of several types—allenes, **2**; certain spiro compounds; and alkylidenecycloalkanes, **3**—in the undiagnosed category. The common aspect of most of these cases of molecular asymmetry was perceived to be the presence of two rings (with two or more members) in two different planes usually perpendicular to each other (13a).

As these insights did not provide new elements of chirality, it was a signal advance when Cahn, Ingold, and Prelog (16) proposed that the various known types of chirality could be separated into three categories: center, axis, and plane. The universal acclaim given to the Sequence Rule, which utilizes this classification, attests to its practical value. The meaning of these categories was made clear by numerous examples. In addition, Cahn et al. presented a theoretical foundation for their scheme of factoring chirality by pointing out that "three-dimensional space can in principle be occupied asymmetrically about the zero-, one-, or two-dimensional elements of symmetry, that is the point (or centre), the line (or axis), and the plane." In their main paper (4) on the specification

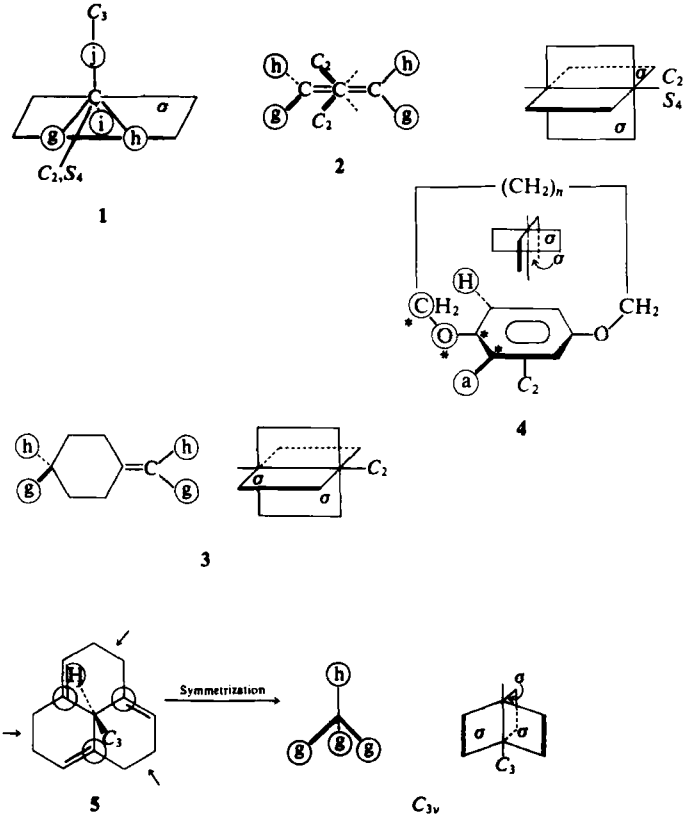


Figure 1. Examples of five point groups and their symmetry elements (19): **1**, T_d, if g = h = i = j (only one of each kind of symmetry element is shown); chiral if g ≠ h ≠ i ≠ j. **2**, D_{2d}, if g = h; chiral, if g ≠ h. **3**, C_{2v}, if g = h; chiral if g ≠ h. **4**, a = H: circled simplex C_s with σ through the two oxygen atoms, but C_{2v} for complete figure; a ≠ H: chiral. The aromatic ring is the symmetry plane desymmetrized by bridging according to ref. 4; * = tetrahedron described according to Sequence Rule. **5**, Chiral; symmetrization is either by ring cleavage (arrows) or by hydrogenation. The circles define the vertices of each tetrahedron.

of molecular chirality they introduced another category, the helix. It was to be used mainly (but not exclusively) to characterize chiral conformations, and was thought to be applicable also to cases of axial as well as planar chirality if the difference between the sterically distinct structures was regarded as conformational rather than configurational. The biphenyls were cited as examples for such alternative factorization of axes and the bridged aromatic rings for that of planes.

The meaning of the defining phrases for the axis and the plane of chirality were now clarified by stating (4) that "the axis of chirality is derived by de-

symmetrization from a four-fold alternating axis of symmetry: that is its fundamental property" and that a plane of chirality "must be derived by desymmetrization of a plane of symmetry." There was no comparable statement about the point and none can be made because the regular tetrahedron (**1**, Fig. 1) from which the asymmetric carbon atom can be thought to be derived by desymmetrization lacks a center of symmetry. Instead, the desymmetrization of methane, which results in the chiral distribution of ligands about a point, abolishes planes and fourfold alternating axes. If it is carried out stepwise, the last element of reflective symmetry to disappear is the plane; the same is true if allene (**2**, g = h = H) is converted stepwise into a chiral structure. If the chiral axis of a substituted methylenecyclohexane (**3**) is derived by desymmetrization of the parent compound, the line about which the ligands can be thought to be chirally distributed is not an alternating but a twofold proper axis, the product of the intersection of two mirror planes. It appears, therefore, that the link between the classification of the chirality types and the elements of reflective symmetry is tenuous at best.

These relationships were never used for true definitions of the three types of chirality and they are no longer mentioned in Prelog's writings and lectures on this topic (5,17,18). His edifice is now built on the *simplex*, the simplest figure with the dimensions of the appropriate space. In 2-space this is the triangle and in 3-space the tetrahedron. If the points defining tetrahedra are properly chosen and made equivalent, achiral figures result that belong to diverse point groups. Their symmetry properties were made (18) the basis of a classification of the steric elements by deriving the center from a tetrahedron with T_d or C_{3v} symmetry, the axis from one belonging to point group D_{2d} or C_{2v}, and the plane from the C_s tetrahedron (19) (Fig. 1—no example of a C_{3v} derived center was provided).

It is easy enough to recognize the T_d symmetry of methane or the D_{2d} symmetry of allene and to appreciate that the tetrahedra formed by their hydrogen atoms would become chiral figures if these atoms were replaced by dissimilar ones. The symmetry classes express the degree of diversification that is required to achieve chirality. Prelog and his co-workers (5,17,18) have generally proceeded from known achiral reference frames to chiral figures by desymmetrization. However, if symmetry properties are to serve as the basis of classification one must also be able to determine them by starting with the chiral compound. This operation presents a number of problems.

Its crucial first step is the selection of the four points that constitute the chiral figure to be symmetrized. The chirality of example **6** (Fig. 2) can be defined by more than one tetrahedron. When examined with all ring atoms in a plane, as is customary, one can find a center of chirality at C(4'), an axis coincident with the extracyclic double bond and extending to C(4'), or a plane containing the ring and rendered chiral by the extraplanar location of the hydroxyl group. To avoid the ambiguity of such classifications, Cahn et al. (4) proposed a priority

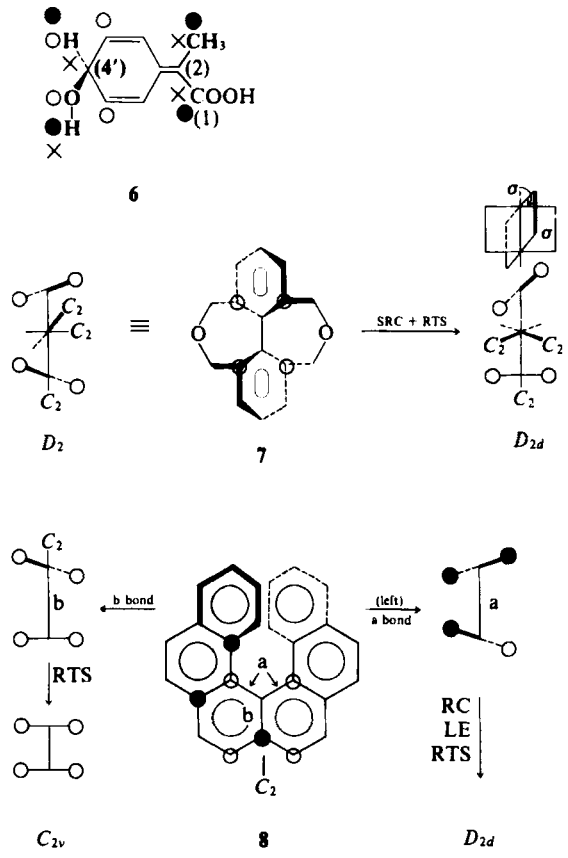
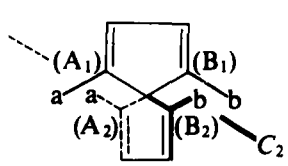


Figure 2. Alternative modes of factorization. *Key:* RC, ring cleavage; SRC, symmetrical ring cleavage; RTS, release of torsional strain; LE, ligand equalization. By their appropriate equalization in **6**, ● vertices yield a C_{2v} tetrahedron; ○, T_d; ×, C_s. For nonequivalence of all ○ vertices of **6**, see Sect. IV.B.

order termed the *factorization rule*, which stipulates that centers are to be considered first, axes next, and then planes, as far as necessary. According to this rule, **6** ought to be classed as having a chiral center. Nevertheless, related chiral alkylidenecyclohexanes were consistently treated (17a,17b,20a) as chiral axes. No justification has been given for this violation (20b) of the factorization rule (4) but possible reasons for this preference are discussed in Sect. VII. It appears that factorization as currently practiced is determined in some instances more by expedience or tradition than geometry.

After having selected a set of four points one needs to define the permissible and necessary changes that are to be made during the symmetrization of the

chiral simplex. No rule has been given. If one symmetrizes **9** by making a = b, the structure becomes achiral and the four ligands of the spiro center are now equal. If one went further and subjected **9** also to a symmetrical cleavage of the rings, one would destroy an essential difference between the centers of **9** and of **1**, namely the degree of ligand diversification that is required for chirality. The difference a ≠ b suffices for **9** but we need four distinct ligands for **1**. There is a similar dependence of the chirality of **5** (4,17) on having the rings



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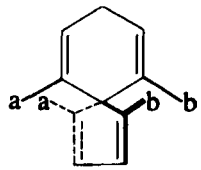
D_{2d} if a = b



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C_{2v} if a = b

intact. It derives not from a difference between the three ring ligands but from the chiral placement of the double bonds, which is possible only because the center of **5** participates in three rings. However, such procedures for obtaining the achiral simplex would present a problem. Whereas the symmetrization of **5** with ring preservation results in a simplex with C_{3v} symmetry, a class that was regarded (18) as characteristic of a center, the simplex of **9** on analogous treatment would acquire D_{2d} symmetry, the same as allene. This point group would change to C_{2v} if one of the rings is enlarged (**10**). Finally, Cahn et al. (4) have regarded a structure as a center of chirality that can only be symmetrized into a C_s simplex (as will be discussed in Sect. VI). By following apparently suitable procedures we have arrived at an obviously unsatisfactory position. We have associated the center with all of the five symmetry categories that were supposed to be used in differentiating the three elements of chirality.

Prelog and Helmchen (5) suggested that the chiral simplex be viewed as an achiral framework that is made chiral by differences between ligands. In order to obtain such a frame from the chiral figure, we have to equalize bond lengths and bond angles. This idealization has a tradition that dates back to van't Hoff and is implied in determining the number of stereoisomers by symmetry analysis (21). Unfortunately, not every chiral simplex can be examined in this manner (5). The chirality of a rigid molecule of hydrogen peroxide cannot be attributed to an achiral frame occupied by different ligands and the interconversion of the enantiomers can be effected only by torsion and not by a permutation. Under these circumstances one must ask whether a classification based on geometry can permit such drastic adjustments of torsional angles as would be required if compounds **7** and **8** are to be treated like ordinary biphenyls (4,16). The chirality

of dioxepin **7** (22), can be attributed to the chiral placement of the $—CH_2OCH_2—$ bridges, but not to any difference between these ligands. They hold the aromatic rings at a dihedral angle of about 45°. If one thus views the dioxepin as a derivative of a tetrahedron with D_{2d} symmetry, the geometric description is purely formal and inapplicable to the actual compound, which has a frame with D_2 symmetry (22). There is even less justification for avoiding the use of a chiral frame when the chirality depends on it as it does in **8**, hexahelicene (23). Cahn et al. have treated it either as a case of axial chirality (16) or as a helix with an unoccupied axis through the center of the molecule and perpendicular to its C_2 axis (4). The axial chirality was located in either one of the two equivalent bonds marked *a*. With this choice, the ligands at either end of the axis are unequal, and the isomerism was viewed as that of a bridged biphenyl. However, the nonequivalence of the ligands is not an essential aspect of the case, because we can derive axial chirality also by choosing as its axis the bond (*b*) coincident with the symmetry axis. If we make this structure achiral by removing the two terminal rings that are responsible for the overcrowding, the axis is no longer twisted. The four points off the axis that define a chiral tetrahedron in hexahelicene collapse into a tetragon with C_{2v} symmetry, which, of course, is no simplex.

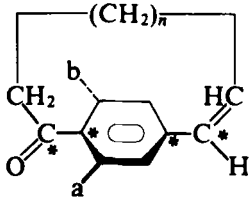
The new description of the chiral plane (5) differs in two respects from the previous one (4). The symmetry plane that characterizes the C_s simplex (5) of a dioxaparacyclophane (**4**), in the words of Cahn et al. (4), is not a natural plane of the molecule. It is perpendicular to rather than coincident with the plane from which the plane of chirality was to be derived by desymmetrization (4). Moreover, the tetrahedron chosen by Cahn et al. for describing the sense of chirality of a chiral plane is not identical with the one now used (5) to define such a plane. Finally, the very fact that we are allowed to choose only four points in defining the simplex can result in a figure with lesser symmetry than the one from which the four points were selected. For example, structure **4** (a = H) belongs to point group C_{2v}, whereas the single tetrahedron chosen (5) to represent it has only C_s symmetry. This disparity can lead to complications that were mentioned in discussing examples 33 and 34 of ref. 1.

Presenting these various problems does not imply that they cannot be solved. Rather, it indicates that more work will be required before we have an adequate theory of factorization that is based on the symmetry of the simplex. It is a matter of individual judgment whether the advantages to be gained in pursuing this objective warrant the effort, or whether we should adopt another approach. This alternative scheme (Sect. IV), which primarily factors stereoisomerism rather than chirality, avoids ambiguity without recourse to a factorization rule, requires no symmetrization by the equalization of ligands, and is not restricted to the simplex.

IV. AN ALTERNATIVE SCHEME

A. Centers and Lines of Stereoisomerism

The closely related structures **11** to **13** indicate the direction one might take in modifying the classification developed by Cahn et al. (4). According to their factorization rule, **11** contains two chiral axes and **12** a plane (left) and an axis. There are two chiral axes in **13** if the unshared electrons of each nitrogen atom are recognized as the equivalent of a bond. If they are not, the elements become



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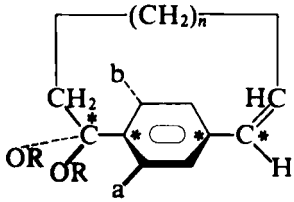

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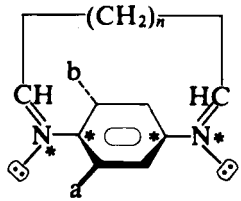

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one or, more appropriately (1), two chiral planes. Although these distinctions can be unambiguously defined (1,24) they seem to be artificial and unnecessary. This notion would even find some support in the work of Cahn et al. (4), because they made faulty (24) classifications of their structures 53 and 55. In the days of Kuhn and Lüttringhaus all three structures (**11,12,13**) would have been regarded as examples of atropisomerism. This unifying idea can be fashioned into a linear element of isomerism with sufficient scope to accommodate all cases of "molecular asymmetry" and even other forms of stereoisomerism.

When we say that the enantiomers of Cghij can be interconverted by the permutation of a pair of ligands, we are not, or at least ought not to be, concerned about whether such an operation is a feasible process of chemistry. Similarly we must not regard an operation that alters the relative positions of the ligands attached to the two ends of a line as anything more than a geometric concept. The magnitude of the force that resists such a twist or even the utter impossibility of carrying it out ought to be of no concern. The structure that maintains the integrity of the line can, therefore, be taken to be unaffected. Consequently, there is no need to retain the original view (13) that atropisomerism ought to pertain only to single bonds (25a). The idea of torsion as now defined is equally applicable to allenes or even to situations where the line of torsion does not coincide with any bond (if this should become desirable or necessary). Such a conceptual torsion would allow not only unlimited stretching and bending of bonds but even their severance and re-formation through the original orbitals,

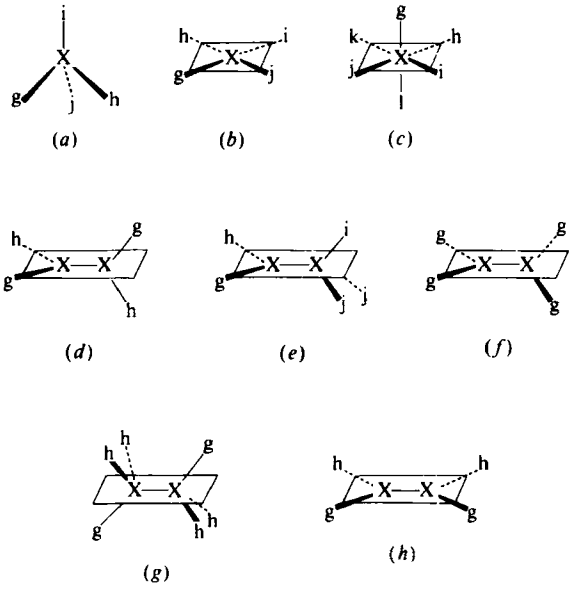


Figure 3. Some major types of centers (X) and lines (X—X) of stereoisomerism. Different degrees of ligand diversity are possible for most of these types.

if this is the only way one can prevent the formation of knots. This permissiveness pertains only to the transition between the isomers. These, of course, must have the same pattern of connectedness (constitution) and represent realizable structures.

It is evident that **11**, **12**, and **13** can all be converted into their enantiomers by conceptual torsions about the bonds that link the starred atoms. The success of the operation does not depend on the number of ligands that are attached to these atoms, which constitute the terminal atoms of the lines of torsion (Fig. 3*d*, *e*, henceforth types d and e). Similarly, there is no place in this scheme for any restriction on dihedral angles; a conceptual torsion can interconvert the stereoisomers of hexahelicene (**8**) or of dioxepin (**7**) (both type f, Fig. 3*f*) as readily as those of ordinary biphenyls (type d) with their perpendicular orientation of the rings. No idealization is required.

This proposal, which was outlined in 1971 (1) as an alternative to the Cahn–Ingold–Prelog scheme of factorization, does more than combine the plane and the axis into a single class. There is no longer a need for having the conformational helix as a separate category to account for the steric differences between rotamers, such as the three staggered forms of butane (type g). Finally, the conceptual torsion about the line allows the interconversion of isomers also if all ligands affected lie in the same plane, as do the cis or trans related ligands of the carbon–

carbon double bond (type h). As the olefins ordinarily are achiral, it is evident that we are no longer factoring three-dimensional chirality but stereoisomerism.

Consistency requires that we reexamine the chiral center and define a more general concept, the center of stereoisomerism. If we do not depend on tetrahedral structures in characterizing a line of stereoisomerism, we ought not to require them for the center. Therefore, we shall have no restriction on the number or relative disposition of ligands that are joined to the center: It may be tetrahedral (type a), tetragonal (type b), octahedral (type c), or of any other type. Such centers of stereoisomerism too can be chiral or achiral. This can be determined most readily if we always examine the center as a whole. According to the Prelog scheme of factorization, this is permissible only if the ligands form a simplex, as they do in the case of the tetrahedral center. If they do not, the structure needs to be factored into the component simplexes. As an octahedron would have to be regarded as the composite of 12 tetrahedra, this approach seems anything but simple. This problem was mentioned (17c), but no solution has been presented.

To make our definitions as discriminating as possible, we have made them more restrictive than those given earlier (1). An atom represents a *center of stereoisomerism* if a permutation of two of its ligands can yield a stereoisomer that can be distinguished from the original compound if we know the identities of all its ligands and the locations of all their points of attachment (26). If four or more distinct ligands are linked to a center, an exchange of any two of them yields an isomer that can be distinguished from the original structure in the manner specified. If there are only three distinct ligands attached to a ligating center that lies in the plane of its three bonds, it may still be possible to produce an isomer by a ligand exchange. However, we need to know more than the positions of the three ligands to characterize the isomers. Such a center, therefore, is not a center of stereoisomerism as we have defined it. For example, fumaric acid yields maleic acid by a permutation of the H and COOH ligands that are attached to the same olefinic carbon. If we place its three ligands, —H, —COOH, and =CHCOOH, at three appropriate and defined positions in space, we cannot predict whether the figure will represent fumaric or maleic acid. We must complement the figure with a second ligand triangle around the other unsaturated carbon atom. This converts the two ligating centers with three ligands each into a line with two terminal atoms to which four ligands are attached. The isomerism is fully defined if one knows their relative positions and it can be expressed as the result of a π torsion about the ligating line. The case of the isomeric allenes is analogous: A torsion about the line connecting the three unsaturated atoms generates the isomer, which is defined by specifying the torsional angle ($\pm\pi/2$). In general, the second element is the *line of stereoisomerism* that exists if a stereoisomer is generated by a conceptual torsion of the ligands attached to the terminal atoms of a line occupied by bonds.

By presenting a scheme of factorization that gives primacy to stereoisomerism rather than to chirality, a major difference from the Prelog–Helmchen proposals (5) has evolved. They advanced the thesis that all stereoisomerism can be presented as being explicable by chiral differences. In this view the isomerism of the olefins ought to be factored further into that of the two trigonal atoms that are chiral in two dimensions. If one locks fumaric acid into a plane coincident with the symmetry plane of the molecule, one can determine whether the triangle formed by the olefinic carbon and its singly bonded ligands (5) has a clockwise (*Re*) or counterclockwise (*Si*) sequence if the three points have a stipulated order of priority (27a). The olefinic carbon is a chiral permutation center in two dimensions because the order is reversed if we exchange the —H and —COOH ligands as in going from fumaric to maleic acid. However, as Prelog and Helmchen point out, chirality in two dimensions vanishes in 3-space because the added dimension allows one to turn over the triangle. This would revert the order for any given triangle but it would not alter the observation that the sequences for two such triangles occupying the same plane are in the same or in the opposite direction.

Prelog and Helmchen suggested that two-dimensional chirality has a significance that goes beyond its contribution to theoretical stereochemistry when they made a statement to this effect: Although the two-dimensional enantiomorphism and enantiomerism (''orientation'') are lost in 3-space, the two-dimensional chirality (''orientability'' in 2-space) plays an essential role for the steric course of reactions on heterogeneous or enzymatic surfaces. This claim seems excessive. Chirality in two dimensions can be considered a condition for steric discrimination in an addition reaction, but it plays no role in directing its steric course. This follows from the fact that one cannot specify which way a substrate has to be locked into a plane unless one knows whether the enzyme (or a defined portion thereof) lies to the front or to the rear of this plane. On the contrary, the steric course of such enzymatic reactions is determined by three-dimensional transition states such as those involved in the formation of the substrate–enzyme complex, in its change to the product–enzyme complex, and in the dissociation of the latter. The trigonal atom binds on its *Re* or *Si* face to the enzyme and it acquires its addendum on its *Re* or *Si* face. These too are three-dimensional concepts because the face of a plane requires an extraplanar point for its definition (27b). As to proper factorization, there is no choice. An olefin with four distinct ligands has four stereoisomers in two dimensions but only two in three-dimensional space. If our results are to be valid in three dimensions, we must admit the existence of achiral elements of stereoisomerism. A trigonal atom is not an element of describable isomerism in three dimensions.

The primacy given by the Prelog school to chirality over stereoisomerism is equally evident when we examine a catalog (17c) that shows various types of ligands occupying the vertices of a regular tetrahedron. The ligands were either

alike or different, chiral or achiral, and so on. The resulting 39 entries were divided into two classes—chiral and achiral—according to their symmetry, and into two subclasses comprising those that are or are not permutation centers. For example, a carbon center with two identical achiral ligands and with one distinct achiral and one chiral ligand [Cgghi$^+$ in our terminology and C(AABF) in that preferred by Prelog, his entry 13] was classed as a chiral model. This designation requires clarification. If it merely signifies that the central carbon does not lie in a symmetry plane, the classification is, of course, unobjectionable. However, it could mean a great deal more. The ligated center also signifies a complete compound, and if it were inferred that such a compound must be chiral, the conclusion would not be valid in all cases. For instance, C(2) of citric acid has a ligand —C(OH)(COOH)CH_2COOH, which is chiral as it lacks a plane of symmetry. However, the molecule has a plane of symmetry that bisects C(3) rather than C(2). Finally, the characterization of Cgghi$^+$ as a chiral model could be interpreted to mean that its central carbon is a center of chirality. If we judged a ligated assembly to be an element of chirality simply because one or more of its ligands are chiral, we would fail to factor chirality. Our objective must be to separate such "imported" chirality from the chiral or achiral character of the distribution of ligands about the elements to which they are attached. Prelog's scheme of factorization fails to make this distinction.

B. Ligands

Before we can develop a procedure that would allow us to achieve such separation, we must make certain that the meaning of the term *ligand* as we shall be using it is precisely understood. Historically, various views have been expressed concerning the constitution of ring ligands (1). If ligands are to be compared, they must have a boundary, and if they are subject to permutation, the boundary of a unidentate ligand (i.e., one joined by only one bond) must separate the ligating center from its nearest neighbor in the ligand, the *proximal atom*. This statement does not imply that ligands must always be examined after their separation from the ligating element. We must study them in situ if we wish to ascertain whether two ligands can be distinguished experimentally (30,31). According to a nomenclature introduced by Mislow and Raban (31), the in situ analysis reveals the *topic relationships* between ligands. For example, the two hydrogens of the methylene group of ethanol which lie across its symmetry plane are enantiotopic (Sect. IX) and, therefore, distinct. The chiral reagent alcohol dehydrogenase recognizes this difference. However, it is irrelevant if we exchange the hydrogens. The entities permuted are the ligands in isolation, and as these can be superposed, the permutation leaves the structure unchanged. Separated ligands are complete objects and hence can be compared by procedures

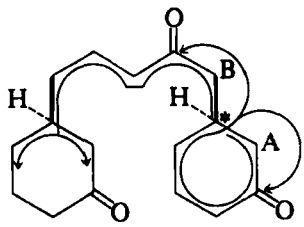
applicable to molecules. Such comparison reveals their *morphic relationships*. Pairs of ligands thus can be described as *homomorphic* (3) if they can be superposed in isolation (like the two methylene hydrogens of ethanol) and as *heteromorphic* if they cannot. Among the latter, the subclass (32) most important to us comprises those heteromorphic groups that can be superposed in isolation by a reflection. Such ligands are enantiomorphic. They can be enantiotopic like the CHOHCOOH groups of an achiral isomer of trihydroxyglutaric acid (**20a**), but they need not be; the same groups are diastereotopic (31) in the 3-(*R*)-lactate of the same acid (**20c**). If ambiguity is to be avoided, a strict distinction between topic and morphic comparisons must be made. Insistence on this point (3) does not prejudge at all which property ought to be used in defining a chiral center.

Our delineation of a ligand requires amplification if the ligand is joined to the ligating element through more than one bond. The need for defining additional boundaries for such ligands is evident if we consider the case of 3-oxocyclohexanol. The carbinol carbon is a center of stereoisomerism, because we obtain the enantiomer by exchanging its —H and —OH ligands. If four unidentate ligands are joined to a tetrahedral center of stereoisomerism, it does not matter which pair is chosen for the exchange operation. To retain the generality of this observation, we ought to define ring ligands in such a way that they provide additional opportunities for an exchange. They do if the additional bond or bonds that connect a ring ligand to the ligating element are made the site of additional boundaries. If we thus break the ring bonds at C(1) of 3-oxocyclohexanol and reconnect the ring in the alternative way, we again obtain the enantiomer. This shows in addition, if proof is needed, that C(2) and C(6) are not equivalent. We can express this fact by regarding either one of these methylene carbons as the proximal atom and the remaining one as the distal atom. This distinction furnishes two ligands. Their morphic relationship can be determined if it is borne in mind that a proximal atom can only be superposed on a proximal atom. The ring ligands differ in constitution because the keto group is either adjacent to or distant from the respective proximal atom. Thus C(1) with four distinct ligands can be represented by the center of stereoisomerism Cghij. A less obvious case is 4-methylcyclohexanol. The ring ligands of C(1) possess no symmetry plane if we regard the proximal and distal end of each as nonsuperposable. They are enantiomorphic, as they can be superposed only by reflection. If we orient them so that their proximal atoms are on top, the methyl appears either on the right or on the left in a Fischer projection. This is a definable difference although the Sequence Rule (4) makes no provision for expressing it. The ligating carbon [C(1)] is a center of stereoisomerism of the type $Cg^{+}g^{-}hi$. The same description would apply to C(4).

The two ring ligands of C(4′) in **6** have the same constitution but cannot be superposed even after a reflection. They are, therefore, diastereomorphic, and as both have a plane of symmetry, the center is of the type Cghij. As expected,

the enantiomer is produced on exchanging two ligands. Because a given proximal ring atom of this center is either cis or trans to the carboxyl group, the diastereomorphic difference results from the presence of a second element of stereoisomerism, the line occupied by the exocyclic double bond. The ring ligands attached to it are enantiomorphic and their torsion about the line again produces the enantiomer. The line, therefore, can be diagnosed to be of the type $g^+g^-C{=}Chi$. The chiral difference between the g ligands and therefore the isomerism of the double bond depends on the presence of the chiral center C(4′). The general problem of mutual interdependence between two steric elements encountered in this and the preceding example will be examined in Sect. VII.

It is not always recognized that the ligands that are being explored under the Sequence Rule can differ widely from those just defined. The rule provides (4) that the comparative exploration of ligands is carried out in situ and does not terminate before a difference is encountered. In order to determine the configuration of the starred center of **14**, one has to establish the priorities of the ligands starting at A and B. Their explorations (arrows) have traversed identical sequences of atoms when the branch points (CH) are reached. Both branches at the starred CH contain carbonyl groups but there is only one in the branches associated with the other ring. Therefore, before it can be shown that the ligand starting at A is to be preferred, its exploration must enter the ligand commencing at B. It is evident that such partially overlapping ligands cannot be permuted and do not provide a suitable model for a generally applicable definition of ligand.



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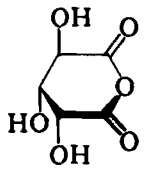


15

The essential role of our concept of ligand in the proper functioning of the Sequence Rule becomes apparent on examining an example taken from the paper by Cahn et al. (4). The authors state that C(3) of their anhydride 25 (**15**) "is symmetric, as in the free acid, and hence receives no label." Both molecules lack symmetry beyond the trivial and ubiquitous one of C_1. The center of C(3) of the anhydride is symmetric only in the sense that it is not linked to four different ligands and therefore is not an asymmetric carbon atom as defined by van't Hoff. However, this observation can be made only if the ring ligands are viewed as open-chain structures, as we are defining them, because only these

are the same. If, on the contrary, ring ligands were explored under the Sequence Rule, a cis–trans difference would have to be recognized as soon as the exploration returns to the ligating center. This example also illustrates our point that the factoring of stereoisomerism is the basic operation that ought to precede the determination of the chiral or achiral character of any partial structure. The center C(3) ought not to receive a label because it is of the type Cg^+g^+hi, which is not a center of stereoisomerism.

C. Graphochirality and Pherochirality

The steps taken thus far are quite conventional. We defined ligands consonant with their role in permutations and examined them (in isolation from the ligating center or from the two terminal atoms of the line of stereoisomerism) to determine (*a*) whether they contained a plane of symmetry and (*b*) whether they could be superposed on each other either as such or after a reflection. This allowed reducing the great diversity of molecular models to relatively few types of steric elements virtually without loss of relevant information (33). If all ligands are achiral, nothing further is required: As the spatial representation of the center Cghij is altered by a reflection, the configuration of this center of stereoisomerism must be chiral. However, we cannot stop at this stage if one or more of the ligands are chiral and if, as was stated before, we wish to distinguish between a chiral distribution of ligands about the ligating element, and the chiral character of the ligands themselves. To make this separation we shall replace all ligands by achiral points. These points will be placed at the sites of the proximal atoms and they are to be regarded as distinct if the ligands that they represent are heteromorphic. To distinguish the two modes of representation, we shall characterize the differentiated points by capital letters. These letters will be identical if the ligands are homomorphic, but different if they are not. An enantiomorphic difference between ligands is to be treated like any other.

With the aid of such a transcription we can test for the chirality of a distribution in two different ways. One can ask whether the figure consisting of the ligating element and its differentiated proximal atoms is chiral. If it lacks reflective symmetry, a second distribution of the proximal atoms must exist that can be distinguished from the first (without comparison to another chiral element in the same molecule) only by a chiral descriptor. We have called such a configuration *graphochiral*, from the Greek *graphein*, to write, to describe a geometric figure (2). One encounters it whenever four distinct proximal atoms are tetrahedrally distributed. This is the case with C(2) of glyceraldehyde [Cghij → X(ABCD)], C(3) of achiral trihydroxyglutaric acid [Cg^+g^-hi → X(ABCD)], and the C═C═C line of the allene ghC═C═Cij [→(AB)X—X(CD)]. In contrast, if the proximal atoms are tetragonally distributed about a center or line that lies within the same plane, the figure is achiral. No chiral descriptor can be used to differentiate the

isomers because any sequence of proximal atoms that appears to be clockwise when seen from one side of the plane is counterclockwise from the other. The configuration is *agraphochiral*. Simple examples are the cis–trans isomerism of the olefins like ghC=Cij and the diastereomerism of the three forms of tetragonal Xghij.

A tetrahedral center of the type Cghij possesses a second chiral attribute: It changes configuration on reflection. We deduce this from the fact that the original assembly of proximal atoms, X(ABCD), cannot be superposed on X(BACD), which is derived from the structure of the mirror image. In these transcriptions homomorphic ligands are represented by the same capital letter. If this form of examination seems unduly cumbersome, its value will become apparent as soon as we examine cases with different complements of ligands before and after reflection. By using the same capital letter for proximal atoms that are presumed to correspond, we still can determine retention of configuration by a superposition test (see, e.g., Fig. 5).

This response of tetrahedral Cghij to reflection is in contrast to that of its tetragonal counterpart Xghij, which retains its configuration. These characteristics of the tetradentate centers were termed *pherochiral* (2) and *apherochiral* [from the Greek *pherein*, "to bear, to cause" (2)] to express the fact that a compound is chiral if it contains a pherochiral element of stereoisomerism (that cannot be paired within the same molecule with another whose ligands can be superposed on those of the first after a reflection). We thus find that Xghij is both graphochiral and pherochiral if the center is tetrahedral; and agraphochiral and apherochiral if the center is tetragonal.

There would be little justification for distinguishing these two manifestations of the chirality of steric elements if there were no exceptions to this parallelism. These are observed if the four distinct ligands include an enantiomorphic pair. We thus find that the graphochiral center of $Cg^{+}g^{-}hi$ is apherochiral because we can superpose the center and its proximal atoms on the corresponding figure obtained by reflection. This is impossible in tetragonal $Xg^{+}g^{-}hi$ if the g ligands occupy adjacent positions. Such a center is pherochiral but agraphochiral. To simplify expressing these dual descriptions, elements that are both graphochiral and pherochiral will be classed as (fully) chiral and those that are neither as (fully) achiral, with *fully* used only if these categories are being contrasted to elements characterized by incomplete chirality. The latter can be referred to as *only graphochiral* or *only pherochiral*. They may be encountered also if the stereoisomerism is with respect to a line; thus, that of the allene $g^{+}g^{-}C{=}C{=}Chi$ is only graphochiral and of the olefin $g^{+}g^{-}C{=}Chi$ only pherochiral.

The new terms, which ought to be used for characterization of steric elements only and not of compounds, permit several generalizations. Any chiral molecule for which all elements of stereoisomerism have been determined must contain at least one that is pherochiral. A compound must be chiral if the total number

of its pherochiral elements is odd. If the number is even (and greater than zero), the compound is also chiral unless two of its pherochiral elements meet the superposition test stated earlier. An illustration of such internal compensation is provided by any meso compound. There can be no element of stereoisomerism that is only pherochiral unless the molecule contains at least one element that is fully chiral. One can therefore deduce that the fully chiral elements play an indispensable role in the chirality of all chiral molecules. This observation, however, ought not to obscure the equally crucial role of elements that are only pherochiral. If one permutes the ligands of tetragonal $Xg^{+}g^{-}hi$ so that the g ligands are shifted from adjacent to diagonal positions, the X center of stereoisomerism changes from being only pherochiral to fully achiral and the molecule ceases to be chiral.

The fourfold classification of the elements of stereoisomerism addresses problems of long standing. Van't Hoff (10a,b) recognized a fundamental difference between the isomerism of the asymmetric carbon atom and that of the olefins. This difference was later expressed by the terms *optical* and *geometrical* (34a). This division was widely adopted although it was recognized (34b,c,e) that there was no sharp and convincing delineation in certain cases. The definition of diastereomers was similarly ambiguous as long as the term was restricted (34f,g) to stereoisomers representative of optical isomerism. This consequence could be corrected because a clear-cut and far more useful classification of stereoisomers resulted from broadening the definition of diastereomers to encompass all stereoisomers that are not enantiomers (25c,34d). The division of stereoisomerism into optical and geometrical then fell into disuse. However, sharp distinctions can be obtained also if one characterizes not stereoisomerism, (i.e., the common property of a whole family of compounds linked by a common constitution), but the elements of stereoisomerism, in individual compounds. Thus the differentiation between elements that are fully chiral and fully achiral (which we are presenting) occasions no overlap but preserves much of the basic idea of the old division into optical and geometrical isomerism. The peculiarities of the elements that are only graphochiral or only pherochiral also attracted attention long ago and led to distinctive names, which, however, did not disclose their complementary characteristics. Thus the isomerism of the pherochiral olefin was termed *geometrical enantiomorphic* (34h) and C(3) of achiral trihydroxyglutaric acid (**20a**) was called a *pseudoasymmetric* atom. The ideas but not the terms embodied in our description of the latter as *graphochiral but apherochiral* were anticipated when Cahn et al. (4,16) provided for it a special set of chiral descriptors (*r/s*) with the distinctive property of being invariant to reflection.

Prelog and Helmchen (5) defined pseudoasymmetry as the duality resulting from the two ways with which one can combine two enantiomorphic ligands with two enantiotopic spaces (Fig. 4). This represents an innovation because it limits pseudoasymmetry to achiral compounds (35). This follows from the fact that enantiotopic spaces can exist only if the molecule possesses an element of

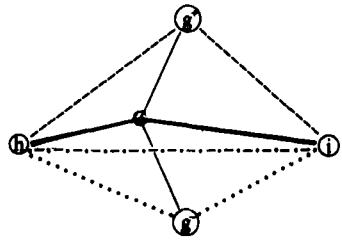


Figure 4. The Prelog–Helmchen definition of pseudoasymmetry. If an alphabetical priority order and an *R* configuration for g^+ are assumed, the *R* ligand is on the *Si* side of the triangle g^-hi (···) and the *S* ligand is on the *Re* side of the triangle g^+hi (---). These spaces are enantiotopic because they are interconverted by reflection in the symmetry plane defined by the points C, h, and i. On permuting the g ligands the association R_{Si},S_{Re} (corresponding to the *s* configuration) is changed to R_{Re},S_{Si} (*r*).

reflective symmetry such as a plane. However, like Cahn et al., Prelog and Helmchen evidently intended to retain the significance of the distinction between *R* and *r*, because they made a statement to the effect that their descriptors of the permutation centers that they regarded as chiral always changed on reflection, whereas those of their pseudoasymmetric atoms did not. We do not dispute the claim if phrased in this manner, but we do question the validity of their criterion for determining retention of configuration on reflection. The compounds involved in this dispute are not of major importance, but it would seem to be a major issue of stereochemistry whether it requires arbitrary assumptions to define "retention of configuration on reflection." To answer this question one must ascertain whether more than one system exists that is free of contradictions. The results presented in the next section have convinced us that this is not the case, but even if it were so, as has been claimed, a preference can still be expressed for the system that affords the greatest economy of thought (38).

V. RETENTION OF CONFIGURATION ON REFLECTION—DIVERGENT VIEWS

In the cases discussed thus far, the complements of ligands did not change on reflection because any that were chiral occurred in enantiomorphic pairs and all others were achiral. Therefore, the issue of retention can be settled by a direct superposition test and no dispute is possible about the result. If, however, the center is ligated with a chiral ligand as in $Cghij^+$, it will change to $Cghij^-$ on reflection. If we wish to compare the configurations, we need to decide whether j^- is to be regarded as the equivalent of the j^+ ligand or of any other of the first set. If anybody should regard this as an unanswerable question he or she would be unable to factor the chirality of a chiral molecule that contains more than one

element of stereoisomerism. Thus the enantiomers of ribose would allow no comparison of the configurations of C(2), C(4) (both $Cghij^+$), or C(3) ($Cghi^+j^+$). However, as far as we are aware, no dissent has ever been expressed from the view that the configurations can be compared and are inverted because any nonpaired chiral ligand corresponds to its enantiomorph in the reflected model, or, to put it differently, because such chirality differences can be ignored in superposing the proximal atoms. In our procedure for ascertaining retention of configuration, they are therefore to be characterized by the same capital letters. Obviously the chirality differences of the enantiomorphically paired ligands of Cg^+g^-hi cannot be similarly ignored, as their sign of chirality is their sole mark of distinction. Although the reflection again converts the g^+ ligand into the g^- ligand and vice versa, we have regarded as corresponding ligands in this conversion those having the same sign of chirality. It is the only conceivable correlation in the case of Cg^+g^-hi; if it were reversed, we would have to deduce that an inversion of configuration occurred on reflection, although the center of the reflected molecule is indistinguishable from the same center in the original. These examples demonstrate that not all chiral ligands can be treated in a uniform way when one tests for retention of configuration on reflection. We have generalized from these simple cases and formulated the following correspondence rule: In comparing the configurations of steric elements before and after reflection, ligands correspond if they are homomorphic, and any that cannot be matched in this manner, if they are enantiomorphic. The consequences of this procedure will be examined in Sects. V-A and V-B. The rule was in accord with general practices (39) when first stated (1) and has not led to any contradictions. If it is followed, the configuration of $Cg^+g^-hi^+$ (**16a**) is retained on reflection (Fig. 5). This conclusion was challenged by Prelog and Helmchen (5), who postulated that enantiomorphic ligands in diastereotopic positions must be treated differently from those that are enantiotopic; the former correspond in the reflection test if they have opposite configurations. According to this rule, the center of $Cg^+g^-hi^+$ is not pseudoasymmetric but chiral (Fig. 5).

A. Main Test Cases: A Tetragonal Center and the Pherochiral Olefin

This altered rule (5) appears to be the only plausible remaining alternative to our correspondence rule. It was justified (40) by the fact that the g^+ ligand in $Cg^+g^-hi^+$ gives rise to the same NMR signals as the g^- of the enantiomer. There is no need to dispute the relevance of this observation because the revised rule of correspondence allows a reductio ad absurdum. A test case is possible if the enantiomorphic ligands are adjacent in the tetragonal center Xg^+g^-hi (**17a**, Fig. 5). Since such g ligands are diastereotopic, the altered (5) correspondence rule would apply, which stipulates that the g^+ ligand of the original structure (**17a**) corresponds to the g^- of the enantiomer (**17b**). Again, the corresponding ligands would have identical NMR signals. With these correlations, superposition would be possible and would signify that the configuration of X has been retained. This

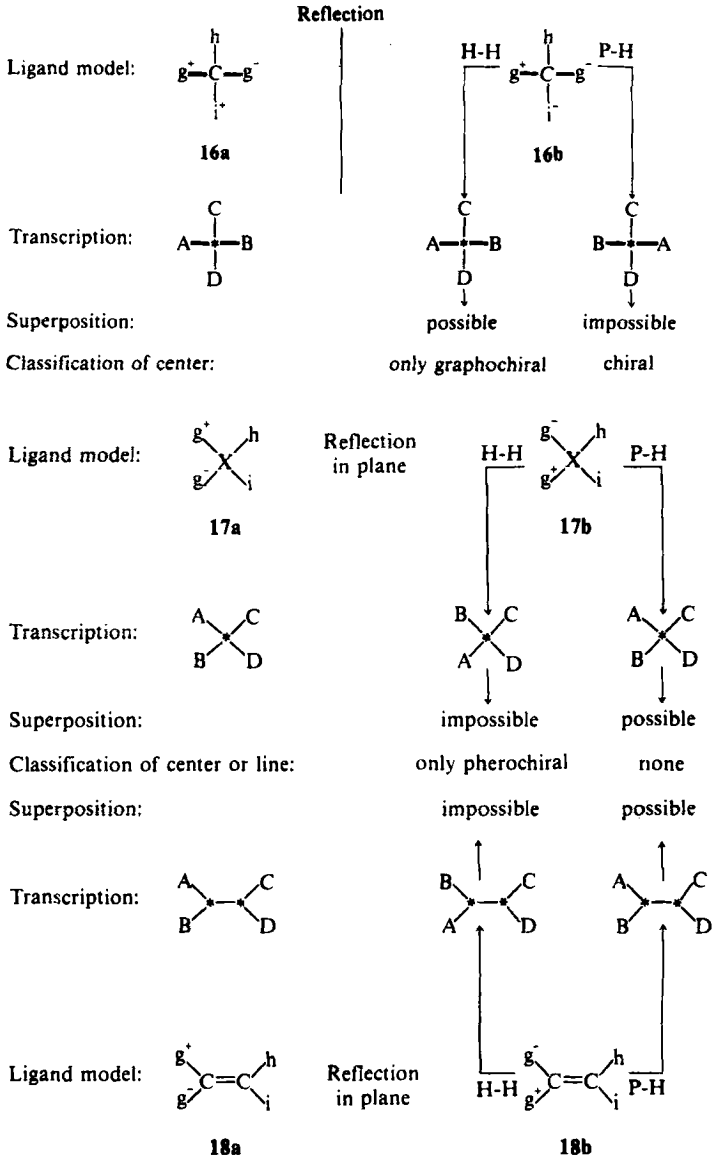
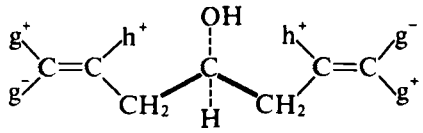


Figure 5. Comparison of configurations of enantiomers according to different rules of correspondence between proximal atoms (A to D). The rule marked H-H is the traditional one as defined by us (1), the one marked P-H is that of Prelog and Helmchen (5). The planes of reflection of **17** and **18** coincide with the molecular planes.

is impossible, as the reflection that has created the enantiomer has caused as the only change an altered distribution of the same four ligands about X. Compounds of this type are known. The first example, a planar coordination compound of platinum, was resolved in 1935 by Mills and Quibell (41). Analogous arguments apply to the geometrically related olefin $g^+g^-C{=}Chi$ (**18**, Fig. 5).

It appears that this anomalous situation was created deliberately. Prelog and Helmchen did not discuss planar centers but they prescribed the configurational description of pherochiral olefins. The *R* and *S* descriptors of their enantiomorphic ligands are to receive subscripts, *Z* or *E*, which would indicate whether a given ligand is cis or trans to the preferred ligand (4) at the other end of the double bond. Therefore, one isomer of the olefin would be described as R_Z, S_E, its enantiomer as S_Z, R_E. As the chiral ligand in the so-called *Z* position was given (5,40) priority over the other, it was assured that the double bond would be *Z* (42) for both isomers, in conformity with our finding that the altered rule for correspondence of enantiomorphic ligands makes it appear as if the configuration of the pherochiral double bond were invariant to reflection. This represents a major change. In the case under discussion (**18**), the terms *Z* and *E* have lost their accepted roles as descriptors of the configurations of double bonds and have become topic descriptors, that is, specifications of the locations of groups within a molecule.

It seems pertinent to ask why the stereoisomerism of pherochiral olefins, in contrast to that of the others, was denied a descriptor of configuration. Soon after the publication of the Sequence Rule (4), it became evident that on rare occasions the rule generated descriptors that were anomalous in the sense that some failed to change on reflection although the centers were indubitably chiral, whereas others changed although the centers were regarded as pseudoasymmetric (1). A pertinent example of an anomaly of the first kind is shown in **19**. Its



19

central atom is chiral because all four ligands are different, and no two are enantiomorphic ($Cijk^+l^-$). (In deriving descriptors for this center it will be assumed that g^+ and h^+ indicate ligands with the *R* configuration and that h has priority over CH_2.) Under the rules of 1966 (4), the configuration of the center has to be determined under Subrule 3 (*seqcis* > *seqtrans*). As the preferred configuration of the double bond is found on the left side, the center is *S*. This assignment is not altered by reflection, as the net change is confined to a conversion of the h^+ to h^- ligands. The revised analysis of the double bonds of

19—which treats them as if both had the same configuration (see earlier)—prevents the application of Subrule 3 and shifts the evaluation to Subrule 4 (like > unlike). This rule finds its pairs in the descriptors of the h ligands and those of the g ligands that are in the preferred Z position, R_Z on the left and S_Z on the right. As the like pair shifts sides on reflection, the old anomaly is removed but at the cost of creating the new one of having to regard the configuration of a double bond as unchanged when this is contrary to fact.

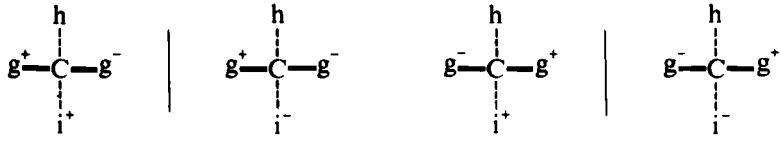
We believe that this cost need not be borne. Unquestionably, cis and trans are scalar differences that cannot interchange on reflection. However, this statement applies to ligands that are distinguished as *seqcis* and *seqtrans* only if their identities are not interchanged by the reflection. (The concepts expressed by cis and *seqcis* are not synonymous.) The ligands are interchanged if the cis–trans relationships prevail between a preferred ligand and both members of an enantiomorphic pair, as in **19**. We have proposed (3) to distinguish the configurations of such double bonds by two new descriptors, *seqCis–seqTrans*, which interchange on reflection. As these terms describe enantiomorphic and not diastereomorphic differences, they may be used under Subrule 5, as members of like or unlike pairs under Subrule 4, but not under Subrule 3. This suggested nothing more novel for the pherochiral double bond than the determination by Cahn et al. that the (apherochiral) characteristics of the pseudoasymmetric atom called for descriptors and subrules different from those applicable to the fully chiral tetrahedral center. The proposal by Blackwood et al. (42) to express the *seqcis* configuration of a double bond by the symbol Z led us to suggest (37) that Z^{Φ} (from ϕ, Greek phi, for pherochiral) be used to signify *seqCis* and that Z^{Φ} and R be considered as like pairs (3). With these minor changes of the Sequence Rule, the configuration of the central carbon of **19** is S (like pair, Z^{Φ} and R on left) and changes to R on reflection (like pair E^{Φ} and S). Again the old anomaly is corrected, but no new one is generated. The other types of anomalous descriptions involving enantiomorphic ligands were observed when these groups were located in a ring. These anomalies, too, could be traced to an inappropriate application of Subrule 3, and they can be prevented by the use of the new *seqCis–seqTrans* descriptors (3).

B. Further Test Cases: Tetrahedral Centers

The remaining cases reclassified by Prelog and Helmchen are tetrahedral centers with four distinct ligands, of which two and only two are enantiomorphic ligands in diastereotopic positions (as in **16a**, Fig. 5). These centers were originally regarded as pseudoasymmetric (39), and had received descriptors that did not change on reflection. Therefore, no anomaly had to be corrected. When these centers were reclassified as chiral (5), the Sequence Rule was also modified:

The descriptors of the enantiomorphic ligands received subscripts derived from their topic characteristics (for examples, see subsequent discussion) with the result that the new descriptors of their ligating centers did change on reflection ($R \rightleftarrows S$). As a descriptor of a center should be in conformity with its character rather than vice versa, this appropriate response to a symmetry operation can hardly be taken as evidence for the validity of the reclassification, especially as the same concordance prevailed before the revision. Evidently it was carried out for the sake of consistency with the cases already discussed. As we had to reject the use of topic descriptors for the determination of configurations in situations where it could be rigorously tested, it hardly seems necessary to argue further against their general use for this purpose. To follow this course, however, would unduly restrict one's perception of the diverse disturbing implications of the Prelog–Helmchen proposal.

If the enantiomorphic ligands are rendered diastereotopic by the presence of another chiral ligand, its configuration is to provide the topic subscript (5). In the (*R*)-lactate (**20c**) of achiral trihydroxyglutaric acid, the descriptor of C(2) (*R*) becomes R_R and that of C(4) S_R. As the parts of the composite descriptor of C(2) are like, and those of C(4) unlike, C(3) is assigned (5) the *R* configuration, which changes to *S* on reflection, because the subscripts will now be *S*. With these interrelationships it becomes impossible to specify the spatial distribution of the four ligands g^+, g^-, h, and $i^{\pm}$ attached to a carbon center described (5) as being *R* unless one knows the configuration of i. Such dependence is called a *relative configuration*. According to Prelog–Helmchen, the configuration of the center of any isomer of **16** is inverted on reflection. As the reference chirality in this assessment is also inverted, the absolute configuration of the central atom must have remained unchanged.



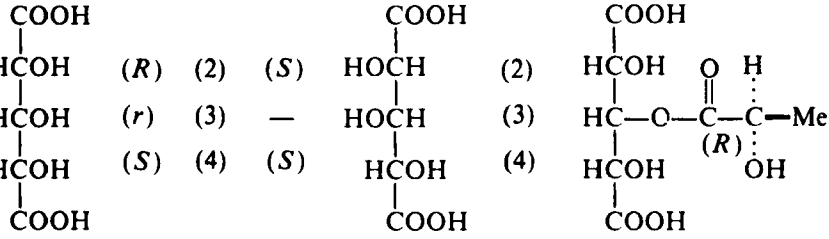
16a **16b** **16c** **16d**

The appropriateness and essence of this distinction between absolute and relative configuration in this case may be illustrated by a hypothetical experiment. By definition, the determination of an absolute configuration involves a comparison with a fixed reference standard. Such a standard may be simulated by an enzyme that can discriminate between the isomers **16a** and **16c**, which differ in the configuration of the central atom. If the reacting isomer **16a** is represented by (2*R*,3*r*,4*S*)-2,4-dihydroxy-3-((*R*)-[2-^{2}H]-propionoxy)glutaric acid, it can be predicted with confidence that the enzyme will also react with the enantiomer

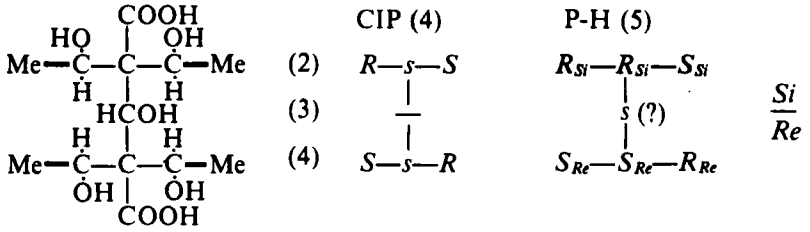
16b but not with **16d**, which according to Prelog–Helmchen has the same configuration at the central atom as **16a.**

Structures **16a** and **16b** are related not only by reflection but also by the exchange $i^+ \rightleftarrows i^-$. As this would leave three bonds undisturbed, the exchange constitutes a substitution with retention of configuration. It was termed *homofaciality* by Ruch (43), and corresponds to a retention of configuration upon reflection according to our rules, but not according to those of Prelog and Helmchen. Unquestionably, one cannot construct a system that would place all carbon centers that are mutually related by substitution with retention of configuration into a single class that could be regarded as having the same configuration (16). However, no ambiguity of correlation is encountered if the only compounds to be compared are enantiomers and if the reactions that interconnect them are limited to the necessary substitutions of enantiomorphic ligands. For example, if the enantiomer of $Cghi^+j^+$ is obtained by the substitutions of i^+ by i^- and of j^+ by j^-, one and only one of these reactions and, therefore, the complete conversion must entail an inversion. This comparison between the configurations of the enantiomers is in full accord with the generally accepted classification of the ligating carbon as a chiral center. Ideally, the results of a comparison of configuration should be independent of the operation, reflection or substitution. This aim is reached for all tetrahedral centers if our proposals are adopted, but it is not under the rules of Prelog and Helmchen. In the absence of demonstrated advantages of their scheme, the exceptions encountered with compounds of type **16** seem to constitute an unwarranted complication.

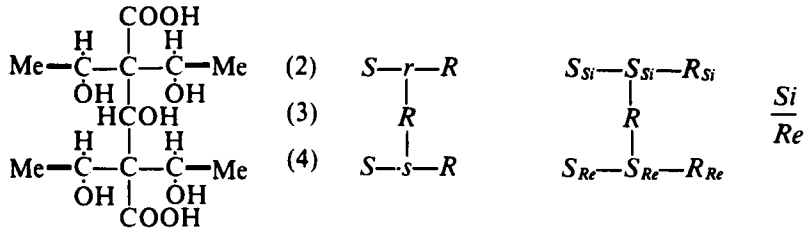
If elements of stereoisomerism occur in a pair of unidentate ligands with the same constitution, the descriptors of their configurations ought to be able to inform us whether the ligands are homomorphic or not, so that we can judge whether a permutation can produce a stereoisomer. It is transparent that (2*R*,4*S*)-trihydroxyglutaric acid can yield a stereoisomer on permutation at C(3), whereas the 2*R*,4*R* isomer cannot. This situation prevails if **20c** is named according to Prelog–Helmchen, because the R_R ligand receives a description different from that of the S_R ligand. However, when they described C(3) as *R*, the result is, as we have seen, the composite of topic and morphic descriptions, and such scrambled information may no longer allow us to recognize homo- (**21a**) and heteromorphic (**21b**) ligands from their descriptions. Although these examples are necessarily somewhat complex, their configurations are easily determined under traditional procedures. Those of C(2) and C(4) in **21a** do not change on reflection and are identical. Their common descriptor, therefore, should be that of a pseudoasymmetric atom (*s*). This is in accord with the facts that these centers lie across a mirror plane and that an exchange of ligands at C(3) yields no isomer; C(3) receives no descriptor. The *R* and *S* ligands of C(2) [and of C(4)] are diastereotopic. If the revised rules (5) apply, C(2) and C(4) are to be classed as chiral, and topic descriptors must be used to determine the priorities of their



20a **20b** **20c**



21a



21b

Only those *Re*/*Si* subscripts are shown that would be needed (3) to derive the configurations of the central atoms of **21a** and **21b** according to Prelog and Helmchen (5).

ligands. The topic descriptor must be common to both enantiomorphic ligands of C(2) to make their relationship diasteric. It can be derived from the fact that C(2) lies in the *Si* space of the three other ligands of C(3): C(4), H, and OH. Hence C(2) is R_{Si}. Analogous reasoning would provide the *Re* subscript for the enantiomorphic ligands of C(4), and the S_{Re} designation for C(4) itself. This result agrees with the expectation that centers classed as chiral should have opposite configurations if they lie across a mirror plane, but it seems utterly misleading to find different descriptions for the two homomorphic ligands at C(3). Its characterization by its ligands R_{Si} and S_{Re} is the same as that of C(3)

in **20a**. This pair of descriptors was stated (5) to be synonymous with the *s* descriptor of pseudoasymmetry. However, we find no such correlation even in simple cases (R_{Si},S_{Re} corresponds to *s* if the priorities are as in Fig. 4 but to 3*r* in **20a**). Moreover, as observed in discussing **15** (Sect. IV-B), ligating centers should receive configurational labels only if they are centers of stereoisomerism. This holds for C(3) of **20a** but not of **21a**. A second meso isomer (a pseudoenantiomer; ref. 36) of **21a** does exist, but it results from an exchange of ligands at the two pseudoasymmetric centers (1), C(2) and C(4), and not from one at C(3).

If one alters **21a** by exchanging ligands only at C(2), the branched ligands of C(3) become diastereomorphic (**21b**), but this is not evident from their description under Prelog–Helmchen rules. As the *Re* and *Si* spaces of **21b** are located as before, the permutation at C(2) has changed its configuration to *S*, the same as that of C(4). Nevertheless, an exchange of ligands at C(3) that places the 2*S* ligand into the *Re* space and the 4*S* ligand into the *Si* space yields the 2*R*,4*R* isomer, which is the enantiomer. All this is in striking contrast to another compound with 2*S* and 4*S* centers, the corresponding trihydroxyglutaric acid (**20b**), which fails to give an isomer on permutation at C(3). The common designations, 2*S* and 4*S*, given (5) to the ligands of these two compounds completely obscure the fact that only one (**21b**) requires a label for C(3). This false analogy is exposed if C(2) and C(4) of **21b** receive their traditional designations (2*r* and 4*s*).

C. Conclusion

It is evident that the various incongruities in determining the configurations of tetrahedral atoms can be avoided if such descriptions are based on the intrinsic properties of the ligands without regard to their steric environments. The need for such a restriction was recognized by Cahn et al. (4) in one specific instance when, in discussing the cyclitols, they stated that "the geometrical characters, now denoted by *seqcis* and *seqtrans*, are internal to either group A or A′, and do not describe a relation of such a group to some other group of the complete set AA′bc." A general self-consistent system for factoring chirality requires that ligands be compared by morphic and not by topic criteria to assess whether a configuration is retained on reflection. Accordingly, ligands correspond in this test if they can be superposed in isolation; if there are ligands that cannot be so matched, these correspond if they are mirror images of each other.

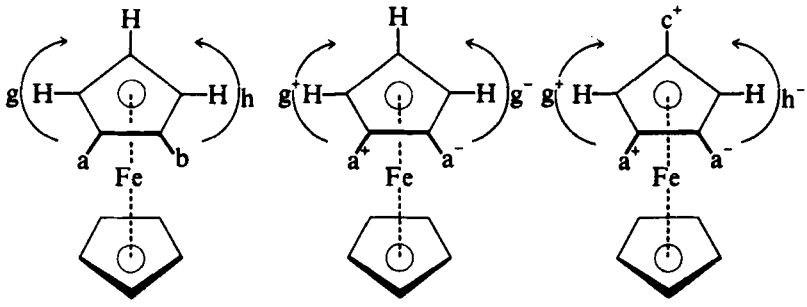
In order to apply this rule we had to transform the original three-dimensional structural formula in two stages (Fig. 5). In the first, the ligand model, the sequences of atoms constituting the ligands of an element of stereoisomerism

were replaced by symbols indicative of the homo- or heteromorphic relationships between the ligands, as well as of their chiral–achiral character. In the second stage, the transcription, we ignored the latter distinction and provided a uniform set of symbols (signifying achiral points) that were different for any ligands that could be morphically distinguished (33). The transcription was subjected to two superposition tests, the first on its own mirror image and the second on the transcription derived from the enantiomeric compound according to the correspondence rule just stated. The first test revealed the graphochiral, the second the pherochiral, properties of the element. As both required the use of the transcription, it seemed proper to regard it as an analytical expression of the configuration. We said so previously (1) and have found it satisfactory in most cases. However, the pherochiral olefin of **18** presents a problem that we feel can no longer be ignored.

The transcription of **18a** results in the planar cyclic sequence (ABDC), which is diasterically related to that derived from the enantiomer (ABCD). Although this observation is in accord with the fact that the reflection is equivalent to a diastereotopic permutation of the actual ligands, it seems paradoxical to deduce a diasteric relationship between the configurations of two lines of stereoisomerism that are mirror images of each other. Examination showed that this conclusion would result from a use of the transcription for which it was not designed, and which is improper if the complement of ligands includes an enantiomorphic pair. If we are determining whether two configurations agree, we are subjecting them to a superposition test of the first kind (i.e., one that does not involve reflection). As we have seen, this test when applied to enantiomers should be conducted with the transcriptions. However, if we wish to ascertain whether two *distinct* configurations are mirror images of each other, we require a superposition test of the second kind. As this operation converts every chiral ligand into its enantiomorph, the chiral character of the difference between enantiomorphic ligands can no longer be disregarded. It is preserved in the ligand model but not in the transcription. Hence, no single space model can reveal all pertinent attributes of such a configuration. We need the transcription to establish that the configuration of the double bond in $g^{+}g^{-}C{=}Ch^{+}i$ changes on reflection, but we need the ligand model to show that this change is an inversion. The use of the ligand model ensures that this is always the case if a configuration is found to be altered by reflection. The association of configuration with both models sets the goals for its proper description. The specification of fully chiral or only pherochiral configurations must include binary descriptors that are interchanged on reflection. In the case of **18a** and **18b** this objective was met with the introduction (3) of *seqCis* and *seqTrans*. These descriptors were derived from both types of models and express the agraphochiral and pherochiral character of and the enantiosteric relationship between the two configurations.

VI. PLANES OF STEREOISOMERISM

The elements of stereoisomerism considered thus far consist of a point occupied by an atom and a line wholly occupied by one or more bonds. The ligands are joined directly to these elements. This emphasis on bonding relationships appears to be proper, as the distinction between constitutional and steric isomerism similarly depends on established patterns of connectedness. From this point of view it seems less than satisfactory if direct connectedness between specific atoms is assumed, when chemical theory envisions no such localized bond. This situation prevails in the description of π complexes such as the metallocenes. Initially (44a), the 1,2- (**22**) or 1,3-heteroligated ferrocenes were considered to



22 **23a** **23b**

be chiral planes, but this mode of factorization was abandoned when Cahn et al. (4) treated such structures as if there were 10 bonds from the iron atom to the carbon atoms of the two rings. This converted every carbon of the heteroligated ring into a chiral center of stereoisomerism, albeit a most unusual one, because it would lie within a face of the tetrahedron defined by its ligands, and because it would acquire C_s symmetry in the unsubstituted compound. The presumed bonding pattern would be inconsistent with the pronounced aromatic character of the ring and with the ready torsion of the rings about a line connecting the ring centers (44a). Unless one sets the factorization rule (4) aside, the bonding model leaves no choice but to attribute the chirality of **22** to the presence of a decaligated iron atom and of five interrelated chiral carbon centers. If the factorization rule is disregarded and the chirality is taken to be that of a plane as defined in the Sequence Rule (4), we must still postulate the existence of iron carbon bonds because the rule stipulates that the pilot atom be chosen from the "atoms directly bound to atoms in the plane." Recent discoveries (44b) render this steric model even less attractive. Under special circumstances the cyclopentadienyl ring can bond on both faces to metal atoms. Thus one would have to consider each ring carbon atom to be pentaligated in these compounds.

As we have abandoned the concept of the chiral plane proposed by Cahn et al. (4), by viewing their cases of planar chirality (Sec. III) as being chiral with respect to one or more lines (Sec. IV), we are free to adopt a definition of the plane of stereoisomerism that fits the metallocenes and the various other stereoisomeric complexes that can result from π bonding of an unsaturated system such as an olefinic or an aromatic one. This would represent a truly separate category: A *plane of stereoisomerism* is a structure containing a planar moiety with stereoheterotopic faces that is bonded *as an entity* on one face to an extraplanar ligand (or on each face to one of a set of heteromorphic ligands). As it should (4), this definition depends only on the bonding graph and not on the nature of the forces that result in bonding.

The operation that interconverts stereoisomeric planes can be viewed as a π rotation of the plane that breaks the bond(s) between the plane and the extraplanar atom(s) and then restores it (or them) in a sterically different way. The axes of this rotation pass through the center of the unsaturated system. As they are infinite in number (46) they cover the plane and in a sense define it. Although several of these axes coincide with bonds, the operation differs profoundly from that characteristic of a line of torsion. Rotation of the plane causes a change in bonding, whereas torsion about a line alters the torsional angles between the ligands that are attached to the terminal atoms of the bond that defines the line.

How can one characterize the stereoisomerism of the planes in terms of a ligand structure? The problem posed by the planar component of the complex is analogous to the one we faced when dealing with a bidentate ligand of a tetrahedral center. We explored the ring in both directions and could observe stereoisomerism resulting from an exchange of the two ligands thus created. In the case of the ferrocenes there are no termini in the planar components but on observation from a *fixed* extraplanar point we similarly can examine any ring in a clockwise and a counterclockwise direction and compare the two resulting circular sequences. The π rotation of the planar component about a horizontal axis which we found to yield the stereoisomeric plane must convert any given sequence into one running in the opposite direction but otherwise identical. As the isomerization operation thus exchanges the sequences, they play the role of ligands in this process and can be examined in the same manner. Therefore, if the planar part has a horizontal C_2 axis of symmetry, the clockwise and counterclockwise sequences are homomorphic. This precludes planar stereoisomerism of the complex. If the planar part has a horizontal plane of symmetry, the sequences are achiral. If it has neither a horizontal axis nor a horizontal plane but a vertical symmetry plane, they are enantiomorphic. Consequently, in **22** they are achiral and heteromorphic (g, h), in **23a** enantiomorphic (g^+, g^-), and in **23b** diastereomorphic (g^+, h^-). By combining the two morphic characterizations with their planar arrows (which represent the plane) and by adding the extraplanar ligand, we obtain a three-dimensional figure that allows us to test

the complex for the possibility of stereoisomerism, for graphochirality, and for pherochirality according to the procedures of Sect. IV. All planes of stereoisomerism are graphochiral (**22**, **23**) but they need not be pherochiral (**23a**). The first example of such an apherochiral plane was realized by Goldberg and Bailey (45). As the extraplanar ligand and the two sequences of atoms that constitute the planar component are joined through the intermediacy of the π electrons (44b), and as these are characterized by a nodal plane, we can see in the π electrons the ligating element associated with a plane of stereoisomerism. Although we derived our concept of the plane from compounds with planar ring structures, it is equally applicable to π-bonded olefins, because the substituents of the double bond constitute analogous elliptical sequences that can be classed in the same manner by a symmetry analysis of the whole planar component.

With the inclusion of such compounds, our survey of factorization has progressed beyond those structures that maintain their integrity by linking all their parts through at least one bond between identifiable atoms. As this extension has prompted us too to adopt a tripartite division of the elements of stereoisomerism, we should point to a basic difference from the scheme proposed by Cahn et al. (4). They factored chirality and sought to relate their three categories to three elements of reflective symmetry (the center, fourfold alternating axis, and plane), a relationship that does not seem to be adequately justified. Our primary classification factors stereoisomerism. Its elements are not those of symmetry but are the three geometric elements of three-dimensional space. The three classes differ in the bonding of the ligands, which may be to a point, to a line, or to a plane.

VII. ELEMENTS AND UNITS OF STEREOISOMERISM

The definitions given in Sects. IV and VI are based on a principle that still has to be stated and justified: The process of factorization is terminated only after the smallest entities have been reached that allow a description of the changes that can result from any steric isomerization of a given structure. These entities are the elements of its stereoisomerism. Such a use of the term *elements* is akin to its meaning when chemists speak of elements of matter. Thus an element of stereoisomerism ought to be something that cannot be factored any further.

Our definitions of the stereoisomeric center, line, and plane all stipulate the existence of bonds between the ligating element and its ligands. The exclusive use of these elements limits our analysis to classical stereochemistry and thus does not encompass the so-called topological isomerism (47) of interlocked rings—catenanes (48)—or of knots. As there is no bond between the rings of the catenanes we cannot expect to handle such compounds with a system based on connectedness. At the present stage of development, this limitation in scope

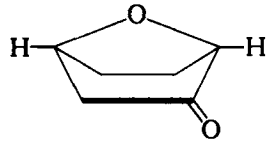
hardly requires justification. It will be assumed as we are examining the merits and demerits of the proposed scheme of factorization.

As far as we could ascertain, such factoring requires no additional elements and no arbitrary choices (49). Moreover, the elements are small in number and easily recognized because the ligands involved in the stereoisomerism must be directly bonded to an atom, or to the atoms at the end of a bond or of a linear sequence of bonds, or to a π system.

These significant benefits must be weighed against two disadvantages. We have encountered elements of stereoisomerism that cannot be characterized by steric descriptors under existing rules (Sect. IV). If it were impossible to meet this problem with altered rules, our factorization would represent a sterile exercise in such cases. We shall show in Sect. VIII that suitable descriptors can be obtained if it were decided that a change of rules would be beneficial. The current lack of descriptors, therefore, should have no bearing on the remaining problem.

It can be argued that the best system for factorization would be one that reduces the number of required descriptors to the minimum. As ours does not always meet this test we should examine whether it ought to be modified. Several circumstances, either by themselves or in combination, can reduce the number of isomers below the number normally associated with a given number of steric elements. Thus 2,3,4-trihydroxyglutaric acid with three centers of stereoisomerism occurs in four rather than eight sterically distinct forms, because this group of compounds has constitutional symmetry. Although a permutation at C(3) of an achiral isomer (**20a**) is equivalent to permutations at both C(2) and C(4), and all isomers of **20a** could thus be obtained by limiting ligand exchanges to C(2) and C(4), we cannot define the difference between the two achiral isomers without specifying the spatial distribution of ligands about C(3). Hence we must recognize three centers of stereoisomerism in **20a**.

A second frequent cause for the reduction of stereoisomers is steric stress. In 1,4-epoxycyclohexan-2-one (**24**) we have two centers of stereoisomerism but



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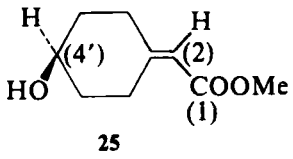
only two isomers. The configurations of C(1) and C(4) cannot be varied independently. If only one of these centers were recognized, its description ought to suffice to deduce the configuration of the other. However, such an elimination requires a choice that is basically arbitrary even if it can be regulated by specific nomenclature such as the Sequence Rule. There would be no need for an arbitrary

selection in a case of configurational interdependence discovered by Glaser, Blount, and Mislow (50). It is a triarylamine, a propeller compound with three distinct mono-ortho-ligated aromatic rings, that allows the existence of 16 torsional isomers. (As the reference plane of the three distinct proximal atoms of the nitrogen has two stereoheterotopic faces, there are two distinct half-spaces, separated by this plane, in which any ortho ligand can be located. The number of isomers ($2^3 = 8$) is doubled because the three rings are not perpendicular to the reference plane but tilted jointly from the vertical by either a positive or negative torsional angle.) The chirality of the structure requires the nitrogen to become pyramidal and to assume a configuration that is determined by the torsional angles. If the sole purpose of factorization were the enumeration and distinction of stereoisomers, the center could be disregarded. However, this is not acceptable because factorization ought to enable us to give a complete steric description of a structure. Thus there is ample precedent for what might be labeled as redundancy in situations where no change in factorization can be justified. (See also the comments of Cahn et al. in ref. 4, page 403, in support of some redundancy in describing configurations.)

A third type of configurational interdependence exists if two elements are so interrelated that a change in the configuration of one automatically alters that of the other. This characterization applies to the two centers of 1,4-cyclohexanediol of the type Cg^+g^-hi (5,51). Consequently only two isomers exist and a single pair of descriptors suffices for their distinction. We can remove the mutual dependence of the two elements by waiving the requirement that a line of stereoisomerism be occupied by bonds. The H and OH ligands have different distributions in the isomers about the line between C(1) and C(4), and the usual terms cis and trans express this relationship. Undoubtedly this is the most convenient description and the only one now available, but should we go further and say that the proper element of stereoisomerism in this case is this achiral line of torsion, and that its further factorization into two graphochiral centers is unwarranted?

The mutually dependent elements of **25** are a pherochiral double bond and a chiral center of steroisomerism. Instead, the isomerism could be viewed as the result of a conceptual torsion of the partially occupied line between C(2) and



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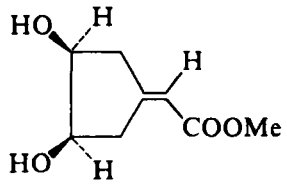

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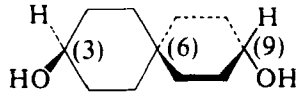
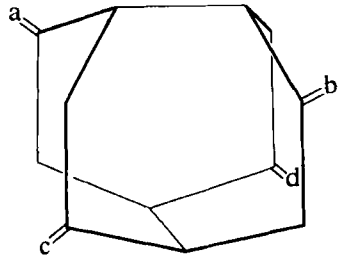
C(4′). The pherochiral character of the double bond of **25** is duplicated in **26**. This analogy might well be recognized by an esterase that distinguishes between the enantiomers of each, but the analogy is lost if only **26** may be factored in this manner. A more complex case is presented by **27**, with three centers of



27

stereoisomerism at C(3), C(6), and C(9) so related that a permutation at any one alters the configurations of the two others. This dependence would be avoided if the isomerism is represented instead by a line of torsion extending from C(3) to C(9). However, this representation would obscure a common property of the spiro atoms of **27** and **9**: An exchange of ligands yields an isomer, an analogy made obvious if both are classed as centers of stereoisomerism.

In contrast to the lines of stereoisomerism described in Sect. IV, these extended lines by themselves do not distinguish between a framework and its ligands. This distinction is needed, as only the latter are twisted against each other. The frames of the extended lines are quite diverse and require individual recognition but can be covered by a single definition (1). In other cases, reducing redundancy requires the introduction of new "elements" of stereoisomerism. Cahn et al. (4) observed that the substitution of adamantane at the four tertiary carbon atoms yields four chiral centers with configurations so interdependent (type 2 dependency) that only a single set of enantiomers exists. The four centers occupy the vertices of a regular tetrahedron whose unoccupied center was classed as a center of chirality (see also ref. 17). This presentation provides a suitable site for the single configurational descriptor required, but it fails to define the ligands to be permuted in the formation of the enantiomer. Their ligating element is not a center but a framework, that of the adamantane skeleton. This view is further supported by considering structure **28** (52).



28

If we regard axial and equatorial cyclohexanol as stereoisomers, we find that they can be interconverted either by a permutation at C(1) or by the joint torsions

of the six ring bonds. If we conduct the permutation by an exchange of the rigid ring ligands, the result is indistinguishable from the joint torsions. This demonstrates the same mutual dependence between the two types of elements as we had observed between those of **25**, **27**, or cyclohexanediol. If this dependence is to be ended also for cyclohexanol, the subsuming element of its isomerism can neither be a point nor a line. Instead it must reflect the altered orientations of a pair of ligands to the sixfold alternating axis of the chair. This is a novel type of permutation. Rings of different sizes would require different constructions for the same purpose.

Even this brief list may suffice to show that it would be a formidable task to develop a system of factorization free of avoidable redundancies, and that such a system would not be satisfactory even if it avoids arbitrary choices. It would require a rule disqualifying certain centers or lines of stereoisomerism on the basis of their relationships to other potential elements in the same molecule. Such definitions would not be self-contained. Moreover, the products of factorization that would take the place of those dropped cannot be limited to points or lines that are merely differently defined. There would have to be a virtually open-ended proliferation of new elements. This highly undesirable feature would not be offset by a major benefit of the revised system such as a correlation between the numbers of elements and of stereoisomers, because a complete elimination of all redundancies does not seem possible. We conclude that the system of choice is the one based on the principle that the elements of stereoisomerism allow no further factoring. Accordingly we think it best to retain the definitions given in Sects. IV and VI and their strictures that all centers and lines be occupied by atoms or bonds.

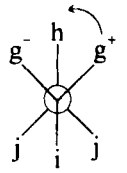
Acceptance of these definitions of the elements does not require that all descriptions of configurations be based on elements. For this purpose it ought to be legitimate to combine them into larger entities if these can be described more simply. We have referred to them as units of stereoisomerism (1) and can point to their use in the distinction of cyclohexanol as axial or equatorial or in the fractional notation for specifying the configurations of the carbon centers of the cyclitols. If the adamantane just discussed is characterized by a single descriptor, the adamantane frame can be viewed as the unit of its stereoisomerism. The selection of appropriate units calls for improvisation and ingenuity, which makes this subject unsuitable for systematic treatment.

VIII. DESCRIPTION

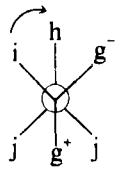
Although the specifics of steric nomenclature are clearly outside the scope of this chapter, a few general principles are closely tied to our subject (53). In Sect. V-C we stressed the need for descriptors that are in proper form. As we

have found it necessary to divide the elements of stereoisomerism into those that are fully chiral, only graphochiral, only pherochiral, and fully achiral, their descriptors are in proper form only if they reflect these characteristics. The main tool in this endeavor has been distinct typography: capital letters for descriptors that changed on reflection and lowercase letters for those that did not so change. The initial introductions were made for graphochiral descriptors: *R/S* and *r/s* (16) for configurations, and *Re/Si* and *re/si* for clockwise–counterclockwise planar sequences (5). This was followed by an application to agraphochiral descriptors by supplementing *seqcis–seqtrans* with *seqCis–seqTrans* (3) (Sect. V). However, if such correspondence between the character of a configuration and its description is to prevail throughout stereonomenclature, further reforms are needed.

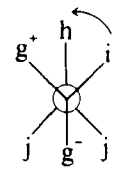
The part of the Sequence Rule (4) that deals with conformations provides terms that are either fully chiral (*M/P* = minus/plus) or fully achiral (*ap/sp* = antiperiplanar/synperiplanar), but none that are suitable if the difference is either only graphochiral or only pherochiral. The torsional difference between **29a** and



29a

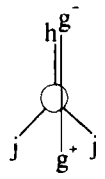


29b

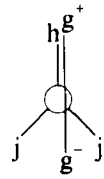


29c

its diastereomer resulting from the exchange $g^+ \rightleftarrows g^-$ is only graphochiral, as neither structure is changed by reflection. To indicate this, the bond shown in **29a** should be described as *m* rather than *M* (54). Its torsional isomers **29b** and **29c** are chiral. In order to describe these we must take note of the principle that descriptors of chiral configurations must not be derived from priorities that would depend solely on enantiomorphic differences such as $R > S$ (55). The difference $g^+ > g^-$ therefore is insufficient to establish either one of these g groups as a preferred unique ligand. Under the Sequence Rule only the i ligand of the frontal carbon is unique and becomes the fiducial group. Therefore **29b** is *P* and **29c** is *M*. This restriction on the use of the preference $g^+ > g^-$ does not apply to **29a**, since its torsional configuration is only graphochiral. It also does not apply to the hypothetical conformations **30a** and **30b**, which are agraphochiral. They



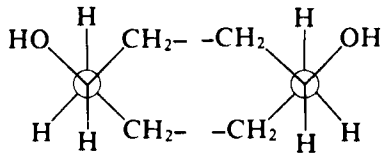
30a



30b

could be distinguished by the new terms *Ap* and *Sp*. These would reflect the pherochiral character of their difference and signify a mirror-image relationship between the descriptors.

According to the Sequence Rule, the 1,2 and 1,6 bonds of equatorial cyclohexanol are both to be described as *ap*. Although this correctly expresses the achiral disposition of the two fiducial groups, the OH at C(1) and the CH_2 at C(2) or C(6), it fails completely in distinguishing between the two bonds (**31a**



31a **31b**

and **31b**), although their distributions of ligands are nonsuperposable mirror images of each other. This objective can be reached if the characterization of such lines of stereoisomerism as *ap* is supplemented by a second descriptor, *ap*(*P*) for **31a** and *ap*(*M*) for **31b**. These terms would designate the torsional relationships that use as their fiducial groups the first- and second-ranking group at C(1) and the unique group at the adjacent carbon atom.

Present rules also can generate anomalous descriptors if tetragonal or octahedral centers are ligated with enantiomorphic ligands. This can be prevented by measures analogous to those just described, namely the appropriate use of capital and lowercase descriptors and restrictions on applying enantiomorphic preferences such as $R > S$.

A second problem that has repeatedly concerned us is the inability of the Sequence Rule to provide descriptors for some elements of stereoisomerism. When Cahn et al. (16) first encountered this problem with the all-cis and all-trans isomers of inositol, they attributed it to the fact that "the symmetry has become so high that they have no asymmetric, nor even a pseudo-asymmetric atom." This interpretation, we believe, is incorrect. If the two ring ligands of any carbon atom of *cis*-inositol were not heteromorphic, their exchange could not yield an isomer, as it clearly does. Each atom is a center of stereoisomerism with a pair of enantiomorphic ligands (Cg^+g^-hi) and indistinguishable from the traditional pseudoasymmetric atom. The description of *cis*-inositol as all-*s* could be accomplished by the same device that would allow one to specify the configurations of C(1) and C(4) of 4-methylcyclohexanol.

On examining this compound (Sect. IV-B), we found an enantiomorphic difference between the ring ligands of C(1). It can be used to derive a priority order for the proximal carbon atoms of C(1). By provisionally assigning them different priorities one can determine which preference order induces the *R*, and which the *S*, configuration at C(4). This induced sense of chirality is mere

scaffolding (compare ref. 4, Sect. 2.4, page 395) and serves only to give final priority to that proximal atom of C(1) that induced the preferred *R* configuration at C(4). This would establish the 1*s* configuration for *cis*-4-methylcyclohexanol. The same procedure is repeated for C(4) without regard for the configuration already established for C(1). We find that the description for the cis isomer (1*s*,4*s*) differs from that for the trans (1*r*,4*r*). Rules based on this idea would also allow us to cope with related cases, such as the configuration of the pherochiral double bond of **25**, of the spiro atom of **27**, the centers (3) of example 22 in ref. 1, or of C(5) of 1,3/5-cyclohexanetriol. A problem of description was also encountered on examining the chiral centers C(3) and C(9) of **27** and C(4′) of **25**. In each of these cases a morphic difference between the ring ligands can be established by noting that one proximal atom is cis and the other trans to a preferred group located *within* the same ligand. By giving priority to the former of these atoms, configurational descriptors can be supplied to the centers. Both extensions of the Sequence Rule are presented not because we believe that they are urgently needed, but to show that decisions on factorization can be based on fundamental considerations rather than on techniques currently available for description.

Cahn et al. (4) thought it beneficial to have two methods available for specifying the sense of chirality of the biaryls, as examples of either axial chirality or conformational chirality. As we have merged both into a single class—the line of stereoisomerism—any justification for two modes of description has vanished. Except for the modifications envisaged earlier, the procedures of Section 4 of the Sequence Rule (4) seem well suited to describe the isomerism of the line. Thus the terms *M*/*P* would become the general descriptors of the chiral line of torsion.

This makes it desirable to have a distinct set of symbols also for the chiral plane. Its description can be accomplished if one specifies which face of the plane is bonded. It seemed that the terms *Re*/*Si* could serve this purpose, but closer examination revealed a logical flaw in this plan. The structures described in Sect. VI are complete chiral objects, whereas the traditional use of *Re*/*Si* (28,29) characterizes, as we shall see (Sect. IX), differences resulting from prostereoisomerism. Hence we still need terms for the chiral plane. As the constellations of the zodiac appear clockwise from the northern and counterclockwise from the southern hemisphere, the symbols *B* (Greek *boreas* for "north") and *N* (Greek *notos* for "south") may deserve consideration for describing the sense of planar chirality, if a more preferred sequence in the plane is clockwise/counterclockwise when seen from the bonded side or from the side bonded to the more preferred ligand. These terms would become *b*/*n* if the configuration is not changed by reflection. Explicit rules for expressing priority orders in a plane are presently available only for the ligands of trigonal atoms (28). However, the desired elaboration for larger planar structures seems to present no serious problem.

IX. STERIC DISCRIMINATION AND THE ELEMENTS OF PROSTEREOISOMERISM

Problems of factorization are not confined to the study of stereoisomerism. They also arise if one is concerned with steric discrimination, which can occur even between homomorphic groups if they cannot be superposed by operations of *gyrosymmetry* (30c). These consist (a) of rigid rotations of the molecular model, (b) of torsions that occur under the conditions of the experiment, and (c) of combinations of both operations. The recognition of this principle (30) called for two kinds of descriptions. One (31) characterizes the mutual relationships between the homomorphic groups. If they can be superposed by an operation of gyrosymmetry, they are called homotopic (30c,56) and are indistinguishable under any conditions. If they are heterotopic, it may be possible to superpose them by an operation of reflective symmetry. Such groups are called enantiotopic (31) and require chiral conditions for their distinction. If they meet neither symmetry criterion, they are either diastereotopic (31) or constitutionally heterotopic (30c) and can be distinguished even under achiral conditions. These concepts are applicable not only to single atoms or interconnected atoms (groups) but also to unshared electron pairs, and to the faces of trigonal atoms or of other planar systems.

The second problem of description derives from the need to identify the individual members of a stereoheterotopic pair. Like the description of isomers, this task requires factorization. Some of the elements involved are those of isomerism. For example, the phosphorylating enzymes that attack either one of the primary hydroxy groups of erythritol (8) differentiate between homomorphic groups that are (indirectly) linked to chiral centers with inverse configurations, C(2) and C(3). This relationship of the primary carbinol groups to the chiral centers suffices for their distinction as, for example, by stereospecific numbering (37). However, we need something more if we wish to identify the hydrogen that is removed stereospecifically by the action of aconitase on citric acid (57). To meet such problems, concepts were introduced that had increasingly wider application: first the meso carbon atom (58), then the prochiral and propseudoasymmetric atom and axis (28), and finally the element of prostereoisomerism (1). We shall not recapitulate these developments but instead consider the most general of these terms in the light of the preceding discussion of the center, line, and plane of stereoisomerism.

An element of prostereoisomerism is a partial structure that can be converted into an element of stereoisomerism not otherwise present, by considering one of a pair of homomorphic groups to be different from the other. The groups involved in this operation are necessarily heterotopic. Depending on the character of the element of stereoisomerism thus produced, one can divide the elements of prostereoisomerism into centers, lines, and planes and subdivide them, as appropriate, into those that are (fully) prochiral, only prographochiral, only

propherochiral, and (fully) proachiral. As these classifications have been reviewed (29), it may suffice to illustrate them by giving a few examples. If we replace the hydrogen of citric acid that is removed by aconitase with an atom that ranks in its priority above the hydrogen but does not differ in its priority relationships to the two other ligands of their common center (e.g., by a deuterium atom), the resulting product is chiral, having chiral centers at C(2) (37) and C(3). These have the 2*R* and 3*R* configurations. Therefore, C(2) and C(3) of the original compound are both prochiral centers, the hydrogen in question may be specified as *pro*-2*R*,3*R*, and the other hydrogen at C(2) as *pro*-2*S*,3*R*. If we similarly replace the hydrogen of propenoic acid that is cis to the carboxyl, we obtain an achiral line of stereoisomerism that has the *Z* configuration. The original compound therefore has a proachiral line of prostereoisomerism and the two hydrogens at C(3) can be distinguished as *pro-Z* (the one cis to the carboxyl) and *pro-E*. Finally, the prochiral plane can be exemplified by a 1,2-homosubstituted ferrocene (45). As unshared electron pairs are often regarded as the equivalents of bonds, an asymmetrically bonded sulfide with two such pairs can be viewed as a prochiral center. The two pairs can be differentiated as *pro-R* and *pro-S*, and can be substituted selectively by a sulfur–oxygen bond in the enzymatic conversion to an optically active sulfoxide (30b).

These developments link all topic distinctions to elements of stereoisomerism or of prostereoisomerism with one important exception: the heterotopic faces of unsaturated planar structures such as double bonds, aromatic rings, or trigonal atoms. If these undergo addition reactions, the face difference can give rise to new stereoisomerism. This is suggestive of prostereoisomerism which we found to be of a novel type. In order to characterize it we shall place two points of observation on opposite sides of the plane, at equal bonding distances from the center of the unsaturated system, and on a line through the center and normal to the plane. To avoid the intrusion of extraneous chirality, we shall assume initially that all substituents of the unsaturated system are achiral. If no distinction is made between the two points, the complete figure is achiral and allows no stereoisomerism other than any already present in the planar part. However, if a preference is given to one of the homomorphic points by making it the sole site of observation, the three-dimensional figure becomes chiral. We can therefore regard the operation of selection (which is equivalent to viewing two potential bonds as if one of these were an actual bond) as an analog to the conceptual diversification of two homomorphic ligands in Cgghi which converts this achiral structure into a chiral center of stereoisomerism. The chiral figure generated from the unsaturated system is isomorphic with a plane of stereoisomerism if the unsaturation to be examined is not confined to a single atom. In this case the structural basis of the face discrimination can be seen in planar prostereoisomerism. If, however, the faces to be distinguished are associated with a single unsaturated atom, its conceptual bonding to an extraplanar point will convert it

into a chiral center of stereoisomerism. It is recognized as such most simply if we allow it to assume the geometry that would result from actual bonding. The discrimination of such heterotopic faces can be attributed to a novel type of central prostereoisomerism. A similarity between ghC=O and ghCii was first recognized by Schwartz and Carter (58).

These concepts can be applied to face discriminations at the olefin ghC=Cij in two different ways. If the unsaturated system is examined as a whole, the prostereoisomerism is that of a prochiral plane. Its enantiotopic faces can be distinguished as *pro-B* and *pro-N* according to the clockwise or counterclockwise direction of a defined priority sequence in the plane when observed from the face under discussion (see Sect. VIII). Conversely, we can study the individual trigonal atoms. Both have nonsuperposable faces (see following paragraph) which can be characterized as *Re* or *Si* (28,29). The planar sequence specified by these terms pertains to the ligands of prochiral centers of prostereoisomerism. Both modes of description have merits of their own. Since additions to the olefinic carbon atoms can proceed from the same or from opposite directions, only the *Re/Si* terminology allows their individual steric descriptions. Furthermore, the faces of the *Z* isomer of ghC=Cgh (maleic acid) are homotopic and cannot be characterized. The C_2 rotation that establishes this fact superposes the upper face of one olefinic carbon on the lower one of the other. However, the upper and lower faces of a single such center cannot be superposed and are enantiotopic. They can be distinguished only as *Re* and *Si*.

The case of hhC=Cgh (propenoic acid) demonstrates that localized face differences of trigonal atoms in open chains ought not to be established by rigid rotations. The molecule lacks a C_2 axis but all we can deduce from this is that the double bond as a whole has two heterotopic faces. In order to examine each trigonal atom individually we must replace the rigid rotation of propenoic acid by a π torsion about its C(2)—C(3) bond. In this test the faces of C(3) can be superposed whereas those of C(2) cannot. Only C(2) is a prochiral trigonal center, a fact equally apparent if we expand the ligands of each center by an extraplanar point. In this situation, recognition of the planar prostereoisomerism contributes further to our understanding. It explains why C(3) of propenoic acid, although not a center of prostereoisomerism, can engage in stereoselective binding to an enzyme surface.

When the *Re/Si* terminology (29) was introduced (28), its use was suggested also for describing the faces of double bonds. This was to be accomplished by citing the descriptors of their trigonal atoms when seen from the same side. Although this extension seems an obvious choice, it is subject to a possible misinterpretation. If one characterizes a face of the olefinic bond of 2-butenoic acid as *Re–Re*, one can deduce that the compound in question must be the *Z* and not the *E* isomer. It might be inferred from this that the cis–trans isomerism of these acids can be factored into two elements of prostereoisomerism. This

interpretation is erroneous because it ignores the fact that the configuration of the double bond can be deduced from the face descriptions only if we know whether the described faces are coincident or not. This additional information is supplied by the convention that was adopted and not by anything inherent in the face description of the individual trigonal atoms. This possibility of misunderstanding is avoided if the planar prostereoisomerism of olefins is described by a single term (*pro-B* or *pro-N*). The preference for the single descriptor is especially clear in cases (propenoic acid), in which only one of the two trigonal atoms previously (28) characterized as *Re* or *Si* warrants such a distinction.

If one or more of the groups attached to the unsaturated atoms are made chiral, no change in the classification can result unless we include an enantiomorphic pair. As always, the classification depends on that of the element of stereoisomerism generated by the appropriate diversification. We thus find that the left carbon of $g^+g^-C{=}Chi^+$ is only prographochiral, whereas the right carbon and the complete double bond are fully prochiral. A different combination is observed for the *Z* isomer of $g^+hC{=}Cg^-h$. Both centers are fully prochiral; the plane is only prographochiral. Planes or trigonal centers that are only prographochiral are described by lowercase terms, *pro-b* and *pro-n* or *re* and *si*.

It follows from our general definition of an element of prostereoisomerism that the classification of any given structure would be affected by any relevant change in the definition of the elements of stereoisomerism. As Prelog and Helmchen (5) regard centers as chiral that were previously classed as pseudoasymmetric, one might anticipate their advocating a corresponding shift from propseudoasymmetric to prochiral. Their actual proposal for prochiral centers entailed a more profound change, because they stipulated (5) that the homomorphic ligands of a prochiral center are enantiotopic. This definition would apply to C(3) of citric acid, but not to C(2), which is linked to two diastereotopic hydrogens. They gave no reason for their restriction and have indicated to us that it may not be needed. However, as no change was made in a subsequent publication (17c), it may be relevant to point to a possible obstacle. If $Cgghi^+$, which contains two diastereotopic homomorphic ligands, is cataloged as a chiral model (17c, see also Sect. IV-A), it would be awkward, if not downright contradictory, to call the same entity chiral and prochiral. However, to accept the restriction that the homomorphic ligands of prochiral atoms must be enantiotopic would defeat the purpose that led to the concept of the prochiral atom (3): There would be no appropriate way to characterize C(2) of citric acid or all the methylene carbons of chiral molecules such as cholesterol.

Although this account has been kept rather brief, it is hoped that it will help to clarify three issues about which there has been much misunderstanding:

1. It should be evident from the comments made that stereoheterotopism and prochirality (or prostereoisomerism) are not equivalent concepts but serve different objectives in a common field.

2. The prochirality concept is useful if it is applied to factored structures within a molecule rather than to the whole, because chiral compounds may also contain centers of prostereoisomerism that would become chiral if their homomorphic ligands were made distinct. The methylene carbons of cholesterol or C(3) of chiral trihydroxyglutaric acid (**20b**) are appropriate examples.
3. The prochirality concept is not necessarily an expression of a precursor–product relationship because there exist stereoselective reactions at prochiral elements that do not generate elements of chirality. An illustration of this is the reversible enzymatic dehydration of citric to *cis*-aconitic acid. In this process two prochiral centers of citric acid disappear and we obtain an achiral line of stereoisomerism that physically coincides with a prochiral plane of prostereoisomerism.

Experimentally, steric discrimination has been a most fruitful field of investigation. Following Ogston's (59) realization that enzymes can be expected to distinguish between certain homomorphic groups, a great body of splendid work in biochemical stereochemistry (29,56,60–63) has appeared that has helped to elucidate the mechanism of many enzymatic reactions. There has also been a spectacular development in NMR spectroscopy that is based on the concept of stereoheterotopic relationships (31). These accomplishments have provided a strong incentive for developing a unified set of stereochemical concepts.

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27. (a) Although *clockwise* ordinarily implies the presence of an extraplanar observer, its use for describing two-dimensional chirality is based on a truly two-dimensional concept, because one can determine the chiral sense of the sequence also by observations made from points entirely within the plane (17c). As we shall see, other applications need to be studied individually to ascertain whether a clockwise planar sequence has a two- or three-dimensional connotation. A clear distinction between both situations is made more difficult by the use of the same descriptor (*Re*). (b) It is in this three-dimensional sense that the terms—originally *re/si* (28) but later changed to *Re/Si* (29)—were introduced by Hanson to describe the faces of trigonal atoms by stating the priority sequence of their ligands. A different three-dimensional use of *Re/Si* proposed by Prelog and Helmchen (5) will be encountered in Sect. V. Attention should also be called to the fact that the points chosen by these workers to define triangles do not always represent ligands, but may consist of the ligating center and of two of its ligands.
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32. The other subclasses can also be designated by familiar terms. Heteromorphic ligands are diastereomorphic if the isolated ligands cannot be superposed by any symmetry operation but have the same constitution (e.g., the unsaturated ligands of the central carbon of **19**); constitutionally heteromorphic if they have the same compositions but different constitutions (e.g., *n*- and *i*-propyl groups); or materially distinct (e.g., H and OH ligands).

    Ligands are symbolized in the text by lowercase letters that express their morphic character. Chirality is indicated by superscripts + or −. If the ligands are homomorphic they receive the same symbol (g and g, or if chiral g^+ and g^+); if enantiomorphic, the same letter but opposite superscripts (g^+ and g^-); and if diastereomorphic or constitutionally or materially distinct, different letters.

33. A center may not be adequately characterized by a morphic description of its ligands if it participates in more than one ring, as do the central carbon atoms of **5, 9,** and **27.** Some of their ligands can be superposed not only in isolation but also in the intact molecule (4)—for example, in **9** by a rotation around the twofold axis. Although this signifies a center of the type Cgghh, which ordinarily does not allow stereoisomerism, we can obtain the enantiomer of **9** if we sever the bonds from the spiro atom to the proximal atoms that carry the (a) substituents and reconnect the ligands in the alternative way. This permutation links the proximal atom at position A_1, which was joined through a two-carbon bridge to B_1, to the proximal atom at B_2. As the ligand exchange has generated a stereoisomer, the proximal atoms A_1 and A_2 cannot be sterically equivalent and we can attribute their difference to their different connectedness to a third proximal atom, say B_1. As the configuration of the center is fully defined by locating the points of attachment of its ligands, the spiro atom meets our definition of a center of stereoisomerism.

    In the tests for graphochirality and pherochirality to be described, this special situation can be met as follows. If any exchanges of homomorphic ring ligands can produce a stereoisomer that agrees with the original compound in the geometry of bridging, the proximal atoms of the rings that coincide with the exchanged ligands must be differentiated, as by distinct subscripts. The resulting terms (e.g., A_1, A_2, B_1, and B_2 of **9**) must be so allocated to the proximal atoms of enantiomers that the bonding relationships between correspondingly labeled atoms are not altered by reflection. Illustrations of these procedures have been given in an earlier publication (1). They establish that the centers of **5, 9, 27,** and the line of **7** are fully chiral. If the center is tetrahedral the exchange of homomorphic ligands cannot alter the geometry of bridging. The need for examining the geometry became evident when we considered two chelates with three g–g rings in trigonal prismatic configurations (Brown, M. F.; Cook, B. R.; Sloan, T. E. *Inorg. Chem.*, **1975,** *14,* 1273, their Figs. 8 and 9). If the rings are parallel to the prism axis, no other isomer with this geometry is possible. All proximal atoms are represented by A and the center is fully achiral. If they are skewed as in 8, isomers having skewing angles of opposite sign exist. Subscripts are required and the center (with proximal atoms A_1 to A_3 in each triangle) is fully chiral. Further illustrations of the procedure are given in the pamphlet mentioned in note 53.

34. (a) The introduction of this terminology appears to be due to Wislicenus (cf. ref. 10c). (b) Shriner, R. L.; Adams, R.; Marvel, C. S. "Organic Chemistry," 2nd ed.; Gilman, H., Ed.; Wiley: New York, 1943; Vol. 1, p. 478. Wheland, G. W. "Advanced Organic Chemistry," 2nd ed.; Wiley: New York, 1949. (c) pp. 217–223; (d) p. 156. Eliel, E. L. "Stereochemistry of Carbon Compounds"; McGraw-Hill: New York, 1962. (e) p. 5; (f) p. 21. (g) Ebel, F. "Stereochemie"; Freudenberg, K., Ed.; F. Deuticke: Leipzig, 1933; p. 643. (h) Lyle, R. E.; Lyle, G. G. *J. Org. Chem.*, **1959,** *24,* 1679.

35. A brief history of the varying interpretations of the term *pseudoasymmetric* has been given (1,3). Prelog and Helmchen (5) have not limited their idea to the pseudoasymmetric center, axis, or plane but have presented the closely related concept of a general pseudoasymmetry

resulting from two different combinations of enantiomorphic ligands with two enantiotopic locations. This idea was taken up by Nourse (36) who explored it with tools of group theory. He introduced two new operations to generate pseudoenantiomers, rotation and reflection, each with the reversal of the chirality of some or all of the chiral ligands. He renamed this form of diastereoisomerism *pseudochirality* because it is compatible with rotational symmetry. Of far greater impact on our topic, however, is the finding that chiral molecules can have pseudoenantiomers, because this strikes at the foundation of the Prelog–Helmchen definition of molecular pseudoasymmetry. A definitive comparison with our category of a center that is only graphochiral is not possible, as Nourse did not define pseudochiral centers. We see little incentive for factoring pseudochirality (37) and anticipate that both concepts, if clearly distinguished, can coexist as they meet different objectives: pseudochirality operations (36) serve to generate stereoisomers and to establish group relationships between them but they do not contribute to the description of the individual members of such groups.

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38. Mach, E. "History and Root of the Principle of the Conservation of Energy," Jourdain, P. E. B., trans.; Open Court: Chicago, 1911; p. 88.
39. "IUPAC Tentative Rules for the Nomenclature of Organic Chemistry. Section E. Fundamental Stereochemistry." *J. Org. Chem.*, **1970,** *35*, 2849.
40. Prelog, V., personal communication. We are indebted to Professor Prelog also for corroborating some inferences we had drawn from ref. 5.
41. Mills, W. H.; Quibell, T. H. H. *J. Chem. Soc.*, **1935,** 839.
42. Blackwood, J. E.; Gladys, C. L.; Loening, K. L.; Petrarca, A. E.; Rush, J. E. *J. Am. Chem. Soc.*, **1968,** *90*, 509.
43. Ruch, E., cited in ref. 5.
44. (a) Schlögl, K. *Top. Stereochem.*, **1967,** *1*, 39. (b) Werner, H. *Angew. Chem.*, **1977,** *89*, 1; *Angew. Chem. Int. Ed. Engl.*, **1977,** *16*, 1. Hoffmann, R. *Science*, **1981,** *211*, 995.
45. Goldberg, S. I.; Bailey, W. D. *J. Am. Chem. Soc.*, **1974,** *96*, 6381.
46. Most of these operations would yield the enantiomer of **22** in a conformation that is not the mirror image of the original one. However, the need for conformational adjustment is nothing unusual. It is equally necessary if we wish to proceed from the preferred conformation of (*R*)-glyceraldehyde to that of its enantiomer by exchanging the H and OH ligands.
47. Frisch, H. L.; Wasserman, E. *J. Am. Chem. Soc.*, **1961,** *83*, 3789.
48. Wasserman, E. *J. Am. Chem. Soc.*, **1960,** *82*, 4433. Schill, G. (a) *Chem. Ber.*, **1967,** *100*, 2021; (b) "Conformational Analysis. Scope and Present Limitations," Ghiurdoglu, G., Ed.; Academic Press: New York, 1971, p. 229. We thank Dr. E. L. Eliel for providing us with the latter references.
49. The claimed lack of ambiguity does not preclude a physical overlap between elements. If one chooses to regard as stereoisomers the three nonsuperposable staggered forms resulting from the torsion of a carbon–carbon bond with six different ligands, we have three separate elements of stereoisomerism, two centers and one line. This is the minimum number required to account for the existence of the 12 stereoisomers.
50. Glaser, R.; Blount, J. F.; Mislow, K. *J. Am. Chem. Soc.*, **1980;** *102*, 2777.
51. Stewart, A. W. "Stereochemistry"; Longmans, Green: London, 1907; p. 142.
52. If there remains any doubt that it is the symmetry of the frame and not of the inscribed tetrahedron that determines the number of isomers, it can be dispelled by considering example **28.** The four points to which the bivalent ligands a, b, . . ., are attached form a tetrahedron with D_{2d} symmetry, slightly compressed from the regular one. This inscribed tetrahedron would allow only half the number of stereoisomers that are actually permitted by the frame which belongs to point group S_4 (5) if $a = b = c = d \neq H_2$.

However, symmetry considerations cannot be the sole determinants in such cases. If we return to the substituted adamantane and replace all its methylene groups by identical $(CH_2)_n$ bridges of sufficient lengths to allow a permutation at one quaternary carbon without disturbing the others, a single descriptor can no longer be used. Thus one must further question the validity of the idea of the unoccupied center if its existence depends on the value of *n*.

53. The various proposals made are merely illustrations. We are well aware that further elaboration is needed to accommodate more complex cases. For every problem discussed we have formulated and tested detailed rules, which will be made available on request. The pamphlet we have prepared for the nomenclature of tetragonal and octahedral centers also contains a correction of a faulty (1) application of the correspondence rule to centers with an unequal number of enantiomorphic ligands such as tetragonal $Xg^+g^+g^-h$ (example 24 of ref. 1) and our proposal for modifying Sequence Subrule 5.
54. In all cases in which we determined specific descriptors, we assumed an alphabetical priority order of the unspecified ligands (g > h > i . . .) and *R* chirality for any ligand marked $^+$.
55. Prelog and Helmchen (5), who first clearly stated such a restriction, attributed it to Cahn et al. (16). It should apply also to the description of the chiral center $Cg^+g^-h^+h^-$. The use of Subrule 5 (4) and of topic subscripts (5) can both be avoided by placing either g^+ or g^- into the first, and the h ligand with the like configuration into the third, position of priority. The initial choice is arbitrary but if followed through in this manner it would have no bearing on determining the configuration. This somewhat novel application of the principle like > unlike (4) greatly simplifies the task of finding proper descriptors for all octahedral centers with multiple pairs of enantiomorphic ligands.
56. Arigoni, D.; Eliel, E. L. Top. Stereochem., **1969,** *4,* 127.
57. Hanson, K. R.; Rose, I. A. *Proc. Nat. Acad. Sci. USA,* **1963,** *50,* 981.
58. Schwartz, P.; Carter, H. E. *Proc. Nat. Acad. Sci., USA,* **1954,** *40,* 499.
59. Ogston, A. G. *Nature,* **1948,** *162,* 963.
60. Bentley, R. "Molecular Asymmetry in Biology"; Academic Press: New York, 1970; Vol. 2.
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62. Cornforth, J. W. *Science,* **1976,** *193,* 121.
63. Wimmer, M. J., Rose, I. A. *Ann. Rev. Biochem.,* **1978,** *47,* 1031.

Asymmetric Reductions with Chiral Complex Aluminum Hydrides and Tricoordinate Aluminum Reagents

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I. INTRODUCTION

A. Definitions

The general subject of asymmetric synthesis has been reviewed extensively (1–5). The term *asymmetric synthesis* has been defined in more than one way (1,4); however, a useful definition is the one given by Morrison and Mosher (1): "a process which converts a prochiral unit [refs. 6 and 7] into a chiral unit so that unequal amounts of stereoisomeric products result." The stereoisomeric products may be enantiomeric or they may be diastereomeric. The substrate molecule must contain either enantiotopic or diastereotopic groups or faces (8,9), since the attack of a reagent at equivalent groups or faces cannot lead to isomeric products.

The major methods for producing optically active compounds have been discussed (1,10). These are

1. Physical separation via enantiomeric crystalline forms.
2. Resolution based on separation of diastereomeric forms.
3. Thermodynamically controlled asymmetric transformations of stereochemically labile diastereomers.
4. Kinetically controlled asymmetric transformations.

Asymmetric syntheses generally fall into the category of kinetically controlled asymmetric transformations. Two types of processes may be considered:

1. Reaction of an achiral (and prochiral) substrate with a chiral reagent.
2. Reaction of an achiral (and prochiral) group within a chiral substrate with an achiral (or chiral) reagent.

Considering, for example, the reduction of a carbonyl group of an aldehyde or ketone, in both cases diastereomeric transition states result from attack of the reagent at either face of the carbonyl group, and the extent of the asymmetric synthesis depends on the difference in the free energies of activation ($\Delta\Delta G^{\ddagger}$) of the competing pathways. It has been noted (4) that a difference in activation energies of 1.5 kcal/mol is large enough to lead to an optical yield of 92% at 25°C.

Asymmetric reduction of ketones or aldehydes to chiral alcohols has received considerable attention. Methods to accomplish this include catalytic asymmetric hydrogenation, hydrosilylation, enzymatic reduction, reductions with biomimetic model systems, and chirally modified metal hydride and alkyl metal reagents. This chapter will be concerned with chiral aluminum-containing reducing re-

agents reacting with prochiral groupings (usually carbonyl groups) within achiral (or sometimes chiral) substrates. Most of the examples cited conform to the more limited definition of asymmetric synthesis given by Marckwald (11) as "a reaction which produces optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials but with the exclusion of all analytical processes."

B. Criteria for Evaluating Asymmetric Reductions

Many studies have been directed toward the empirical development of synthetically effective reagents for asymmetric reductions. Criteria for an efficient asymmetric synthesis have been summarized by Eliel (12) as follows:

1. The desired enantiomer (or diastereomer) should be formed with high stereoselectivity (10) and in high chemical yield.
2. The chiral product must be readily separable from the chiral auxiliary reagent employed in the synthesis.
3. Unless the chiral auxiliary reagent is much cheaper than the desired product, the auxiliary reagent must be recoverable in good yield and with no loss in enantiomeric purity.

Consideration should also be given to the possibility of stereoisomeric enrichment after the asymmetric synthesis step. Examples will be encountered in which products formed with relatively high stereoselectivity in an asymmetric synthesis were converted to essentially isomerically pure material by further purification, for example, recrystallization.

The degree of asymmetric induction* is often specified by reference to the percent optical purity of the product:

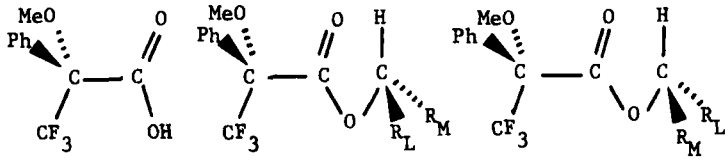
$$\% \text{ optical purity} = \frac{\text{specific rotation of the enantiomeric mixture}}{\text{specific rotation of the pure enantiomer}} \times 100 \quad [1]$$

This definition refers to an enantiomeric mixture produced in an asymmetric synthesis. In some cases where a diastereomeric mixture is produced, the definition has to be altered accordingly. *Percent optical purity* is an operational term that depends on optical rotation measurements. It is not necessarily equal to the percent enantiomeric purity (13), which is a more meaningful term and is the extent to which one enantiomer is formed in excess over the other:

*Asymmetric induction refers to the creation of a new chiral unit in which one configuration is produced in excess over the other (4).

$$\% \text{ enantiomeric excess} = \frac{\text{moles } R - \text{moles } S}{\text{moles } R + \text{moles } S} \times 100 = \% R - \% S \quad [2]$$

where R and S are enantiomers and R is in excess over S. An analogous term, *percent epimeric excess*, would be useful where chiral substrates are involved. The term *percent enantiomeric purity* is equivalent to *percent enantiomeric excess* (% e.e.) (1), which can be determined directly by nonpolarimetric methods (14). A particularly useful method (15) for the direct determination of the % e.e. of secondary alcohols involves their conversion to a diastereomeric mixture of esters of α-methoxy-α-trifluoromethylphenylacetic acid (MTPA, **1**). Quantitative anal-



1 **2** **3**

(R)-(+)-MTPA

ysis of the NMR spectrum based on either proton or fluorine signals can directly determine the % e.e. The MTPA reagent offers the advantage that signals in the fluorine NMR spectrum may be separated in cases where overlapping signals prevent the use of the proton NMR spectrum. In employing this method to determine % e.e. it is important that the reaction be quantitative with respect to the substrate, since the diastereomeric esters may be formed at different rates. It is also important that the reagent, MTPA-acid chloride, be enantiomerically pure. An empirically derived correlation of configuration and NMR chemical shifts for diastereomeric MTPA esters has been developed (16). A further development in this technique for the determination of configuration and enantiomeric purity of secondary alcohols employs the lanthanide shift reagent Eu(fod)$_3$ (17). In the presence of Eu(fod)$_3$ the separation of methoxy proton signals of esters **2** and **3*** of **1** is enhanced. It was observed that the ^{1}H NMR signal from the OMe group of the *R,R* diastereomer—*S,S* if (*S*)-(−)-MTPA is used—undergoes a greater downfield lanthanide-induced shift (LIS) with a given molar ratio of Eu(fod)$_3$ than the corresponding signal for the *R,S* (or *S,R*) diastereomer. This correlation was associated with the difference in steric bulk of the groups R_L and R_M. Esters corresponding to diastereomer **2**† show larger LIS values of the OMe resonance than those corresponding to **3**. When the carbinol substituent

*R_M and R_L in structures **2** and **3** symbolize medium- and large-sized R groups, respectively.

†Which will generally correspond to the *R,R* isomer when R_L and R_M are simple alkyl groups and R_L takes precedence over R_M in the *R,S* nomenclature.

groups are *t*-butyl and phenyl (Ph), Ph acts as the larger group (1,17). However, care must be exercised in using the method to assign configuration, since exceptions to the correlation were noted for α- and β-tetralol, *cis*-3-methylcyclohexanol, and *trans*-carveol. The enantiomeric purity of chiral primary 1-deuterio alcohols prepared by asymmetric reduction has been determined by use of a chiral lanthanide shift reagent, tris-[(3-heptafluoropropylhydroxymethylene)-*d*-camphorato]europium III, $Eu(HFC)_3$ (18). Once converted to diastereomeric compounds, the enantiomeric mixture may be analyzed by methods other than NMR, such as high-pressure liquid chromatography or gas–liquid chromatography.

Reliance on the use of optical purity as a means of evaluating an asymmetric synthesis may give erroneous results (3). Optical rotation measurements may be sensitive to the presence of impurities. Furthermore, the optical rotation of the pure enantiomer may not be accurately established. Even in the absence of nonenantiomeric impurities, and where the rotation of a single pure enantiomer is known, there are cases where the enantiomeric purity is not equal to the optical purity (19).

C. Considerations in the Construction of Transition State Models

In many studies of asymmetric reductions no attempts were made to rationalize either the extent or the sense of the observed asymmetric induction, that is, the absolute configuration of the predominant enantiomer. It is believed that it is premature in certain cases to attempt to construct a model of the transition state of the key reaction step, given the present state of knowledge about the mechanism of these reduction processes. The complexity of many of the reducing systems developed is shown by the fact that the enantiomeric excess or even the sense of asymmetric induction may depend not only on the nature of the reducing agent and substrate, but also on temperature, solvent, concentration, stoichiometry of the reaction, and in some cases the age of the reagent.

Investigations of the structures of complex metal hydride reagents in solution, and kinetic studies of reductions of ketones with $LiAlH_4$, have been carried out. The results have been reviewed by Boone and Ashby (20). Theories concerning the factors involved in the stereochemical control of ketone reductions have been extensively reviewed (20–22). These topics will therefore not be discussed here. A consideration of the mechanism of reduction should include the effects of solvent and cation. Cation effects play an important role in the regioselectivity of metal hydride reductions of α-enones (23,24), which are important substrates for asymmetric reductions. A study of the reduction of 2-cyclohexenone and several methyl-substituted derivatives with $LiAlH_4$ and $LiBH_4$ has demonstrated that the degree of coordination of the carbonyl oxygen by Li^+ has a large effect on the regioselectivity of hydride attack, that is, attack at C(1) (carbonyl carbon)

or at C(3) (Michael attack at the C=C double bond (24). The regioselectivity of the reduction process is controlled by the relative C(1) and C(3) atomic coefficient values in the LUMO of the enone. The larger coefficient corresponds to the predominating site of nucleophilic attack. Calculations indicate that when Li^+ is complexed by the α-enone, the C(1) coefficient is greater than that at C(3), and C(1) attack is favored. Thus reduction of 2-cyclohexenone with $LiAlH_4$ in THF gave an 86:14 ratio of C(1):C(3) attack. However, on addition of the Li^+ complexing [2.1.1] cryptate, a reversal in regioselectivity was observed, with a 14:86 ratio of C(1):C(3) attack. In the absence of carbonyl complexation of Li^+, the C(3) coefficient is greater than that of C(1) in the LUMO, accounting for this reversal. The strength of the carbonyl–Li^+ interaction depends also on the nature of the solvent and on the interaction between Li^+ and the reducing agent anion. The carbonyl–Li^+ interaction is stronger in diethyl ether than in THF. Reduction of 2-cyclohexenone with $LiAlH_4$ in diethyl ether gave a 98:2 ratio of C(1):C(3) attack. Similar effects were observed with methyl-substituted 3-cyclohexenones. A stronger Li^+–anion interaction implies a correspondingly weaker carbonyl–Li^+ interaction. For tight or intimate ion pairs, the carbonyl–Li^+ interaction will be weaker than for loose or solvent-separated ion pairs. Reduction of 2-cyclohexenone with $LiBH_4$ in THF (involving intimate ion pairs) gave less C(1) attack [52:48 C(1):C(3) attack] than reduction by $LiAlH_4$ involving solvent-separated ion pairs (20,40).

Reductions of certain aromatic ketones with metal hydrides have been shown to involve radical intermediates formed by an electron-transfer mechanism (25). For example, the reaction of aluminum hydride with dimesityl ketone in THF produced a violet solution that gave an EPR spectrum indicative of the presence of a paramagnetic species. The paramagnetic species is an intermediate in the reduction of the ketone, and is believed to be a radical cation–radical anion pair (25).

In most cases the identity of the reactive reducing species is not known with certainty. For example, the species initially formed by the reaction of lithium aluminum hydride (LAH) with alcohols may not be stable with respect to disproportionation. The degree of association of reducing species may be an important unknown factor in a particular case. Processes other than disproportionation or association may also make it difficult to predict the structure of the reagent formed from the reaction of LAH with sterically hindered alcohols (see Sect. II-A-1).

In considering which face of a carbonyl group is more likely to be attacked by a nucleophile, the direction of approach of the nucleophile (26), may play an important role. A nonperpendicular approach to the plane of the carbonyl group has been shown to be favored (27). Orbital factors may in part determine the direction of asymmetric induction, in addition to steric and/or torsional

effects. Calculations have shown (28) that σ–π mixing occurs in the carbonyl group in various aldehydes and ketones. A dissymmetric π-electron cloud results, which leads to a different electron density on each diastereotopic face of the carbonyl group. This causes a difference in reactivity of the two faces toward an approaching nucleophile, which is assumed to attack preferentially at the more positive face.

Despite the uncertainties of mechanism and of the identity of reactive species, attempts have been made to analyze stereochemical control in asymmetric reductions in terms of a model of the transition state in which steric or other interactions can be assessed. These models could prove useful in suggesting modifications for improving the design of selective reducing agents or for predictive purposes. However, it should be kept in mind that there are only two possible outcomes in the direction of asymmetric induction at a prochiral unit undergoing reaction, and confidence in the predictive usefulness of a given model can only be obtained after a considerable number of examples have been examined.

II. CHIRAL DERIVATIVES OF LITHIUM ALUMINUM HYDRIDE

A. Reaction of $LiAlH_4$ with Alcohols and Phenols

1. Stability of Lithium Alkoxyaluminum Hydrides

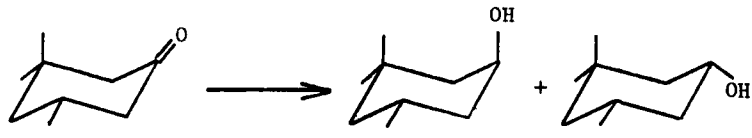
The stability of lithium alkoxyaluminum hydrides directly bears on the subject of chiral derivatives of LAH, since most of the latter reagents are prepared by the reaction of LAH with alcohols of various types and complexity. An understanding of the factors controlling asymmetric induction ultimately requires a knowledge of the identity of the active reducing species. The reaction of LAH with "simple" alcohols—compounds containing a single hydroxy functional group—or with aldehydes or ketones gives rise to lithium alkoxyaluminum hydrides,

$$\underset{\mathbf{4}}{LiAlH_{4-n}(OR)_n} \qquad n = 1\text{–}4$$

The utility of these species as selective reducing agents has been thoroughly studied (29). Brown and McFarlin discovered that *t*-butyl alcohol reacts with LAH in a 3:1 molar ratio to give lithium tri-*t*-butoxyaluminum hydride (**4**, R = Bu^t, n = 3) in ether, tetrahydrofuran (THF), or diglyme (30,31).* The

*The fourth mole of hydrogen could be evolved on extended heating with additional *t*-BuOH.

stereoselectivity of the reduction of 3,3,5-trimethylcyclohexanone (**5**) (see eq. [3]) to the *cis*- and *trans*-epimeric alcohols **6** by reagents formed from the reaction of alcohols with LAH was studied in ether and in THF (32). It was observed



[3]

5 trans-6 cis-6

that the stereoselectivity with the reagent formed from the reaction of Pr^iOH with LAH (3 : 1 molar ratio) was the same as reduction of **5** by LAH itself (direct or inverse addition). On the other hand, reagents formed from the reaction of primary or tertiary alcohols with LAH were more highly stereoselective, giving a greater proportion of *trans*-**6**. On the basis of observations of this type, it was suggested (32) that lithium *sec*-alkoxyaluminum hydrides are generally unstable in ether solvents and disproportionate to LAH, the effective reducing agent,* and to $LiAl(OR)_4$. In the reaction of primary or tertiary alcohols with LAH, reduction of **5** clearly did not involve AlH_4^- as the sole reducing species.

It was recognized (32) that not all species **4** (R = *sec*-alkyl) undergo disproportionation readily, since the reagent formed from camphor and LAH was more stereoselective than LAH in the reduction of **5**. This was attributed to the bulky isobornyloxy complex formed in the reaction of camphor with LAH, which is analogous to the tri-*t*-butoxy complex. Disproportionation to the tetraalkoxyaluminum species in these cases is disfavored by steric hindrance.

In a study of the reaction of simple alcohols with LAH, Brown and Shoaf (34) showed by chemical analysis that Pr^iOH reacted in ether to give a precipitate of $LiAl(OPr^i)_4$, with LAH remaining in solution. 2-Butanol reacted in a manner very similar to Pr^iOH.

A slightly modified view of the reaction of primary or secondary alcohols added to LAH (3 : 1 molar ratio) may be considered. The rapid consecutive reactions of alkoxyaluminum hydride species with a local excess of alcohol could lead to formation of the tetraalkoxy species, particularly under conditions of inefficient mixing. This result is summarized in eq. [4]. In the case of a simple unhindered primary alcohol such as methanol, a "back" reaction of the tetraalkoxy species with LAH leads to the trialkoxyaluminum hydride species (eq. [5]). The net result of the reaction of methanol with LAH (3 : 1 molar ratio) is

*It has been suggested (33) that under the relatively inefficient mixing conditions encountered in preparative work, the reduction of **5** with LAH in ether actually involves the monoalkoxyaluminum hydride species as well as AlH_4^-.

the formation of lithium trimethoxyaluminum hydride (sum of eqs. [4] and [5]). The process shown in eq. [5] has been demonstrated for MeOH in diglyme (34). In the case of a more hindered alcohol such as Pr^iOH, the reaction corresponding to eq. [5] may not occur, and therefore the net result of adding Pr^iOH to LAH (3 : 1 molar ratio) will be formation of $LiAl(OPr^i)_4$ (precipitated) and unreacted LAH in solution.

$$4\ LiAlH_4 + 12\ ROH \longrightarrow 3\ LiAl(OR)_4 + LiAlH_4 + 12\ H_2 \qquad [4]$$

$$3\ LiAl(OR)_4 + LiAlH_4 \longrightarrow 4\ LiAlH(OR)_3 \qquad [5]$$

In an X-ray and IR study of the solid products of the reaction of LAH with 2 molar equivalents of MeOH, EtOH, and Pr^iOH, the data were interpreted as showing that the products were mixtures of LAH and $LiAl(OR)_4$ (35). Although X-ray data on the solid products do not reveal the species present in solution, the authors suggested that complexes of the type $MAlH_4 \cdot nMAl(OR)_4$ exist in solution.

The stereoselectivity of reduction of **5** with a series of reagents formed by reacting LAH with acyclic alcohols having increased branching at the β carbon was studied (36). High stereoselectivity was found with the hindered alcohols $Me_3CCHOHMe$ and $Me_3CCHOHCMe_3$ (the latter reagent was formed by the reaction of LAH with di-*t*-butyl ketone). This demonstrated that these hindered acyclic secondary alkoxy species do not undergo disproportionation to LAH.

The disproportionation of tertiary and primary alkoxy species **4** has been reported. The NMR spectrum of an equivalent molar mixture of $LiAlH_3(OBu^t)$ and $LiAlH(OBu^t)_3$ was the same as that of $LiAlH_2(OBu^t)_2$, suggesting disproportionation of the nonsymmetrical compounds (37). Kinetics of the reduction of several aromatic ketones in ether with reagents formed by the reaction of LAH with Bu^tOH were consistent with partial disproportionation of species **4** (38):

$$4\ LiAl(OBu^t)H_3 \overset{K_1}{\rightleftharpoons} (LiAlH_4)_2 + 2\ LiAl(OBu^t)_2H_2 \qquad [6]$$

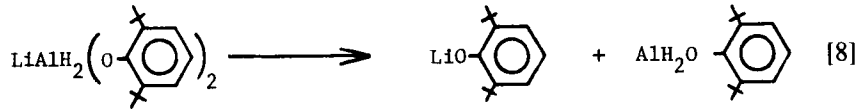
$$2\ LiAl(OBu^t)_2H_2 \overset{K_2}{\rightleftharpoons} LiAl(OBu^t)H_3 + LiAl(OBu^t)_3H \qquad [7]$$

$LiAlH(OBu^t)_3$ does not undergo disproportionation to the tetraalkoxy species. Reduction of the aromatic ketones studied involved either monomeric LAH or both this species and the monoalkoxy species, depending on the steric hindrance of the substrate. In a similar study of the reduction of camphor in THF (39), the kinetic results were also consistent with disproportionation of *t*-butoxy species (eqs. [6] and [7]), active reducing species being LAH and $LiAl(OBu^t)H_3$. In the reduction of camphor with a series of reagents prepared by the reaction of LAH

with various molar proportions of MeOH, the disproportionation of species **4** (R = Me) to LAH and $LiAl(OMe)_4$ were consistent with the kinetic results, with only LAH regarded as an active reducing agent.

The slow disproportionation of $LiAlH(OMe)_3$ in THF was also observed by Ashby and co-workers (40). It should be noted that Brown and Shoaf had earlier (34) found that the reaction of LAH with EtOH did not lead to simple, unique reaction products.

Aside from the mixture of species **4** resulting from disproportionation, the reaction of LAH with highly hindered alcohols (or phenols) may lead to unexpected products. Refluxing a THF solution of lithium bis(2,6-di-*t*-butylphenoxy)aluminum hydride (**7**) resulted in the reduction of THF to 1-butanol (41).



[8]

7

It was shown that direct attack of **7** on THF was unlikely, and the reduction was attributed to dissociation of **7** to a tricoordinate aluminum hydride derivative, as in eq. [8].

Reaction with a deuterated reagent gave 4-deuterio-1-butanol resulting from hydride cleavage of the complexed THF ring at the α carbon (41). In an attempted preparation of lithium tris(2,4,6-tri-*t*-butylphenoxy)aluminum hydride (**8**), LAH was allowed to react with 3 molar equivalents of 2,4,6-tri-*t*-butylphenol in refluxing ether solution. Although 3 molar equivalents of hydrogen were evolved, the product was shown to be not **8** but rather a tricoordinate aluminum species, probably **9**:

$$LiAlH_4 + 3\ ArOH \xrightarrow[\text{reflux}]{Et_2O} \underset{\textbf{9}}{LiOAr} + AlH(OAr)_2 + 3\ H_2 \qquad [\textit{not}\ \underset{\textbf{8}}{LiAlH(OAr)_3}]$$

Ar = 2,4,6-tri-*t*-butylphenyl [9]

Evidence for this was based on chemical properties of the ether solutions of the reagent as well as IR spectra of the solutions compared with independently prepared **9** (42).

In summary, the structure of a reagent formed from the reaction of LAH with an alcohol cannot be assumed on the basis of the stoichiometry of the reagents, because of the possibility of disproportionation. With very highly hindered alcohols or phenols, tricoordinate species* may be formed.

*Species such as **9** are written as tricoordinate even though they would probably exist as dimers or higher oligomers, and without regard to solvation.

2. *Chiral Lithium Alkoxyaluminum Hydrides*

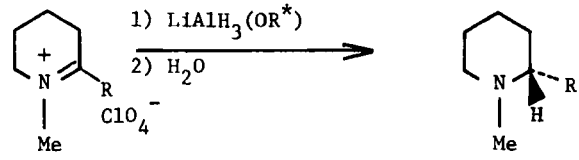
The first attempt at converting LAH into a chiral alkoxy derivative was made by Bothner-By (43) by reacting LAH with 1 or 2 molar equivalents of (+)-camphor. The resulting reagent was reported to effect asymmetric reduction of 2-butanone and pinacolone. These results were later shown to be in error by Portoghese (44) and by Landor and co-workers (45,46), who obtained only optically inactive alcohols and showed that Bothner-By's product was probably contaminated with camphor. Bothner-By's pioneering concept of using LAH as the basis for preparing chiral reducing agents eventually led to the development of highly successful reagents. It is of interest that the asymmetric reduction of 2-butanone has in fact been reported with the (+)-camphor-LAH reagent, in which the molar ratio of camphor to LAH varied from 1 to 3 (47). However, the degree of asymmetric induction was low, with 2-butanol of approximately 2% optical purity being formed. This reagent was used in the preparation of an optically active polymer by the reduction of poly[methyl vinyl ketone].

Landor and co-workers (46) found that a reagent formed by reacting LAH with 2 molar equivalents of (−)-menthol also failed to give optically active alcohol in the reduction of pinacolone. Only racemic pinacolyl alcohol was formed.

The failure to obtain optically active alcohols in these reductions cannot be attributed solely to disproportionation of the reagent. It was observed earlier that the (+)-camphor-LAH reagent reduced **5** with greater stereoselectivity than LAH (32). Furthermore, the (+)-camphor-LAH and (−)-menthol-LAH reagents have been shown to be capable of effecting asymmetric reductions. Reduction of methyl benzoylformate $PhCOCO_2Me$ with a 3:1* (−)-menthol-LAH reagent gave a 4% e.e. of the corresponding (*R*)-carbinol (48). Similarly, reduction of $PhCOCO_2Et$ with a 3:1 (+)-camphor-LAH reagent gave a 5% e.e. of the (*R*)-carbinol (48).

Červinka has employed these reagents in the asymmetric reduction of immonium salts (49,50) and imines (51). The reduction of 2-substituted *N*-methyl-Δ^1-tetrahydropyridinium perchlorates (**10**) with (−)-menthol-LAH in ether or THF led to optically active piperidine derivatives (eq. [10]). The optical purity obtained for the Pr^n derivative was 12%. In the case of R = Me and Pr^n the configuration of the predominant enantiomer was shown to be *S*. The (−)-menthol-LAH reagent was similarly shown to reduce 1-methyl-2-alkyl-Δ^1-dihydropyrrolinium perchlorates (**11**) to optically active pyrrolidine derivatives (eq. [11]). The optical yield could be calculated only for R = CH_2Ph, and was only 6% (*R* enantiomer) obtained with a 1:1 (−)-menthol-LAH reagent. With 2:1 or 3:1 molar ratios of menthol:LAH, the optical yield decreased. The

*Molar ratio of menthol to LAH. Molar ratios will often be expressed in this manner.

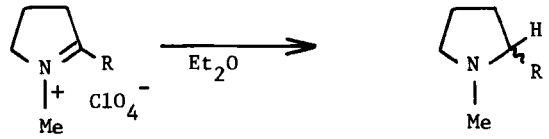


[10]

10

R = Me, Et, Pr^n, Am^n, Ph, CH_2Ph, α-naphthyl

Molar ratio LAH: (−)-menthol : substrate = 1 : 1.1 : 0.5. For R = Pr^n the ratio was 1 : 1.1 : 1.

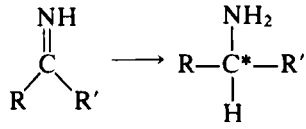


[11]

11

R = Et, Pr^n, Pr^i, CH_2Ph

configuration of the predominant enantiomer also depended on the menthol : LAH ratio. Similar reductions of imines **12** were carried out with (−)-menthol-LAH and (+)-borneol-LAH reagents (51). Optical yields were low (<10%) in those examples where it could be calculated (R = Ph; R′ = Me, Et).

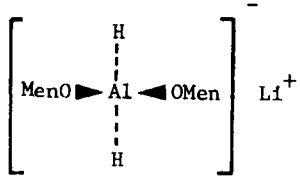


[12]

12

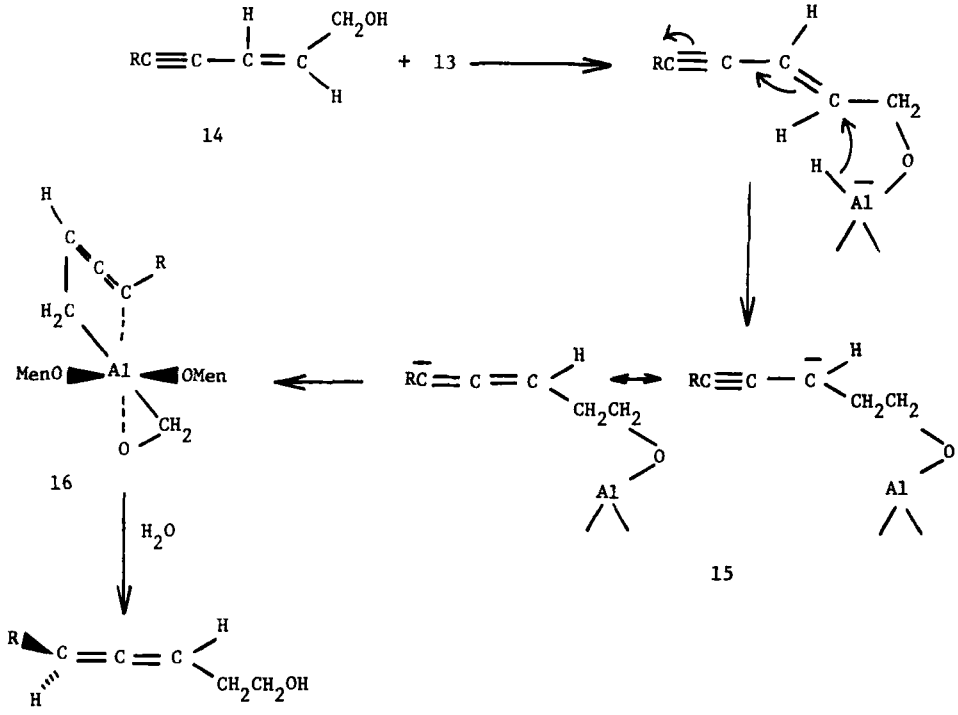
R = Ph; R′ = Me, Et, Pr^n, Naph$^\alpha$, *o*-tolyl
R = *o*-tolyl; R′ = Naph$^\alpha$

Evans, Landor, and Regan found that lithium bismenthoxyaluminum hydride (**13**) reduced alk-2-en-4-yn-1-ols (**14**) to optically active allenic alcohols (52,53).



13 MenO- = menthoxy

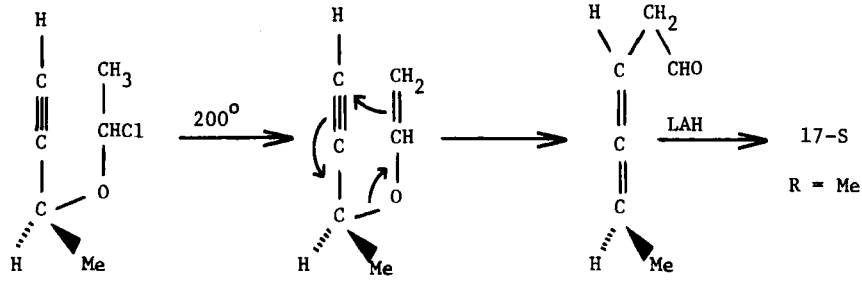
The reaction is thermodynamically controlled and was postulated to involve an achiral, delocalized anion **15**, which cyclizes to a somewhat strained 7-membered ring complex **16** capable of existing in isomeric forms. The more stable form could be hydrolyzed to the predominant (+)-(*S*)-allenic alcohol **17** (Scheme 1)



Scheme 1

Hex- and hept-2-en-4-yn-1-ol gave hexa-3,4-dienol and hepta-3,4-dienol, respectively. The absolute configuration of (+)-hexa-3,4-dienol was determined to be *S* by thermal conversion of (−)-(*S*)-α-chloroethyl 1-methylprop-2-ynyl ether (**18**) to an allenic aldehyde **19**, which was reduced with LAH to (+)-hexa-3,4-dienol (**17**, R = Me). (See Scheme 2.)

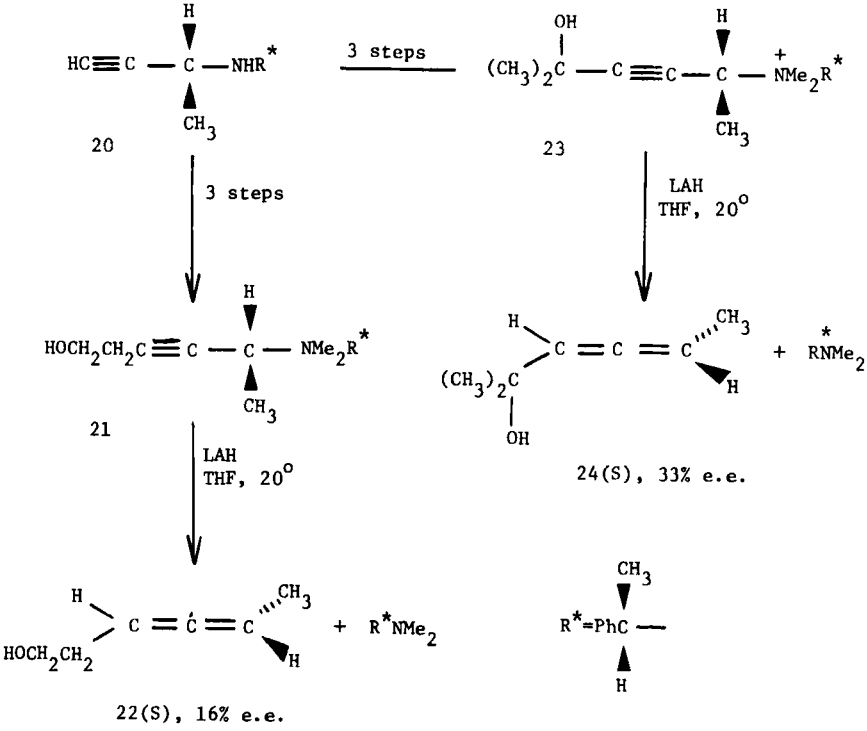
Methyl isobutyl ketone was reduced with (−)-menthol-LAH in ether to give the (+)-(*S*)-carbinol (53) in low optical yield. Methyl neopentyl ketone was similarly reduced to the (+)-carbinol, although pinacolone was reduced to only racemic alcohol. Maximum stereoselectivity in the reduction of both ketones and alkenynols was obtained with a 2:1 (−)-menthol-LAH reagent. The observed low stereoselectivity was attributed mainly to insufficient interaction of the remote isopropyl substituent on the menthyl group with the substituents on



Scheme 2

the ketone or allene complex, leading to small energy differences between the competing transition states or intermediate complexes.

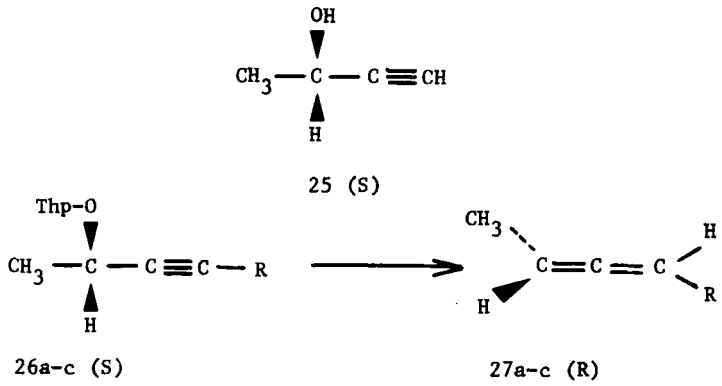
A synthetic method for the preparation of chiral α- and β-allenic alcohols starting with a chiral acetylenic amine **20** and involving an LAH reduction as a key step was reported by Claesson and Mosher (54). This is illustrated in Scheme 3. Based on the stereochemistry of **20** to **24**, it can be deduced that the attack



Scheme 3

of hydride must be from the same side (suprafacial) from which the tertiary amino group departs in the formation of **22** and **24**. The enantiomeric purities of the allenic alcohols were determined with the aid of the chiral lanthanide shift reagent, tris(3-heptafluorobutyryl-*d*-camphorato)europium(III), $Eu(hfbc)_3$ (55).

An improved procedure for the synthesis of α-allenic alcohols in good yields and with approximately 90% e.e. was reported by Olsson and Claesson (56). (−)-(*S*)-3-Butyne-2-ol (**25**) was converted into the monotetrahydropyranyl derivatives **26a** to **c**, which gave on reduction with LAH in ether or THF the chiral allenes **27a** to **c** (Scheme 4). The absolute configurations of **27b** and **c** were



a, R = CH_2CH_2OH

b, R = CH_2OH

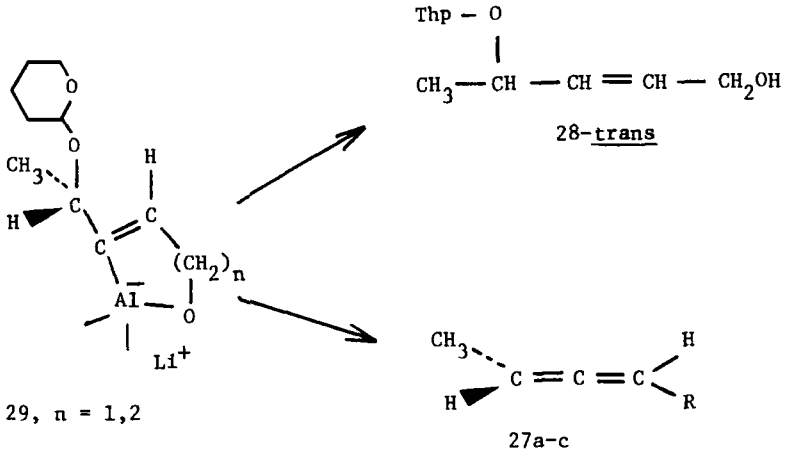
c, R = $C(CH_3)_2OH$

Scheme 4

assigned as *R*, according to the Lowe–Brewster empirical rule (57), whereas the configuration of **27a** was known (53). Alcohols **27c** and **27a** were formed in 90% e.e. and 75% e.e., respectively, as determined with $Eu(hfbc)_3$* (54). In an LAH reduction of racemic **26b** in ether at −10°C, compound **28** was isolated and shown to have the trans configuration (Scheme 5). The overall sequence (*S*)-**26** to (*R*)-**27** involves anti addition of LAH across the acetylenic triple bond to possibly give the cyclic intermediate **29** at the low temperature, followed by an anti 1,2-elimination of metal alkoxide. Yields of the allenic alcohols varied from 35 to 65%.

Yamaguchi and Kabuto (58) studied the effect on stereoselectivity of various

*The e.e. of **27b** could not be determined with the shift reagent and was estimated as ca. 90% on the basis of optical rotation comparison with **27c**.



Scheme 5

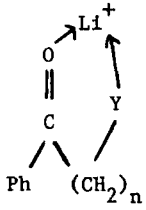
functional groups Y in the reduction of ω-substituted alkyl phenyl ketones (**30**) with lithium tris-(−)-menthoxyaluminum hydride in ether at 0°C (eq. [13]). Synthetic yields of 80 to 100% were reported. However, the highest enantiomeric

$$\mathrm{PhCO(CH_2)_nY} \xrightarrow[\text{ether, } 0°\mathrm{C}]{\mathrm{LiAlH(}O\text{-menthyl)_3}} \mathrm{PhCHOH(CH_2)_nY} \qquad [13]$$

30

n = 1 to 4; Y = NMe_2, OMe, SMe, H, Me, Et, —N⟨ ⟩

excess obtained was 38% (for n = 3, Y = OMe). The observed stereoselectivities depended on n and on the nature of Y. The methoxy substituent (n = 2, 3) increased stereoselectivity, as did Y = NR_2 (n = 2), compared with Y = Et, which can exert only a steric effect. The nature of the group Y plays an important role in determining the stereoselectivity, probably by coordination of Li^+ together with the carbonyl group, involving cyclic structure **31**. The size of the ring, determined by n, clearly affects the stereoselectivity but the effect is not well understood. It was found that Y = SMe did not enhance stereoselectivity, since



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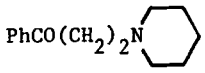

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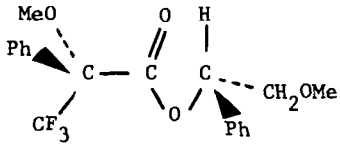


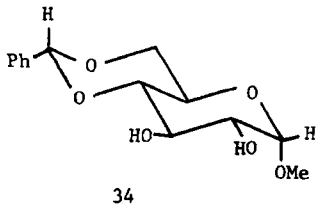
33

this group does not coordinate well with Li^+. The reduction of 3-piperidinopropiophenone (**32**) in toluene was studied in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA), which can coordinate with Li^+. The results showed that TMEDA interfered with coordination of the piperidino nitrogen with the reducing agent and led to lower stereoselectivity.

TMEDA/LAH (molar ratio):	0	1.0	2.0	4.0
% optical yield:	23	13	12	12

The absolute configuration of many of the alcohol products was assigned by the (*R*)-(+)-MTPA-Eu(fod)$_3$ method (17). For example, for PhCHOH—CH_2OMe, the major isomer formed was the *R*-(−)-carbinol as shown by a larger LIS value corresponding to MTPA ester **33**.

In an earlier and similar study Angeloni and co-workers (59) reduced several β-aminoketones with (−)-menthol-LAH reagents and obtained higher optical yields in the reduction of **32** and of **30** (n = 2, Y = NMe_2) than were obtained by Yamaguchi and Kabuto (58). These results are summarized in Table 1. The yields of alcohols were essentially quantitative, and the highest optical yields were obtained with the 3 : 1 (−)-menthol-LAH reagent at the lower temperature.



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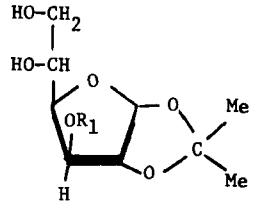
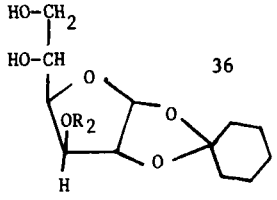


35

R_1 = H,Me,CH_2Ph



36 R_2 = (a)H, (b)Me, (c)Et, (d)CH_2Ph

B. Reaction of $LiAlH_4$ with Monosaccharides and Diols

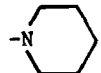
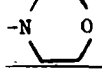
1. Monosaccharide Derivatives

In 1966 Landor and co-workers reported the preparation of chiral derivatives of LAH by its reaction with monosaccharide derivatives (46,61). These studies have been reviewed by Inch (62). Landor and co-workers planned to construct

Table 1

Reduction of β-Aminoketones with (−)-Menthol-LAH (59)

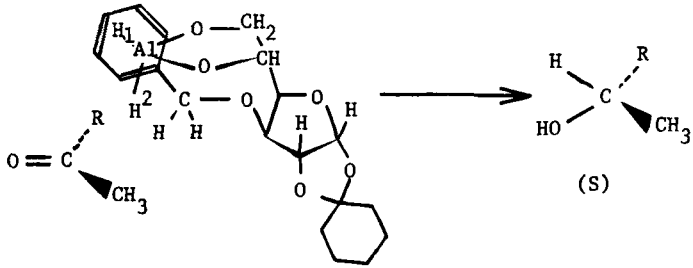
$$PhCOCH_2CH_2NR_2 \xrightarrow[\text{ether}]{(-)\text{-menthol-LAH}} PhCHOHCH_2CH_2NR_2$$

		Optical yield (%)			
—NR_2	T (°C)	LAH(*O*-menth)	LAH(*O*-menth)$_2$	LAH(*O*-menth)$_3$	% e.e.[a]
—NMe_2	0	1.3	17.4	73.2	77.5
	35	1.1	4.4	53.6	
	0	2.2	19.1	67.9	66.0
	35	1.6	5.5	45.4	
	0	2.1	33.3	58.7	58.7
	35	1.6	22.8	38.6	

[a]The enantiomeric purity was checked by the ^{1}H-NMR method of Mislow and Raban (60). The absolute configurations of the major alcohol isomers were all *R*.

rigid chiral structures based on readily available monosaccharide derivatives having two or three hydroxy groups. It was reasoned that cyclic complexes are more stable than acyclic ones and that cyclic complexes with LAH would therefore be less likely to undergo disproportionation. Complexes of LAH were prepared by reaction with methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**34**), 1,2-*O*-isopropylidene-α-D-glucofuranose (**35**), (R_1 = H) and its 3-*O*-methyl (R_1 = Me) and 3-*O*-benzyl (R_1 = CH_2Ph) derivatives, and 1,2-*O*-cyclohexylidene-α-D-glucofuranose (R_2 = H) and its 3-*O*-methyl (R_2 = Me), 3-*O*-ethyl (R_2 = Et) and 3-*O*-benzyl (R_2 = CH_2Ph) derivatives (**36a** to **d**).

The monosaccharide–LAH complexes were used to reduce ketones of varied steric and electronic types: Bu^{t}COMe, PhCOMe, Me_2C=CH—COMe, 2-$C_{10}H_7$—COMe, and R—CO—C≡CH (R = Me, Pr^n, Pr^i, Ph). The LAH complexes derived from **34** and all the derivatives of **35** gave products of very low optical purity (up to 10%). The complex derived from **36a** showed relatively low selectivity (up to 14% optical purity), whereas those from **36b** and **36c** gave



Scheme 6

Table 2
Reduction of Ketones with the Complex **36d**-LAH[a]

Entry	Ketone	EtOH[b]	*sec*-Carbinol		Reference
			Optical purity (%)	Configuration	
1[c]	PhCOMe	—	34	*S*	61
2[d]	PhCOMe	1.9	71	*R*	63
3[c]	PhCOMe	2.5	64	*R*	63
4[c]	PhCOEt	—	37	*S*	61
5[c]	PhCOEt	1.3	39	*R*	63
6[d]	PhCOEt	1.9	46	*R*	63
7[c]	Bu^{t}COMe	—	25	*S*	61
8[c]	Bu^{t}COMe	1.3	14	*R*	63
9[d]	Bu^{t}COMe	1.9	17	*R*	63
10[c]	Bu^{t}COMe	—	2	*S*	61
11[d]	Bu^{t}COMe	1.4	18	*R*	63
12[c]	Me_2C=CHCOMe	—	31	*S*	61
13[d]	Me_2C=CHCOMe	1.4	24	*R*	63
14[c]	2-$C_{10}H_7$COMe	1.0	40	*R*	63

[a]Molar ratios LAH:**36d**:ketone, 1:1:1 (entries 1, 4, 7, 10, 12); 2.4:1.3:1 (entries 9, 11, 13); 4.6:2.0:1 (entry 2); 3.2:2.0:1 (entry 3); 1.9:1.9:1 (entry 5); 3.8:2.0:1 (entry 6); 1.2:1.3:1 (entry 8); 2.7:1.9:1 (entry 14). Reductions were carried out in ether at reflux.
[b]Molar equivalents based on LAH added to complex **36d**-LAH.
[c]Complex prepared using a standardized ether solution of LAH.
[d]Complex prepared from an ether suspension of LAH.

inconsistent results with very low selectivity. The most consistent results with highest selectivity were obtained with the benzyl derivative **36d**. Reduction of a variety of ketones with **36d**-LAH gave products of up to 37% optical purity (Table 2) and synthetic yields were in the range of 55 to 83%. Maximum selectivity was obtained with a 1:1 **36d**-LAH complex, which supports the formation of a cyclic complex between LAH and the hydroxy group on C_5 and C_6 of **36d**. The complex and approach of a prochiral methyl ketone leading to the (*S*)-carbinol are shown in Scheme 6.

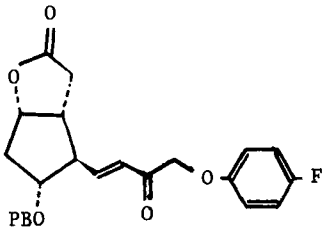
The complex is seen to have two diastereotopic hydrogens H_1 and H_2 available for reaction. Models suggest that H_1 is more highly shielded by the benzyl group and that H_2 is principally responsible for reduction. The lowest-energy transition state is assumed to orient the ketone with its carbonyl group pointing away from the oxygens of the aluminum complex. The model rationalizes the *S* configuration for the predominant carbinol, but does not explain the surprisingly low stereoselectivity found in the reduction of *t*-butyl methyl ketone.

Removal of the more reactive H_2 of the **36d**-LAH complex (Scheme 6) by reaction with one equivalent of ethanol led to transfer of H_1 to ketone substrates

to give carbinols of predominant *R* configuration (63), as shown in Table 2. Optical yields approaching 70% were achieved. Increasing quantities of added ethanol led to increased selectivity until a maximum was reached, presumably reflecting complete removal of the more reactive (and less selective) H_2. Table 2 shows selected data representing maximum optical yields in the reduction of a variety of ketones. The use of benzyl alcohol as an additive did not give significantly different results than ethanol.

Landor's ethanol-modified reagent **36d**-LAH-EtOH was used in the reduction of a prostaglandin precursor **37** (64). The best stereoselectivity achieved was 24% epimeric excess in a mixed solvent (25% THF in ether) at −78°C. Modification of Landor's reagent by increasing the size of the alkoxide group attached to aluminum to 1-adamantyloxy, 2-adamantyloxy, or 1-adamantylmethoxy led to poorer stereoselectivity and to lower reactivity of the reagent. Reduction of **37** at −78° with cyclic reagents derived from LAH and pinanediol (**38**), readily

PBO = p-phenylbenzoate



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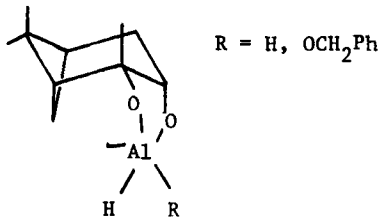
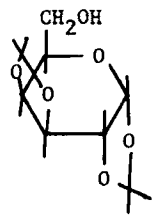


38

available from pinene (65), gave unsatisfactory nonselective results, as did reduction by a polymeric diol-LAH complex.

LAH complexes of the monohydroxy carbohydrate derivatives 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**39**) and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**40**) have been reported to effect asymmetric reduction of



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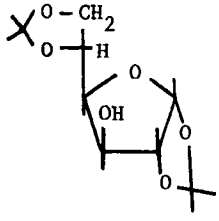


40

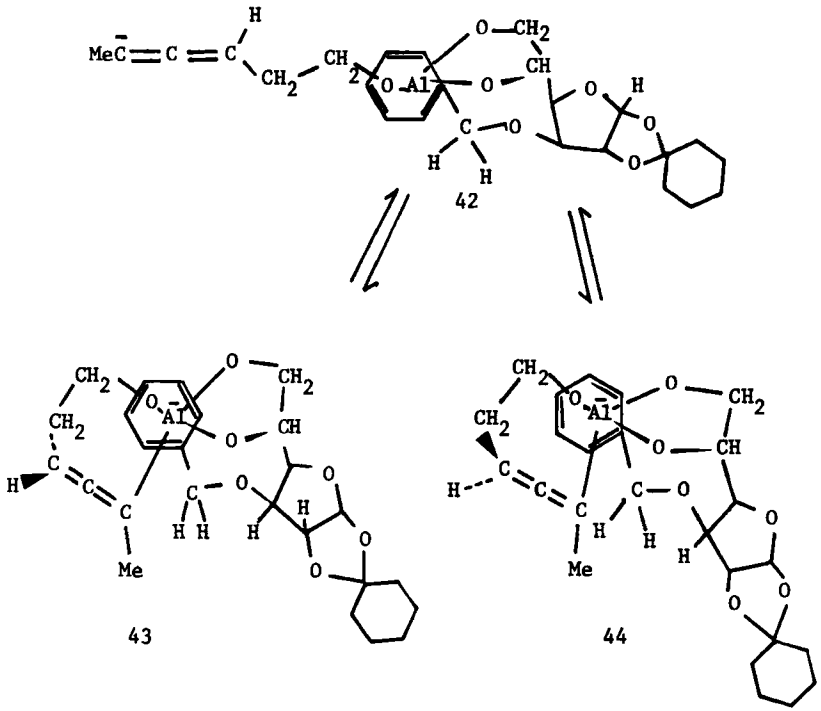
several prochiral ketones with very low enantiomeric excess (66). Similarly, a number of complexes of LAH with diacetal derivatives of D-mannitol (67) have been shown to reduce several dialkyl and aryl alkyl ketones in low optical yield (less than 12% optical purity). The most successful chiral monosaccharide auxiliary reagent for use in complexing LAH is **36d** and its ethanol-modified derivative.

The **36d**-LAH complex has been used in the asymmetric synthesis of β-allenic alcohols by reduction of enynols (**41**) as shown in eq. [14]. Although similar

$$RC{\equiv}C{-}CH{=}CH{-}CH_2OH + LiAlH_2C_{19}H_{24}O_6 \longrightarrow RCH{=}C{=}CH{-}CH_2CH_2OH \quad [14]$$

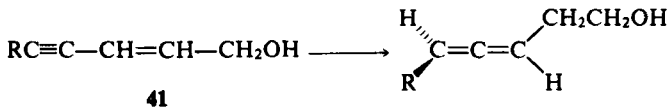
41

reduction with lithium bismenthyloxyaluminum hydride (**13**: see also Sect. II-A-2) gave the (*S*)-allenic alcohol, predominantly as the result of thermodynamic control, the more stable complex involving **36d**-LAH is the *R* form. Thus reduction of hex-1-en-4-yn-1-ol with **36d**-LAH gave (*R*)-(−)-hexa-3,4-dienol, and the results of several other reductions are shown in Table 3. Scheme 7 illustrates



Scheme 7

Table 3
Asymmetric Reduction of Alkenynols to (−)-(*R*)-Allenic Alcohols with **36d**-LAH (68)



R	Configuration	$[\alpha]_D^{25}$(°)	Optical purity (%)
Me	*R*	−10	—
Et	*R*	− 8.9	—
Bu^n	*R*	− 7.4	—
Ph	*R*	−12.5	—
Bu^{t}C≡C	*R*	−12.5	—
Ph—C≡C	*R*	− 3.1[a]	—
H(C≡C)$_2$	*R*	−26.6	—
Me(C≡C)$_2$	*R*	−11.3[a]	3.3
Me(CH$_2$)$_{10}$	*R*	− 3.0[a]	6.3
Me—CH=CH(CH$_2$)$_8$	*R*	− 5.8	11.6

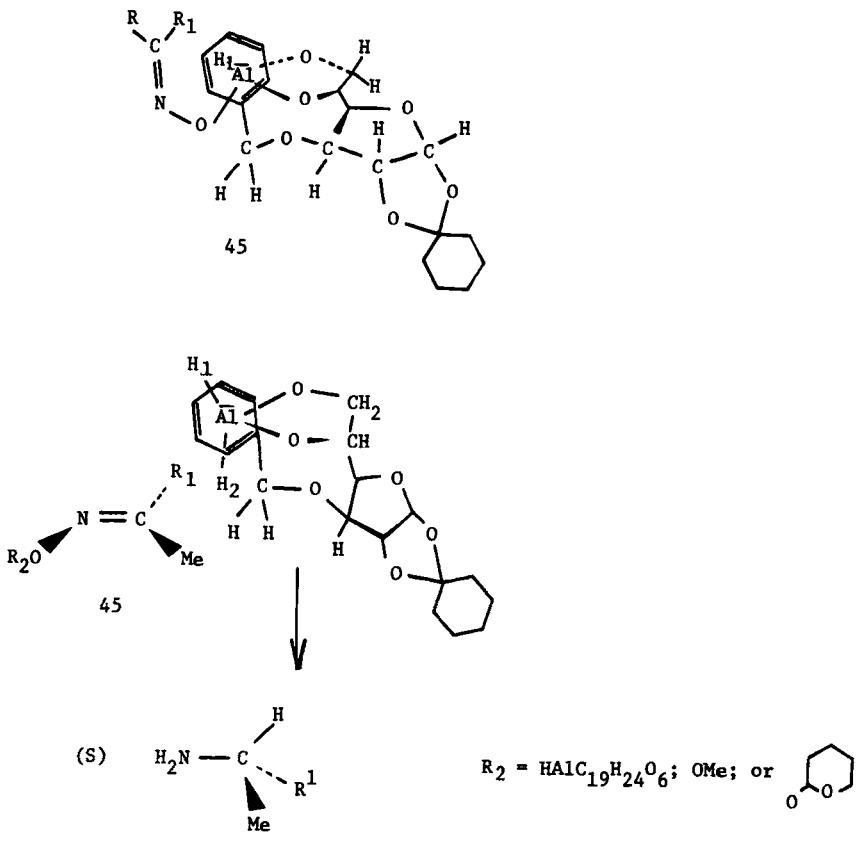
[a]These experiments were carried out with a 1 : 1 ratio of LAH to **36d**. Maximum stereoselectivity is obtained with LAH : **36d** = 1 : 0.73 and a fourfold excess of reducing complex.

the reversible formation of the diastereomeric 7-membered cyclic allene complexes from the initial planar trigonal aluminum allenide anion **42** (cf. Scheme 1). Complex **43** is the more stable form, having the fewest nonbonded interactions, and leads to the (*R*)-allenic alcohol on hydrolysis. An alternative strainless 14-membered cyclic complex that predicts the same stereochemical result was considered, but the 7-membered ring complex is the more convenient representation. The reduction was applied (Table 3) to the synthesis and determination of the absolute configuration of the naturally occurring diynallenols marasin* (**41**, R = H[C≡C]$_2$) and 9-methylmarasin (**41**, R = Me[C≡C]$_2$).

The **36d**-LAH complex was applied to the reduction of ketone oximes and their *O*-tetrahydropyranyl and *O*-methyl derivatives to optically active amines (69). Results for a variety of phenyl alkyl and dialkyl ketones are shown in Table 4. The predominant amines formed all were of the *S* absolute configuration with optical purities up to 56%. The oxime hydroxy group presumably reacts with the less hindered H_2 in the **36d**-LAH complex (cf. Scheme 6) to form an oxime complex (**45**), which probably undergoes *inter*molecular hydride transfer† of H_2 from a second molecule of the **36d**-LAH complex (Scheme 8). Asymmetric reduction with the ethanol-modified **36d**-LAH reagent gave amines of *R* con-

*Previous synthesis of (+)-marasin using reagent **13** led to difficulties in the separation of (+)-marasin from traces of (−)-menthol in the product (53).

†*Intra*molecular hydride transfer is sterically improbable due to coplanarity of the Al, O, N, and C atoms in **45**.



Scheme 8

figuration. The ethoxy group presumably replaced H_2, and reduction occurred only by transfer of H_1.

Extension (70) of this investigation to the reduction of *N*-phenylazomethines with **36d**-LAH gave optically active secondary amines (eq. [15]). The products had the *S* configuration, as predicted by reference to Scheme 9, with hydride transfer of the less shielded H_2 occurring preferentially when the phenyl points away from the shielding 3-*O*-benzyl group of the sugar derivative.

$$\text{PhN=C(Ph)R} + \textbf{36d}\text{-LAH} \longrightarrow \text{PhNH—CH(Ph)R} \qquad [15]$$

2. *Noncarbohydrate Diols*

A variety of readily prepared chiral cyclic diols have been complexed with LAH and studied as reducing agents. The reduction of a series of diphenylmethyl alkyl ketones (**46**) by complexes prepared (eq. [16]) from LAH and (−)-*cis*-2,3-

Table 4

Reduction of Ketone Oximes and *O*-Tetrahydropyranyl and *O*-Methyl Derivatives with **36d**-LAH[a] (69)

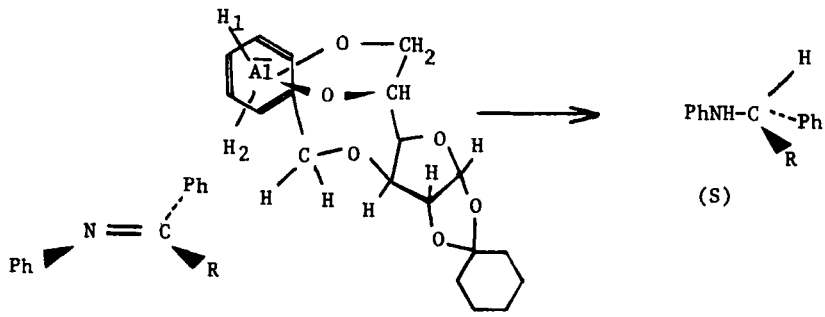
$$R_1R_2C{=}X + \textbf{36d}\text{-LAH} \xrightarrow{\text{ether}} R_1R_2CHNH_2{}^{b}$$

R_1	R_2	Optical purity (%)		
		X = NOH	X = NOThp[c]	X = NOMe
Me	Ph	10.7	3.6	12.8
Et	Ph	14.1	16.5	18.0
Me	$PhCH_2$	21.2	22.0	18.0
Ph	$PhCH_2$	24.8	25.6	27.2
Me	1-$C_{10}H_7$	9.5	11.3	13.8
Me	Et	14.6	20.9	18.0
Me	Bu	21.8	24.3	23.0
Me	Bu^i	19.5	18.5	18.4
Me	$(CH_2)_5Me$	24.0	26.8	22.6
Me	C_6H_{11}	56.2	49.8	44.0

[a]Maximum stereoselectivities were obtained with 1 : 1 molar ratios of LAH : **36d**. Yields of amines varied from ca. 60% to >70%.

[b]The amines all had the *S* configuration.

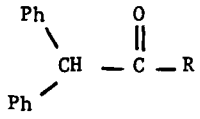
[c]Thp = tetrahydropyranyl.



R = Me, Et, Pr, Pr^i

Scheme 9

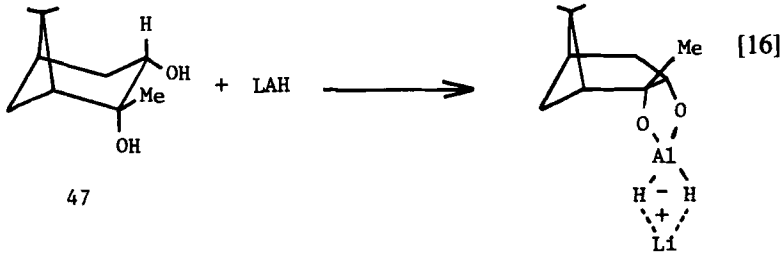
pinanediol (**47**) was investigated (71). Stereoselectivity was influenced by the introduction of a benzyloxy substituent in the chiral reagent. *cis*-Pinanediol is derived from (−)-α-pinene (65). A 25% optical yield of the (*S*)-carbinol was



R = Me, Et, Pr^n, Bu^n, Pr^i

46

obtained from the reduction of **46** (R = Pr^n) with the complex prepared from **47**, LAH, and benzyl alcohol in equimolar amounts. In a previous report (65),

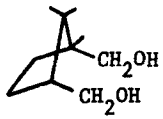


47 [16]

this reagent was used to reduce 6-dimethylamino-4,4-diphenyl-3-hexanone (**48**) to the (*S*)-(−)-amino alcohol (**49**) in a 32.8% optical yield (eq. [17]).

48 (S)(-)-49 [17]

Johnson and Klein (72) prepared the chiral diol (+)-1,2,2-trimethyl-1,3-bis(hydroxymethyl)cyclopentane (**50**) by the LAH reduction of (+)-camphoric acid. Consideration of models of the complex of **50** with LAH suggested that

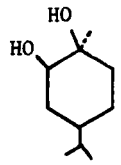


50

one diastereotopic hydride was in a hindered and the other in an unhindered environment. The complex was allowed to react with one equivalent of a number of simple achiral alcohols or with benzyl alcohol in the expectation that the

unhindered hydride would preferentially react, and that the remaining hindered hydride would provide greater asymmetric induction. Acetophenone was reduced with these reagents in a 3:1 ether–THF solvent with a ratio of ketone, LAH, **50**, and the achiral alcohol of 1:1:1:1. The best optical yield was 18.5%, obtained with 2-propanol as the alcohol addend. When the molar ratio of acetophenone with LAH, **50**, and 2-propanol was 1:2:2:2, the optical purity of the product fell to 8.3%. This suggested that disproportionation was occurring, since achiral species formed from disproportionation are presumed to be the more reactive reducing agents. In the absence of added alcohol, the optical purity of methylphenylcarbinol was 7.7%. When one molar equivalent of methanol was added to LAH (in the same solvent mixture) and **50** was then added, reduction of acetophenone gave (+)-methylphenylcarbinol with 7.4% optical purity. This was taken as evidence that lithium methoxyaluminum hydride undergoes disproportionation to LAH (73). Similar disproportionation occurred with lithium *t*-butoxyaluminum hydride.

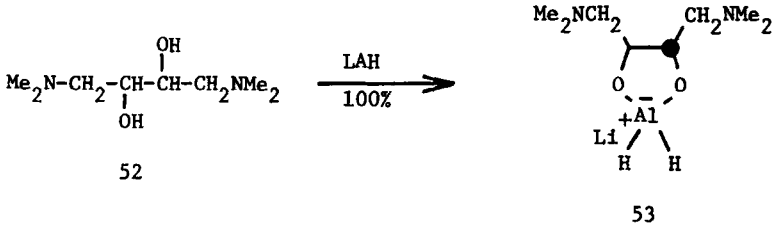
Several optically active glycols were prepared from (+)-limonene and (+)-α- and (−)-β-pinene by oxidation with $KMnO_4$ (74). An extensive study of the reduction of acetophenone by a complex of LAH and (+)-1-hydroxycarvomenthol (**51**) was made varying solvents and temperature, and the effect of added



51

ethanol and benzyl alcohol was examined. The highest optical yield of (+)-methylphenylcarbinol was 30% obtained with a molar ratio of acetophenone, **51**, ethanol, and LAH of 1.0:2.0:8.7:4.6 in ether at 25°. The reducing agents derived from the other glycols gave lower optical yields.

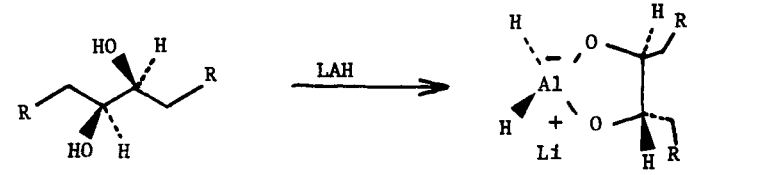
Seebach and Daum (75) investigated the properties of a chiral acyclic diol, 1,4-bis(dimethylamino)-(2*S*,3*S*)- and (2*R*,3*R*)-butane-2,3-diol (**52**) as a chiral auxiliary reagent for complexing with LAH. The diol is readily available from diethyl tartrate by conversion to the dimethylamide and reduction with LAH. The diol **52** could be converted to a 1 : 1 complex (**53**) with LAH (eq. [18]), which was used for the reduction of aldehydes and ketones in optical yields up to 75%. Since both enantiomers of **53** are available, dextro- or levorotatory products may be prepared. The chiral diol is readily recoverable without loss of optical activity. The (−)-**52**-LAH complex reduced dialkyl and aryl alkyl ketones to products enriched in the (*S*)-carbinol, whereas (+)-**52**-LAH gives the opposite result. The highest optical yield of 75% was obtained in the reduction of 2,4,6-



52 53 [18]

trimethylacetophenone with (−)-**52**-LAH to (−)-(*S*)-1-(2,4,6-trimethylphenyl)-1-ethanol. However, optical yields of 53% and less were generally obtained, with dialkyl ketones in the 2 to 20% range (75,76). Reduction of aldehydes with **53** gave low optical yields.

A more extensive series of chiral diols (**54**) were prepared by Seebach and co-workers (77) from tartaric or malic acids. These diols were converted to the cyclic 1 : 1 complexes (**55**) with LAH (eq. [19]). Reduction of a variety of aryl



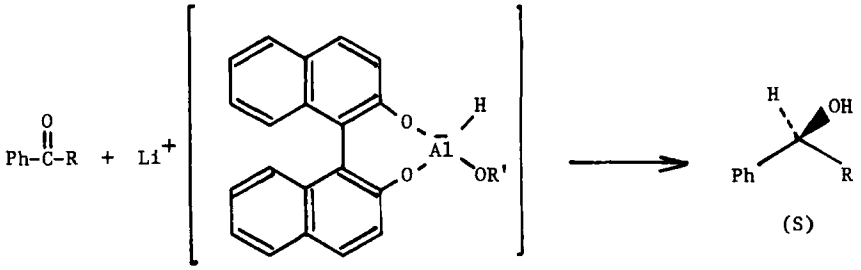
54a-g 55a-g [19]

R R

(a) pyrrolidino
(b) piperidino
(c) $N(CH_3)C_8H_{17}$
(d) $N(CH_3)C_6H_5$
(e) $N(CH_3)$-$[CH_2CH_2O]_3CH_3$
(f) OCH_3
(g) OC_6H_5
(h) RCH_2/RCH_2=H/$CH_2CH_2N(CH_3)_2$

alkyl and dialkyl ketones was explored with reagent **55a** in ether. Reduction of 2,4,6-trimethylacetophenone gave the corresponding (*S*)-carbinol in a 87% optical yield. However, reduction of 12 other ketones by **55a** gave optical yields of 45% and lower. Relatively low optical yields were obtained (<40%) in reductions of acetophenone with reagents **55a** to **h**.

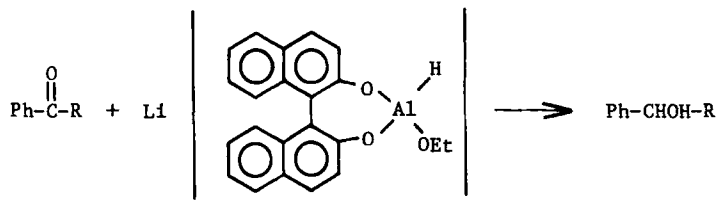
A very interesting and effective hydride reducing agent was prepared by Noyori and co-workers (78), based on the axially dissymmetric 2,2′-dihydroxy-1,1′-binaphthyl (79) as chiral auxiliary ligand. Reaction of the diol with LAH and one equivalent of an achiral alcohol in THF gave the chiral reducing agent **56**. The reagent is highly effective in the asymmetric reduction of phenyl alkyl ketones and benzaldehyde (eq. [20]), giving high optical yields of the corresponding carbinols (Table 5). Since both enantiomers of the chiral auxiliary reagent are accessible in optically pure form, both enantiomers of the carbinols



(S)-56 [20]

can be synthesized. The diols could be recovered without racemization. Satisfactory optical yields were not obtained, however, with dialkyl ketones. For example, reduction of methyl benzyl ketone gave the corresponding carbinol in only 13% optical yield. A systematic study of **56** was made by varying the nature of the achiral component —OR′ and the temperature, using acetophenone as substrate. The optical yield increased at lower temperatures, as expected. The extent and sense of asymmetric induction varied with the nature of the achiral —OR′ group. The ethoxy group gave the highest optical yield. With simple alkoxy groups, (*R*)-**56** gave the (*R*)-carbinol. However, with 3,3,3-trifluoro-

Table 5
Reduction[a] of Phenyl Alkyl Ketones with **56** (78)



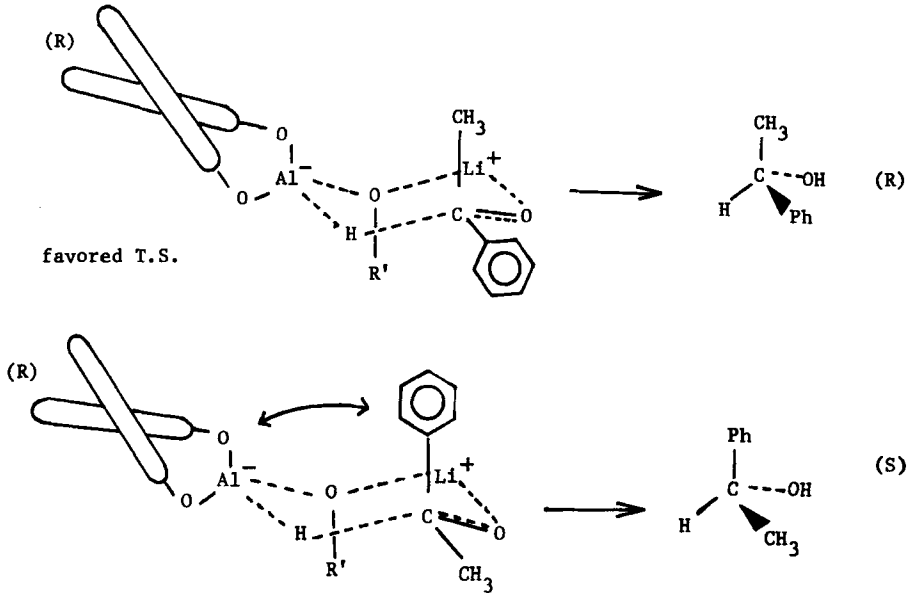
56

Substrate	Hydride[b]	Chemical yield (%)	Optical yield (%) Configuration
PhCDO	(*R*)-**56**	75	82 *R*
PhCOMe	(*R*)-**56**	61	95 *R*
PhCOEt	(*S*)-**56**	62	98 *S*
PhCOPr^n	(*S*)-**56**	78	100[c] *S*
PhCOBu^n	(*S*)-**56**	64	100 *S*
PhCOPr^i	(*S*)-**56**	68	71 *S*

[a]Reductions in THF at −100°C for 2–3 hr, then at −78°C for 16 hr.
[b]R_1 = Et.
[c]Optical purity checked by NMR analysis of the MTPA ester.

ethoxy or with 2,6-di-*t*-butylphenoxy groups as the achiral ligand, (*R*)-**56** gave the (*S*)-carbinol. The origin of this reversal in the sense of enantioselection is not explained.

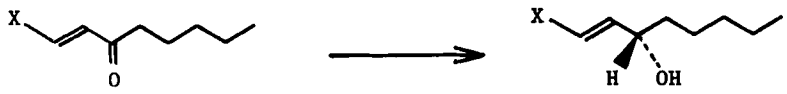
The observed enantioface differentiation in the reduction of the phenyl alkyl ketones was rationalized by postulating a 6-membered ring transition state for hydride transfer (Scheme 10). The transition state leading to the (*S*)-carbinol has an "axial" phenyl group interacting sterically with the binaphthoxy oxygen.



Scheme 10

The —OR′ oxygen is postulated to be the bridging atom because it has the highest basicity among the three oxygens attached to aluminum.

Application of Noyori's reagent to the synthesis of prostaglandin intermediates was highly successful (80). The iodovinyl ketone **57a** was reduced to the (*S*)-carbinol **58a** in a 95% synthetic yield and a 97% optical yield with (*S*)-**56** (OR′ = OEt). The analogous bromovinyl ketone **57b** gave the corresponding (*S*)-carbinol in 96% synthetic and optical yield (eq. [21]). These intermediates

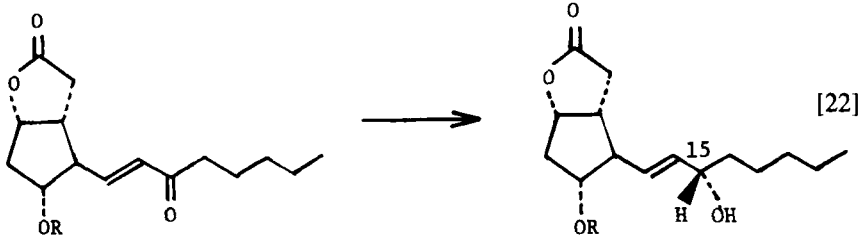


[21]

57 a X = I
b X = Br

58 a X = I
b X = Br

can be used for the synthesis of prostaglandins having the natural 15*S* configuration. The reagent (*S*)-**56** has been shown to be highly stereoselective in conversion of the enone sidechain of the bicyclic lactones **59** to the allylic alcohols **60** containing the 15*S* configuration. The tetrahydropyranyl derivative **59a** gave the carbinol **60a** in 95% yield and 99.5% optical purity, while the acetate derivative **59b** was reduced to the corresponding carbinol **60b** in 96% yield and 99.4% optical purity (eq. [22]). Reduction of the unprotected hydroxy enone

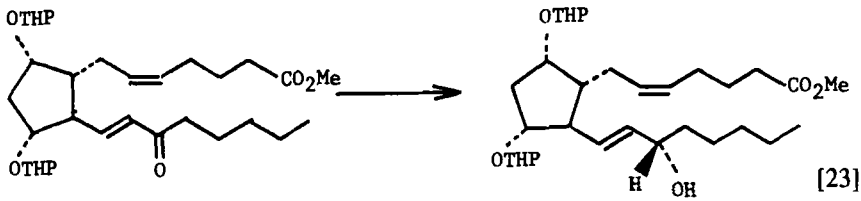


[22]

59a R = THP
b R = CH_3CO

60a R = THP
b R = CH_3CO

(**59**, R = H) gave the 15*S* alcohol (**60**, R = H) exclusively, but in 40% isolated yield. Reduction of the monocyclic enone **61** under the standard reduction conditions* gave the $PGF_{2\alpha}$ derivative **62** as a single stereoisomer in 76% isolated yield (eq. [23]).



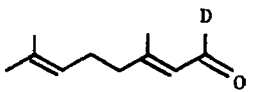
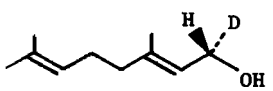
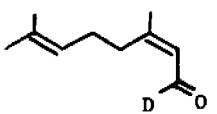
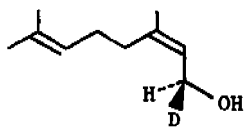
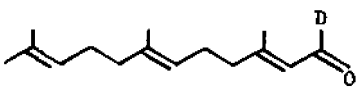
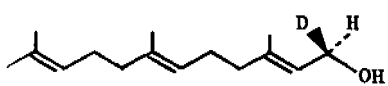
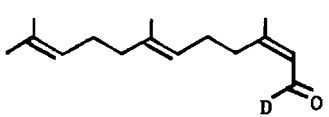
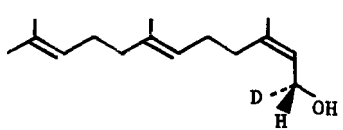
[23]

61 62

Nishizawa and Noyori (81) applied the reagent **56** to the asymmetric synthesis of chiral geraniol-1-*d* and related terpenic alcohols (Table 6). For example, reduction of geranial-1-*d* (entry 1, Table 6) with (*S*)-**56** gave (+)-geraniol-1-*d* of 91% optical purity. The absolute configuration of the dominant enantiomer was established by comparison with (*S*)-alcohol from the reduction of geranial-1-*d* with yeast alcohol dehydrogenase and NADH. A value of 84% e.e. was obtained by NMR analysis using the chiral lanthanide shift reagent $Eu(hfbc)_3$.

*In THF using 3 equivalents of **56** at −100°C for 2 hr and then at −78°C for 1 hr.

Table 6
Asymmetric Synthesis of Chiral Terpene Alcohols[a] (81)

Entry	Aldehyde	Reagent	Product	% e.e.[b]	Configuration
1		(*S*)-**56**		91,[c] 84	*S*
2		(*S*)-**56**		72	*S*
3		(*R*)-**56**		88	*R*
4		(*R*)-**56**		82	*R*

[a]Reductions carried out with 3 equivalents of **56** (R' = Et) in THF at −100°C for 2 hr. Isolated yields were 90 to 93%.
[b]Determined by NMR in the presence of Eu(hfbc)$_3$.
[c]Determined using optical rotation.

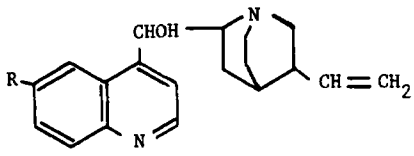
The four aldehydes studied were reduced in high optical yield and excellent synthetic yield. Either enantiomeric alcohol can be prepared using (*S*)- or (*R*)-**56**.

Alkynyl ketones **63** are reduced to chiral propargylic alcohols with the same reagent* in high optical and synthetic yields (82). The results are shown in Table 7. Reagent (*S*)-**56** gave (*S*)-alkynylcarbinols, whereas (*R*)-**56** gave the (*R*)-alcohols. Several of the acetylenic alcohols are useful for transformation into insect pheromones.

C. Reaction of $LiAlH_4$ with Amino Alcohols

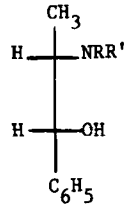
1. Alkaloids and Derivatives

Červinka and co-workers have extensively investigated the asymmetric reduction of prochiral ketones with LAH modified with alkaloids and related amino alcohols. Most of this work has been reviewed in detail by Morrison and Mosher (1) and will not be discussed extensively here. Modification of LAH was effected with (−)-quinine (**65**), (−)-cinchonidine (**66**), (−)-ephedrine (**67**), (−)-*N*-ethylephedrine (**68**), (−)-1-phenyl-2-dimethylaminoethanol (**69**), (+)-quinidine (**70**), (+)-cinchonine (**71**), and (+)-pseudoephedrine (**72**).



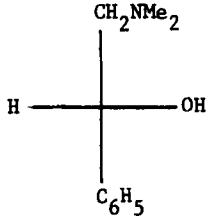
R = H cinchonine, cinchonidine

R = OMe quinine, quinidine

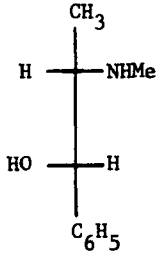


67, R = Me, R' = H

68, R = Me, R' = Et



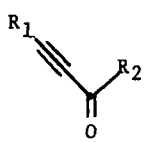
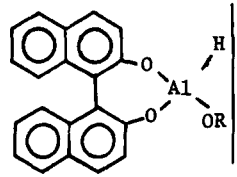
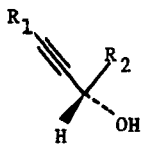
69



72

*Reagent **56** has been abbreviated to BINAL-H.

Table 7
Asymmetric Reduction[a] of Alkynyl Ketones with BINAL-H (82)

Ketone		56		Carbinol product[b]	
R_1	R_2	OR	Config.	% e.e.[c]	Config.[d]
	+ Li				
63		(S)-BINAL-H 56			64
H	n-C_5H_{11}	OMe	*S*	84	*S*
H	n-C_5H_{11}	OEt	*S*	84	*S*
H	n-C_8H_{17}	OMe	*S*	96	*S*
H	n-C_8H_{17}	OMe	*R*	94	*R*[e]
H	n-C_8H_{17}	OEt	*S*	90	*S*[e]
H	n-C_8H_{17}	O-Al[e]	*R*	92	*R*[e]
H	n-$C_{11}H_{23}$	OMe	*S*	92	*S*
H	Pr^i	OMe	*S*	57	*S*
n-C_4H_9	CH_3	OMe	*R*	84	*R*
n-C_4H_9	n-C_5H_{11}	OMe	*S*	90	*S*
CO_2Me	n-C_8H_{17}	OMe	*S*	87[f]	*S*[g]
n-C_8H_{17}	$CH_2CH_2CO_2Me$	OMe	*R*	84[h]	*R*[i]

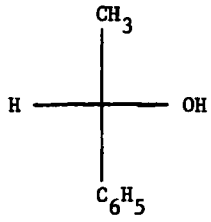
[a]Reduction carried out in THF with 3 equivalents BINAL-H at −100°C for 1 hr, then at −78°C for 2 hr.
[b]Isolated yields were 64 to 90%.
[c]Determined by HPLC analysis of MTPA derivatives.
[d]Determined by comparison of optical rotations.
[e]H_2O (0.5 equivalent) used to prepare BINAL-H.
[f]Determined by HPLC analysis of the 3β-acetoxyetienate derivative.
[g]Determined by conversion to (*S*)-(−)-2-acetoxydecanoic acid.
[h]Determined by NMR analysis of the MTPA derivative in the presence of a shift reagent.
[i]Determined by conversion to 5-tetradecyn-4-olide.

The reduction of phenyl mesityl ketone was studied with LAH modified with amino alcohols **65** to **72** in ether (the ratio LAH : alcohol : ketone = 1.1 : 1.1 : 1) (83). Optical yields were modest, with the highest 39%, obtained with **65** as the chiral auxiliary reagent. It was observed that there is a relationship between the preferred enantiomeric product and the structure and absolute configuration of the carbons carrying the hydroxy and amino groups. Thus the threo

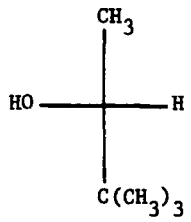
configuration of **72** gave preferential formation of the (*R*)-alcohol, while the erythro configuration of **67** gave the *S* isomer.

Coordination of the aluminum atom of the reducing complex was proposed to take place both to the oxygen atom of the hydroxy group and to the nitrogen atom of the amino group. The asymmetric reduction of enamine perchlorates and ketimines with menthol and borneol chiral auxiliary reagents (50,51) presumably involves coordination of aluminum to the nitrogen atom of the substrate.

Asymmetric reduction of acetophenone led to (*R*)-(+)-1-phenyl-1-ethanol with **65** to **69**, and with **72**, whereas the (*S*)-(−)-alcohol was formed with **70** and **71**. Again the optical yields were relatively low, with the highest 48%, obtained with **65**. Asymmetric reductions in very low optical yields were observed with the simple alcohols (−)-1-phenyl-1-ethanol (**73**) and (−)-3,3-dimethyl-2-butanol (**74**) as chiral auxiliary reagents.



73



74

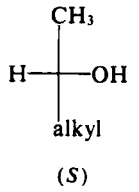
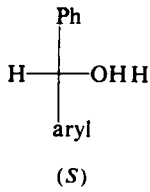
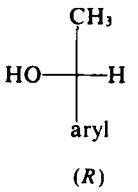
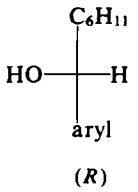
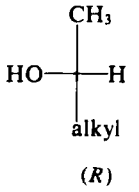
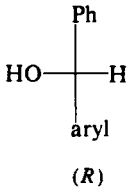
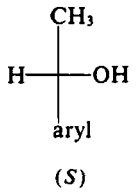
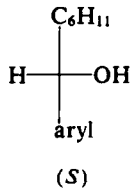
A marked solvent effect on the sense of asymmetric induction was observed. For example, reduction of acetophenone with **65** in refluxing ether gave the (*R*)-alcohol in 48% optical yield, and reduction in boiling THF gave the (*S*)-alcohol in 9.5% optical yield. A number of other similar reversals were observed. In ether solvent, an empirical relationship can be drawn between the configuration of the alcohol used for preparation of the reducing complex and the configuration of the enantiomeric product alcohol formed in excess. The relationship depends on the type of substrate used and is summarized in Table 8.

On the basis of this empirical relationship, the absolute configuration of the dextrorotatory alcohols formed in the reduction of a series of aryl alkyl ketones (**75**) with (−)-quinine-LAH in ether was assigned as *R* (84). Reduction of a series of α,β-unsaturated ketones (**76**) with (−)-quinine-LAH gave a product mixture consisting mainly of dextrorotatory unsaturated alcohols (**77**) (85). The unsaturated alcohols **77** were shown to have the *R* configuration.

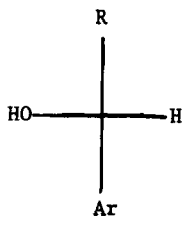
The analogous reagent prepared from (−)-quinine and $LiAlD_4$ reduced arenecarbaldehydes to the corresponding (*S*)-(+)-1-deuterio alcohols in 16 to 35% e.e. (86).

Vigneron and co-workers have developed an *N*-methylephedrine-LAH com-

Table 8
Relationship between Amino Alcohol Auxiliary Reagent and Absolute Configuration of Product Alcohol (83)

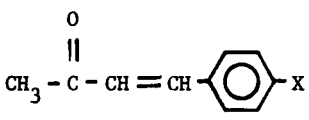
Amino alcohol	Absolute configuration of product alcohols[a]			
65 to **68**				
	(*S*)	(*S*)	(*R*)	(*R*)
70, **71**				
	(*R*)	(*R*)	(*S*)	(*S*)

[a]In ether solvent; ratio LAH : amino alcohol : ketone = 1.1 : 1.1 : 1.

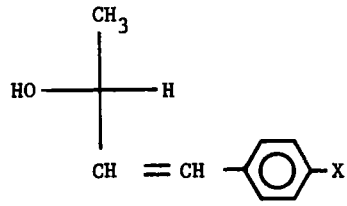


R	Ar
Et	Ph
Me	1-$C_{10}H_7$
Me	o-CH_3-C_6H_4
Me	m-CH_3-C_6H_4
Me	p-CH_3-C_6H_4

75



76

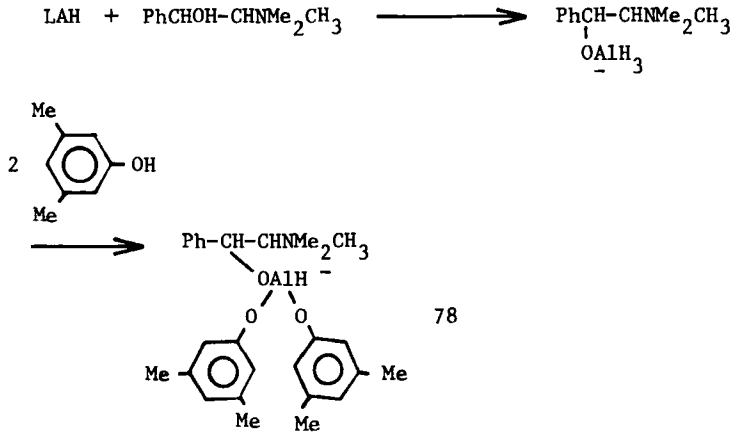


77

X = H, Me, MeO, NMe_2, Cl, Br, F

plex into a synthetically useful tool (87,88). A thorough study was made of the effect of a variety of reaction condition parameters on the optical yield of reduction of acetophenone with a reducing complex formed from one molar equiv-

alent of LAH, one equivalent of *N*-methylephedrine, and two equivalents of an achiral alcohol or phenol. After testing a wide variety of alcohols and phenols, a reducing complex (**78**) formed using 3,5-xylenol as the achiral component was found to be the most effective reagent (eq. [24]). The stoichiometry chosen leaves a single hydride attached to the aluminum of the reducing complex, which facilitates interpretation of the results. The chiral auxiliary reagent *N*-methyl-



[24]

78

ephedrine is readily prepared from the available (+)- or (−)-ephedrine by the Eschweiler–Clarke method.

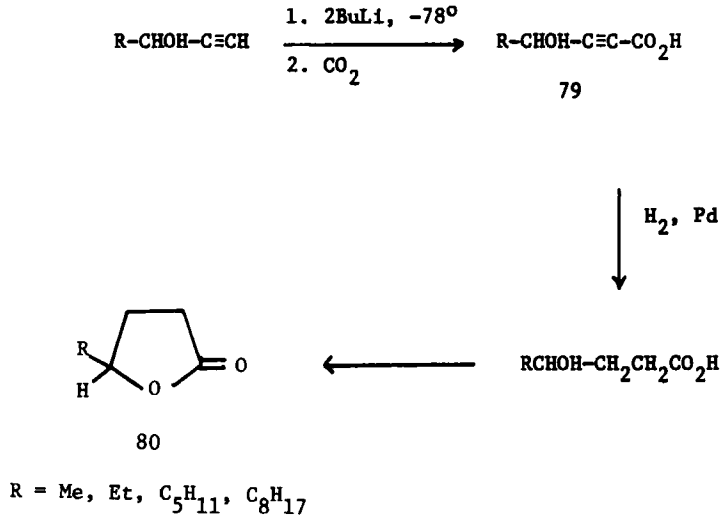
The optical yield was found to be very sensitive to structural modifications of the achiral agent. For example, use of the more bulky Pr^i or Bu^t substituents in the 3,5-positions of phenol resulted in lower optical yields. In some cases a reversal of the sense of asymmetric induction was observed. Systematic variation of reaction conditions using the best achiral component, 3,5-xylenol, established that optimum results were obtained in ether solvent at about −15°C. There was also a minor but definite influence of the rate of addition of ketone as well as an effect of concentration on optical yield, with a slower rate being advantageous. The results of reduction of aryl alkyl ketones are shown in Table 9, along with comparative results of reduction with similar chiral auxiliary reagents.

Reduction of aryl alkyl ketones with **78** was quantitative and (−)-*N*-methylephedrine was recovered with no loss in rotatory power. High optical yields were obtained with linear aliphatic chains in the ketone, but branching α to the carbonyl group lowered the optical yields significantly. Reduction of aliphatic methyl ketones with **78** at 0°C gave (*S*)-carbinols in low optical yield (14 to 46%).

The reagent **78** was found to be highly effective in the asymmetric reduction of α-acetylenic ketones (89). Acetylenic carbinols were prepared in 75 to 90%

e.e. with 70 to 90% chemical yields of isolated carbinols. Reduction was carried out at $-15°C$ with a three equivalent excess of the reagent. The results are summarized in Table 10 (entries 1 to 10). The high optical yields of acetylenic carbinols obtained are attributable to the presence of the electronic cloud of the acetylenic group, analogous to the role played by phenyl group in phenyl alkyl ketones. However, the effect is not clearly understood.

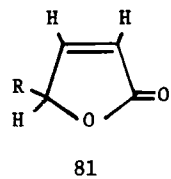
The α-acetylenic alcohols were used in a synthesis of optically active 4-alkyl-γ-lactones (**80**) (90), as shown in Scheme 11. Lactones with optical purity >



Scheme 11

95% of the *R* configuration could be obtained by recrystallization of the intermediate acids **79**.

In a similar manner, optically active butenolides (**81**) were prepared in overall



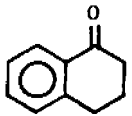
81

R = Et, n-C_8H_{17}, n-$C_{13}H_{27}$

yields of ca. 70% (91). The butenolides could be obtained optically pure by recrystallization of the acetylenic hydroxyacids **79**. NMR spectra of the lactones in the presence of chiral europium complexes revealed optical purities > 98%.

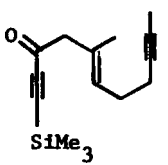
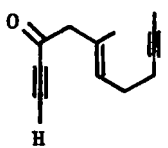
Table 9
Asymmetric Reduction of Aryl Alkyl Ketones with Amino Alcohol–LAH Reagents

ArC(=O)—R		Reagent									
		78[a]		**86**[b]		**90**-LAH		**98**b-LAH[c]		**105**[d]	
Ar	R	% ee[e]	Configuration	% ee[e]	Configuration	% ee	Configuration	% ee	Configuration	% ee[e]	Configuration
Ph	Me	84	*R*	88[f]	*S*	75[g,h](75)[i]	*R*[g](*S*)[i]	60[j]	*S*	65	*R*
Ph	Et	85	*R*	90	*S*					62	*R*
Ph	Pr	89	*R*	—	—	62[g,k]	*R*				
Ph	Bu	78	*R*	80	*S*						
Ph	Pr[i]	17	*R*	78	*S*	28[h,k]	*R*			43	*R*
Ph	c-C_6H_{11}[l]	11	*R*								
Ph	Bu[i]	84	*R*								
Ph	Bu[t]	31	*S*			35[h,k]	*R*				
p-Me—C_6H_4	Me	63	*R*								

p-Et—C_6H_4	Me	58	*R*
		68[m]	*R*

[a](−)-*N*-methylephedrine is the chiral component. Reaction temperature −15°C, solvent ether (88).
[b]Reductions were carried out in ether at −78°C (94).
[c]Reduction at −70°C (103).
[d]Mole ratio **104**:LAH = 2.3:1. Reduction in THF at −78°C. Product yields 78 to 81% (106).
[e]Based on optical rotation.
[f]Reaction at −100°C.
[g]Molar ratio LAH:**90**:ketone = 1.0:2.30:0.64. Reaction at −65°C with heterogeneous reagent used immediately on preparation.
[h]Analysis based on NMR of MTPA esters in presence of $Eu(fod)_3$ shift reagent.
[i]Reagent is aged homogeneous ether solution. Molar ratio LAH:**90**:ketone = 1.0:2.30:0.21; reaction at room temperature.
[j]Determined by GC of MTPA ester. Yield of product 83%.
[k]LAH:**90**:ketone ratio = 1.3:3.0:1.0 insoluble reagent; reaction at 0°C.
[l]Cyclohexyl.
[m]*T* = 0°C.

Table 10
Asymmetric Reduction of Acetylenic Ketones with Amino Alcohol–LAH Reagents

Entry	Ketone	Reagent	% e.e.	Configuration	Reference
1	Me—CO—C≡CH[a]	**78**	79[b]	*R*	89
2	Et—CO—C≡CH[a]	**78**	86	*R*	89
3	Bu—CO—C≡CH	**78**	85	*R*	89
4	Am—CO—C≡CH	**78**	84	*R*	89
5	Pr^i—CO—C≡CH	**78**	86	*R*	89
6	Bu^t—CO—C≡CH	**78**	90	*R*	89
7	Bu^i—CO—C≡CH	**78**	88	*R*	89
8	$C_6H_{11}CO$—C≡CH	**78**	83	*R*	89
9	$C_{11}H_{23}CO$—C≡CH	**78**	75	*R*	89
10	Bu^iCO—C≡C—Me	**78**	88	*R*	89
11	Me—C≡C—CO—Bu^i	(+)-**90**-LAH[c]	82[d]	*R*	101
12	HC≡C—CO—C_5H_{11}	(+)-**90**-LAH	72[d]	*R*	101
13	Me_3SiC≡C—CO—C_5H_{11}	(+)-**90**-LAH	66[d]	*R*	101
14	$C_5H_{11}C$≡C—CO—C_5H_{11}	(+)-**90**-LAH	62[e,f]	*R*	101
15		(+)-**90**-LAH	78[f]	*R*	101
16		(+)-**90**-LAH	82[f]	*R*	101

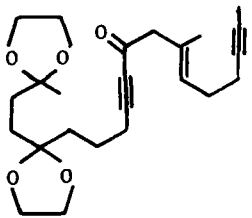
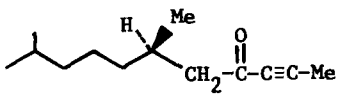
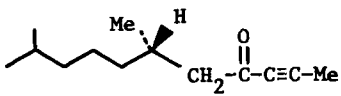
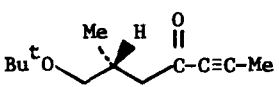
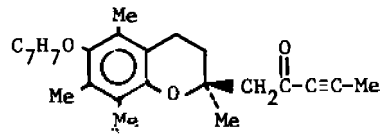
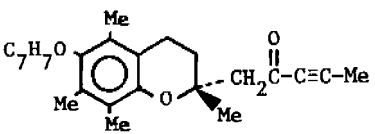
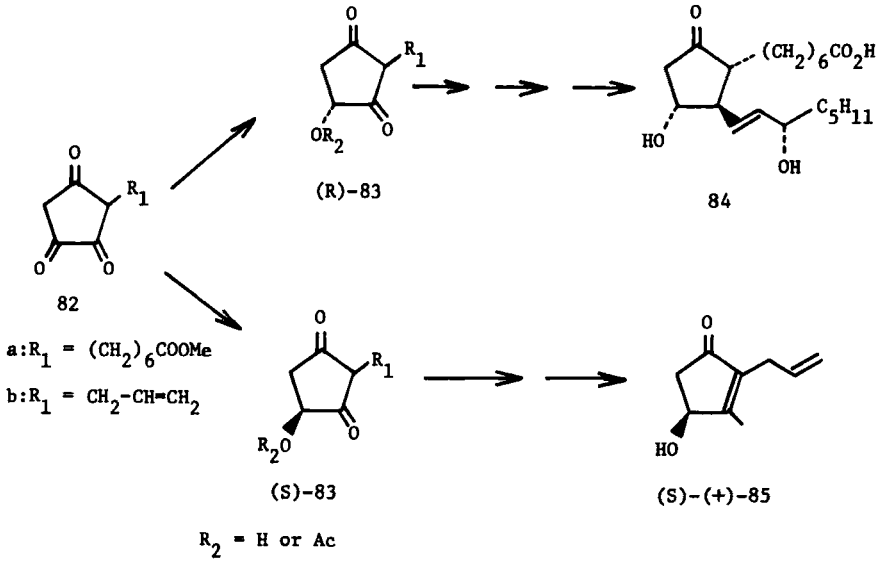
17		(+)-**90**-LAH	84[f]	*R*	101
18	$Bu^i—C(=O)—C\equiv C—Me$	(+)-**90**-LAH[g]	82[h]	*R*	103
19	$Bu^i—C(=O)—C\equiv C—Me$	**98b**-LAH[g]	36[h]	*S*	103
20	$Bu^i—C(=O)—C\equiv C—Me$	**98c**-LAH[g]	34[h]	*S*	103
21		**90**-LAH[g]	64[h,i]	R^i	103
22		**90**-LAH[g]	68[h,i]	R^i	103
23		**90**-LAH[g]	86[i,j]	R^i	103

Table 10 (*Continued*)

Entry	Ketone	Reagent	% e.e.	Configuration	Reference
24		**90**-LAH[g]	34[i,k]	*R*[i]	103
25		**98a**-LAH[g]	90[i,k]	*S*[i]	103
26		**98b**-LAH[g]	72[i,k]	*S*[i]	103
27		**90**-LAH[g]	90[i,k]	*R*[i]	103
28		**98b**-LAH[g]	34[i,k]	*S*[i]	103

[a]Products were isolated in 30 to 50% yield.
[b]Determined by analysis of the MTPA esters in entries 1 to 10.
[c]Reduction at −78°C with molar ratio **90**:LAH = 2.53:1.1 in entries 11 to 17. Synthetic yields 70 to 97%.
[d]Determined by optical rotation.
[e]Determined by GC of MTPA derivatives.
[f]Determined by conversion of the active alcohol from entry 12 to the alcohol corresponding to this reduction.
[g]Mole ratio amino alcohol:LAH = 4.1:1.8. Reaction carried out at −70°C with insoluble, freshly prepared complexes in ether.
[h]Analysis by GC of MTPA ester derivatives.
[i]Data refer to carbinol center.
[j]Analysis by GC.
[k]Analysis by direct ^{1}H NMR of the epimer.

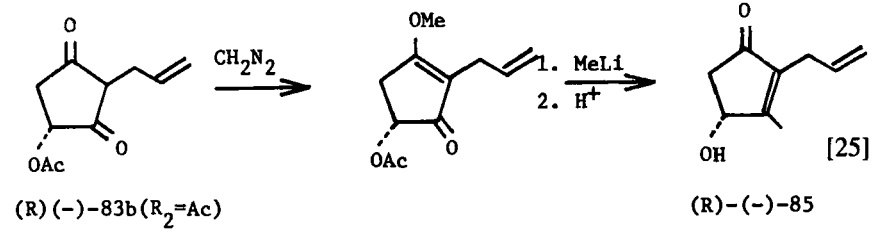
In a synthesis of optically active allethrolone and prostaglandin intermediates, Yamada and co-workers (92) studied the reduction of certain 2-alkyl-1,3,4-cyclopentanetriones (**82**) with a reagent prepared by the reaction of LAH with 3 equivalents of (−)-*N*-methylephedrine in THF. Reduction of the cyclopentanetriones **82** with this reagent gave (*R*)-**83** in 55 to 58% e.e. (Scheme 12). Thus (*R*)-**83b** (R_2 = Ac, after acetylation) was obtained in 48% yield and 55% e.e. from **82b**. The steric course and enantiomeric excess in the reduction were



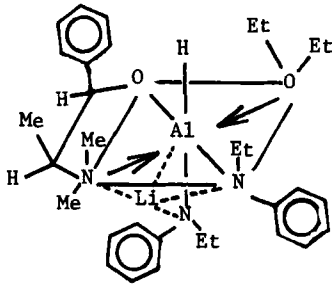
Scheme 12

established by chemical correlation of (*R*)-(−)-**83b** (R_2 = Ac) with (*R*)-(−)-**85** (eq. [25]). Since (+)-*N*-methylephedrine is available, this sequence of reactions is expected to give (*S*)-(+)-**83b** (R_2 = Ac), and finally allethrolone (*S*)-(+)-**85** (shown in Scheme 12).

Similar reduction of **82a** gave (*R*)-(+)-**83a** (R_2 = H) in 58% yield, with ca.



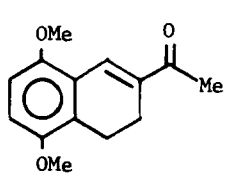
[25]



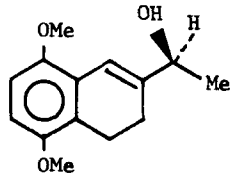
86

54% optical purity (70% after recrystallization). Intermediate (*R*)-(+)-**83a** has been converted (93) to PGE_1 (**84**).

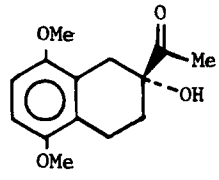
A chiral hydride complex, tentatively assumed to be **86**, prepared by partially reacting LAH with (−)-*N*-methylephedrine (1 equivalent) and *N*-ethylaniline (2 equivalents) was found to reduce 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (**87**) quantitatively to the (−)-carbinol (**88**) with 92% e.e. (94,95). Carbinol **88**, which was obtained optically pure by recrystallization, could be converted to (*R*)-(−)-2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (**89**). The lat-



87



88



89

ter is a key intermediate in the synthesis of anthracyclinones, the aglycones of the anthracycline antibiotics. The asymmetric reduction of simple ketones with **86** was explored. Reduction of phenyl alkyl ketones generally gave alcohols with high optical purity (Table 9). It is of interest that branching at the α carbon of the alkyl group again lowered the optical yield. 1-Indanone, α- and β-tetralones gave lower optical yields (51 to 71%), and alkyl methyl ketones gave poorer optical yields. Synthetic yields were uniformly high.

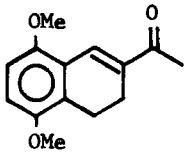
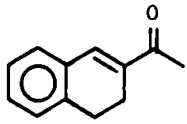
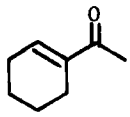
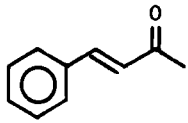
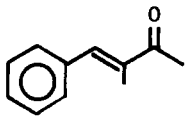
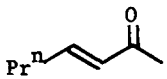
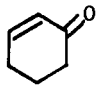
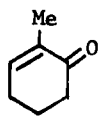
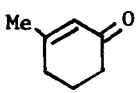
A variety of α,β-unsaturated ketones have been reduced with **86** (96) with moderate to excellent optical yields (Table 11).

2. *Darvon Alcohol and Other Amino Alcohols*

Yamaguchi, Mosher, and Pohland (97,98) studied the properties of a chiral reducing reagent prepared by the reaction of 2 to 3 equivalents of (+)-(2*S*,3*R*)-

Table 11

Reduction[a] of α,β-Unsaturated Ketones with **86** (96)

Ketone	Optical yield (%)[b]	Configuration
	92	*S*
	>90[c]	*S*[d]
	78	*S*
	98	*S*
	>90[c]	[e]
	88	*S*
	32	*S*
	58[c]	[e]
	24[c]	[e]

[a]Reduction in ether at −78°C.

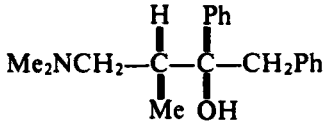
[b]Based on optical rotation except where indicated otherwise.

[c]Determined by NMR in presence of $Eu(hfc)_3$.

[d]Tentative assignment.

[e]Not determined.

4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol, (+)-(**90**). Reduction of acetophenone with a 2.3 : 1 **90**-LAH reagent within 3 min after its preparation gave (*R*)-(+)-methylphenylcarbinol with 75% e.e. (at −65°C). However, when the reagent was allowed to stand for 10 min or longer, reduction of acetophenone

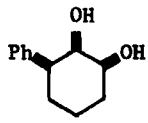


(+)-**90**

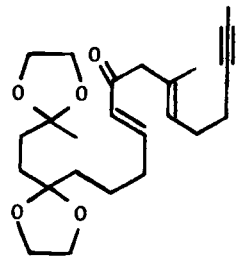
gave the (*S*)-(−)-carbinol in up to 66% e.e. This reversal in the sense of asymmetric induction on aging was observed using other molar ratios of **90** to LAH. Results of reductions of several phenyl ketones are shown in Table 9.

A 2 : 1 (−)-**90**-LAH reagent was employed in the asymmetric synthesis of a *cis*-diol (**91**) by reduction of *cis*-2-acetoxy-6-phenylcyclohexanone (99,100). Diol **91** is of interest as the tetrahydro derivative of a metabolite obtained from the microbial oxidation of biphenyl. Diol **91** was obtained in 46% e.e. as determined by NMR in the presence of a chiral shift reagent. It was shown to have the absolute stereochemistry (1*S*,2*R*)-dihydroxy-3(*S*)-phenylcyclohexane by oxidation to (+)-2-(*S*)-phenyladipic acid of known absolute stereochemistry.

Brinkmeyer and Kapoor (101) reported that the chiral hydride complex formed from LAH and (+)-**90** (Darvon alcohol) gave high enantiomeric ratios of chiral propargylic carbinols in the reduction of acetylenic ketones (Table 10, entries



91



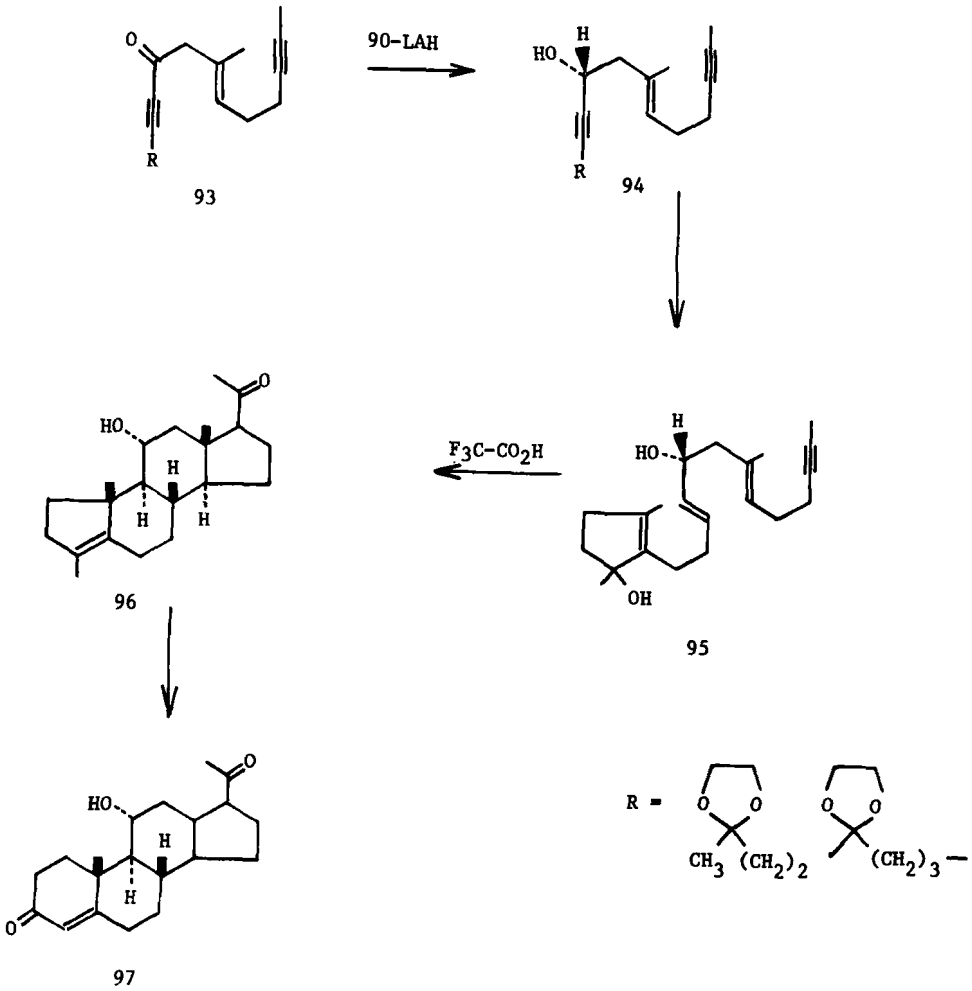
92

11 to 17). The enantiomeric excesses and absolute configurations of the carbinols are similar to those obtained with reagent **78**. In contrast to the acetylenic bond, the olefinic bond did not enhance asymmetric induction of an adjacent carbonyl group, since reduction of **92** gave the (*R*)-carbinol in only 25% e.e.

The Darvon alcohol–LAH complex was used in the reduction of the acetylenic ketone (**93**) in one step of an asymmetric total synthesis of 11α-hydroxyprogesterone (**97**), a key intermediate in the production of hydrocortisone acetate

(Scheme 13) (102). The acetylenic carbinol **94** was obtained in a 93% yield with 84% optical purity.

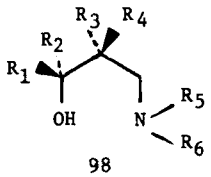
In the course of a synthesis of vitamin E intermediates, a study was carried out of the reduction of α-β-acetylenic ketones with the Mosher–Yamaguchi LAH–Darvon complex, as well as with a series of new chiral 1,3-amino alcohols (103). The results of the reductions with the Mosher–Yamaguchi complex* and



Scheme 13

*Darvon alcohol corresponds to R_1 = $PhCH_2$; R_2 = Ph; R_3 = CH_3; R_4 = H; R_5 = R_6 = CH_3. Note that **98a** is the enantiomer of Darvon alcohol, that is, (−)-**90**.

with several of the newly synthesized chiral 1,3-amino alcohols (**98**) are shown in Table 10 (entries 18 to 28). Reductions with the Mosher–Yamaguchi complex gave predominantly the (*R*)-carbinol, in generally high enantiomeric excess, whereas complexes prepared from **98b** and **98c** gave a preponderance of the

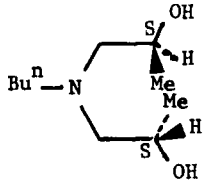


98

	R_1	R_2	R_3	R_4	R_5	R_6
a:	Ph	$PhCH_2$	H	CH_3	CH_3	CH_3
b:	H	H	CH_3	H	CH_3	CH_3
c:	H	H	CH_3	H	$-(CH_2)_4-$	

carbinol of opposite chirality. Synthetic yields of isolated products were generally very good (60 to 99%) in the reductions shown in Table 10, entries 18 to 28.

Systematic studies aimed at designing new effective reducing agents have been initiated. Morrison and co-workers (104) have prepared four chiral 1,2-aminodiols (**99** to **102**) in which the configuration and location of chiral centers were varied in a systematic manner. In **99** the chiral carbinol centers are responsible for asymmetric induction; **100** involves induction by the chiral center



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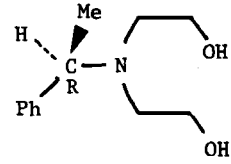

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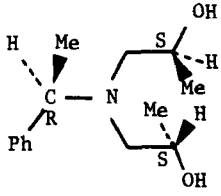

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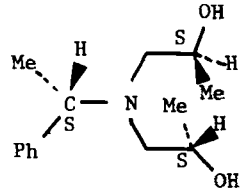
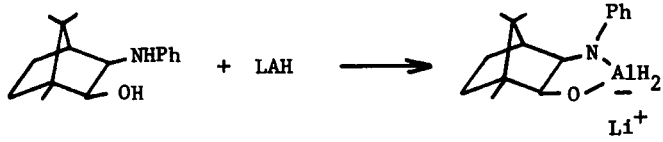


102

next to the nitrogen atom; **101** involves carbinol center induction opposed by that of the chiral center next to nitrogen, and **102** involves carbinol induction reinforced by that of the chiral center next to the nitrogen. Reduction of acetophenone and propiophenone by complexes of the 1,2-amino diols with LAH

using the general procedure of Cohen and co-workers (103) showed that **102** was the most effective chiral auxiliary reagent of the group. Acetophenone and propiophenone were reduced with 82% and 77% e.e., respectively, and in 98% yield. The tertiary amine function coordinates Li^+, which is also coordinated to the carbonyl oxygen, activating it for hydride acceptance.

A 1,2-amino alcohol, (+)-(1*R*,4*S*)-3-exo-anilino-2-exo-hydroxybornane (**103**), was synthesized from (+)-camphor and converted to its LAH complex (eq. [26]). Reduction of acetophenone, propiophenone, and butyrophenone at low

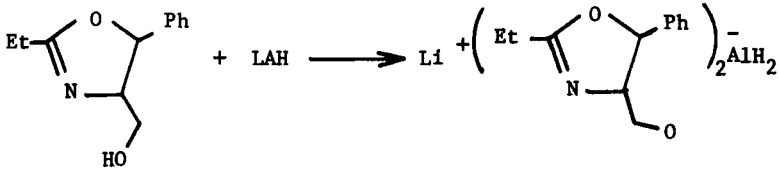


[26]

103

temperatures (−78° and −98°C) gave (*R*)-carbinols with moderate optical yields of 26 to 43% (105).

Moderate optical yields of phenyl alkyl carbinols were also obtained (Table 9) with a reagent (**105**) prepared by the reaction of chiral oxazolines (**104**) with LAH (106) (eq. [27]). Dialkyl ketones and α-tetralone gave very low optical yields. The oxazoline was recoverable from the reaction mixture.

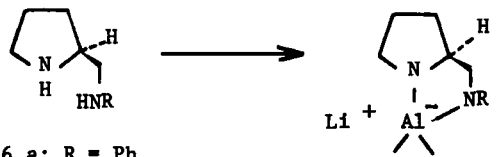


[27]

104 105

D. Reaction of $LiAlH_4$ with Chiral Amines

A series of chiral diamine auxiliary reagents (**106**) were synthesized from (*S*)-proline by Mukaiyama and co-workers (107,108). Reaction of the diamines with LAH gave reducing complexes (eq. [28]), which were then evaluated by reduction of acetophenone under a variety of experimental conditions. A large number



[28]

106 a: R = Ph
b: R = cyclohexyl

of *R* substituent groups in **106** were examined, with R = Ph the most effective. The best conditions with the diamine (*S*)-2-(anilinomethyl)pyrrolidine (**106a**) involved reduction in ether at −100°C with a molar ratio of LAH : **106a** : PhCOMe = 2.36 : 2.73 : 1. (*S*)-1-Phenylethanol was obtained in a 93% yield with 92% optical purity. Results of the reductions of other ketones are shown in Table 12.

As with most other reducing agents, dialkyl ketones were reduced in low optical yields. The reactivity of the two hydrogens in the chiral reagent were markedly different. Only one hydrogen was reactive with ketones, the other being unreactive presumably because of steric hindrance. The reagent is assumed to have a rigid structure containing the cis-fused 5-membered rings. Addition of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) or 1,2-dimethoxyethane (DME) lowered the optical yields (Table 12). Therefore Li^+ plays a role in the reduction, presumably coordinating to the nitrogen atoms on the pyrrolidine ring and/or on the sidechain in the reducing complex, and affecting the direction of approach of the ketone.

Chiral *tert*-diamines complexed with LAH gave very low optical yields in reductions of prochiral ketones. *N,N,N',N'*-Tetramethyl-1,2-cyclohexanediamine complexed with LAH or $LiAlD_4$ reduced phenyl alkyl, dialkyl ketones or benzaldehyde in <15% optical yields (109).

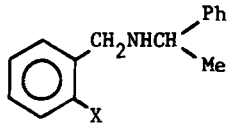
In order to study the role of a variety of functional groups present in a chiral

Table 12
Asymmetric Reductions with **106**-LAH[a] (108)

Ketone	Diamine	Yield (%)	Optical purity (%)[b]
PhCOMe	**106a**	84	84
PhCOMe	**106b**	78	59
PhCOMe	**106a**	67[c]	18[c]
PhCOMe	**106a**	84[d]	38[d]
PhCOEt	**106a**	90	85
PhCOEt	**106b**	40	63
PhCOPr^i	**106a**	80	57
PhCOPr^i	**106b**	83	51
α-tetralone	**106a**	94	50
α-tetralone	**106b**	80	4
$PhCH_2COMe$	**106a**	85	31
n-$C_6H_{13}COMe$	**106a**	77	13

[a]Reductions probably were carried out in ether at −78°C, although temperature was not stated.
[b]All carbinols had *S* configuration.
[c]Reaction in ether at −78°C, in presence of TMEDA. Molar ratios: **106a**:LAH:TMEDA = 3.07:2.66:2.66.
[d]Reaction in ether at −78°C in presence of DME. In the additive experiments molar ratios LAH:**106a**:PhCOMe = 1.75:2.00:1.

secondary amine reagent, a series of (*S*)-(−)-*N*-(*o*-substituted benzyl)-α-phenylethylamines (**107**) were synthesized from corresponding *o*-substituted benzaldehydes (110). These chiral amines were reacted with LAH and used to reduce acetophenone at different temperatures and with different mole ratios of **107** : LAH.



107

	X =
107a	H
b	Me
c	NMe_2
d	OMe
e	SMe
f	2,4,6-Me_3

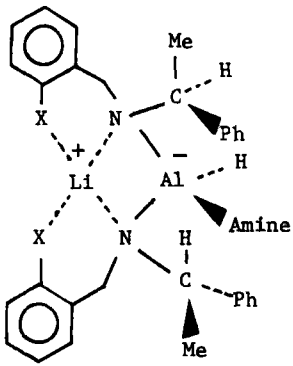
Toluene was chosen as the solvent in order to eliminate coordination involving solvent. Inconsistent variations were observed; however, the most selective reagent was prepared with **107c** in a 3 : 1 molar ratio of **107c** : LAH (Table 13), and this reagent was used to reduce several other aryl alkyl ketones (Table 13).

Table 13
Asymmetric Reductions with **107**-LAH[a] (110)

Ketone	Amine	% e.e.	Configuration
PhCOMe	**107a**	10.7	*R*
	107b	8.4	*R*
	107c	43.0	*R*
	107d	1.2[b]	*S*
	107e	4.4[c]	*R*
	107f	10.8[d]	*R*
PhCOEt	**107c**	52[e]	*R*
	107c	3.2[f]	*R*
	107c	1.4[g]	*S*
	107c	54[h]	*R*
PhCOBu^t	**107c**	47	*R*
$PhCOC_6H_{11}$	**107c**	14	*R*
Mesityl-COMe	**107c**	20	*R*

[a]Molar ratios **107**:LAH = 3.1. Complexes are soluble in the toluene solvent. Reactions carried out at 0°C.
[b]Reaction at −78°C gave (*S*)-carbinol in 15.3% e.e.
[c]Reaction at −78°C gave (*S*)-carbinol in 18.0% e.e.
[d]Reaction at −78°C gave (*R*)-carbinol in 18.0% e.e.
[e]% e.e. determined through its (*R*)-(+)-MTPA ester. Other analyses based on optical rotations.
[f]In presence of TMEDA, 2 molar equivalents based on hydride.
[g]In presence of DME, 2 molar equivalents based on hydride.
[h]In presence of 1,2-dimethylmercaptoethane, 2 molar equivalents based on hydride.

Asymmetric induction in the presence of the additives TMEDA or DME decreased dramatically, and 1,2-dimethylmercaptoethane had no effect. These results imply an important role of the NMe_2 group in controlling the stereochemistry of the reduction by coordinating with Li^+, an effect observed also by Mukaiyama and co-workers (108). Yamaguchi suggests structure **108** for the reducing complex.



$X = NMe_2$, OMe, SMe

108

In summary, a number of effective chiral reducing agents have been developed based on the modification of LAH. Excellent results have been obtained with aryl alkyl ketones and α,β-acetylenic ketones. However, dialkyl ketones are reduced in much lower enantiomeric excess. This clearly indicates that steric effects alone do not control stereoselectivity in these reductions. Systematic studies have been carried out with the objective of designing improved reagents. A better understanding of the mechanisms and knowledge of the active species is required in order to provide more accurate models of the transition states of the key reduction steps.

III. CHIRAL TRICOORDINATE* ALUMINUM REAGENTS

A. Aluminum Alkoxides and Derivatives

1. Aluminum Alkoxides and the Meerwein–Ponndorf–Verley (MPV) Reduction

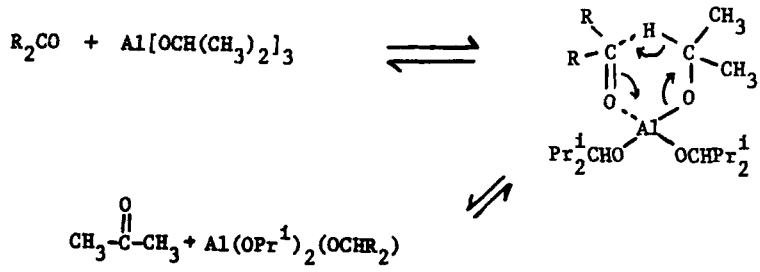
The Meerwein–Ponndorf–Verley (MPV) reaction is an important route in the reduction of ketones with aluminum alkoxides (111). The mechanism has been

*Many species that are tricoordinate in monomeric form are actually tetracoordinate in oligomeric form, or when complexed with donor ligands (e.g., in ether solvents).

formulated (112) as involving the following:

1. Coordination of the ketone to the alkoxide monomer.
2. Hydride transfer.
3. Separation of the ketone from the complex produced in step 2.
4. Alcoholysis of the mixed alkoxide, liberating the free alcohol.

Woodward (113) proposed that the hydride transfer occurs via a cyclic transition state (Scheme 14).



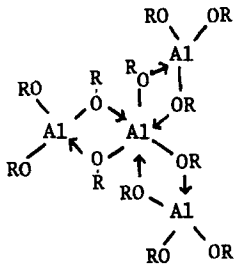
Scheme 14

Aluminum isopropoxide is shown as a monomer in Scheme 14, but it is known to exist in several oligomeric forms (114). Freshly distilled $Al(OPr^i)_3$ is mainly trimeric and is slowly transformed to a tetrameric form (**109**) in which a central octahedral aluminum atom is surrounded by three tetrahedral aluminum atoms (112).

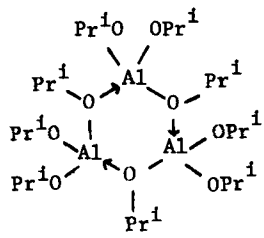
Structure **109** was confirmed using ^1H NMR by Shiner and co-workers (115) for solutions of the tetramer. This structure was further confirmed in a number of studies, for example a multinuclear NMR study involving ^{27}Al, 220 MHz ^1H, and ^{13}C spectra (116). Structure **110** was proposed for the trimer in solution (115).*

In an NMR study of the MPV reduction of acetophenone with $Al(OPr^i)_3$, Shiner and Whittaker (118,119) showed that the trimer is more reactive than the tetramer. Furthermore, the rate-determining step is alcoholysis of the mixed alkoxide, and not hydride transfer. They proposed that the ketone coordinates directly with trimer or tetramer by expansion of the coordination number of aluminum, and not with monomeric aluminum alkoxide.

*However, a different structure for the trimer was suggested by Turova and co-workers (117).



R = Pr^i 109



110

Other aluminum alkoxides are known to exist as oligomers (114). For example, $Al(OBu^t)_3$ is dimeric (115,120,121), as is the mixed alkoxide $Al(OPr^i)(OBu^t)_2$ (121,122).

2. *Chiral Aluminum Alkoxides and Derivatives*

Early studies of the asymmetric reduction of prochiral ketones by chiral aluminum alkoxides have been reviewed by Morrison and Mosher (1). Doering and Young (123) reported the reduction of methyl cyclohexyl ketone with chiral 3-methyl-2-butanol in the presence of a catalytic amount of aluminum alkoxide to give the (*S*)-(+)-carbinol in a 22% optical yield. Jackman and co-workers (124) similarly reduced methyl *n*-hexyl ketone with chiral 3,3-dimethyl-2-butanol to the (*S*)-(−)-carbinol in a 6% optical yield. Other attempts resulted in similar low optical yields or gave only racemic products. Since the reductions were carried out under equilibrium conditions, racemization could have accounted for the low optical yields.

A chiral catalyst prepared by the reaction of optically active 2-methyl-1-butanol with aluminum powder, or by an exchange reaction with aluminum isopropoxide, was reported to reduce 2-butanone in high optical yield (125). The asymmetric reduction of acetophenone and 3-methylcyclohexanone was also reported (125). These reductions are of interest, since with this aluminum alkoxide the chiral center is not incorporated into the cyclic transition state of the hydride-transfer step, and the stereoselectivity is not expected to be high. Baker and Linn (126a) had earlier attempted to carry out the first asymmetric MPV reduction with the aluminum alkoxide derived from (−)-2-methyl-1-butanol, but were unsuccessful. However, Morrison and Mosher (1) have pointed out discrepancies in the optical rotations of (−)-2-methyl-1-butanol and (+)-2-butanol reported by Yamashita (125), as well as maximum literature values for these alcohols. This reduction was reinvestigated by Lardicci and co-workers (126b). The catalyst prepared from the reaction of (−)-(*S*)-2-methyl-1-butanol by exchange with aluminum isopropoxide reduced 2-butanone to give (*S*)-(+)-

2-butanol with very low optical purity. The high degree of asymmetric induction reported with tris[(*S*)-2-methylbutoxy]aluminum (125) was apparently due to contamination of the product by (*S*)-(+)-2-methylbutanal.

Modified MPV-type reductions carried out with chiral magnesium alkoxides and with chiral Grignard reagents have been discussed in detail (1). These reagents differ from the aluminum alkoxides since the Grignard reaction is essentially irreversible. Chiral alkali metal alkoxides have also been used to effect asymmetric reductions (1).

Eliel and Nasipuri (127) studied the reducing properties of alkoxyaluminum dichlorides formed by the reaction of ketones or alcohols with "mixed hydride" ($HAlCl_2$) (128). They discovered that isobornyloxyaluminum dichloride (**111**) formed from the reaction of $HAlCl_2$ with isoborneol* is a good reducing agent, and also that camphor is unreactive toward $ROAlCl_2$ reagents. The reduction of ketones with **111** is therefore virtually irreversible and is also subject to marked steric approach control due to the size of the reagent.

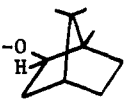
Horeau and co-workers (130) found that an ether solution containing four molar equivalents of (+)-camphor added to one molar equivalent of LAH, followed by addition of $AlCl_3$, reduced 2-butanone or pinacolone. The reagent involved is presumably the same as that prepared by Eliel and Nasipuri (**111**), although the reaction leading to the formation of **111** is different (eq. [29]). The

$$LiAlH_4 + 4(+)\text{-camphor} \longrightarrow LiAl(OR^*)_4 + 4\ H_2$$

$$LiAl(OR^*)_4 + 3\ AlCl_3 \longrightarrow LiCl + 4\ AlCl_2OR^* \qquad [29]$$

111

$-OR^*$ =

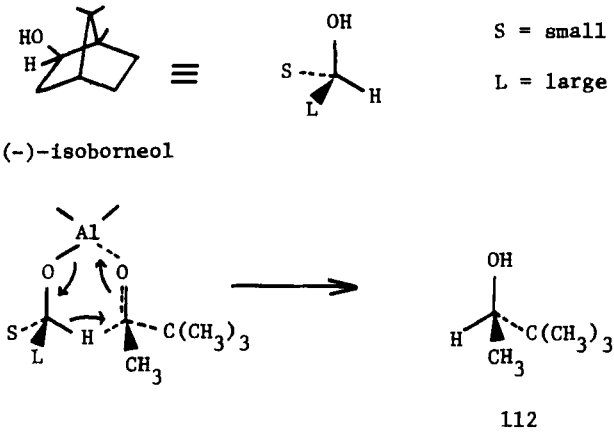


reduction of pinacolone with **111** gave (*R*)-(−)-methyl *t*-butylcarbinol (**112**) in a 20% optical yield. Preferential formation of the (*R*)-carbinol can be explained in terms of the cyclic hydride-transfer mechanism, as shown in Scheme 15. In general, the preferred transition state for reductions of ketones with **111** is shown in structure **113**, where S and L refer to small and large alkyl groups, respectively, or L is phenyl.† The (*R*)-carbinol (**114**) is formed from **113**.

Nasipuri and co-workers have extensively investigated complex **111** as a chiral reducing agent (131–138). The results of these investigations are summarized

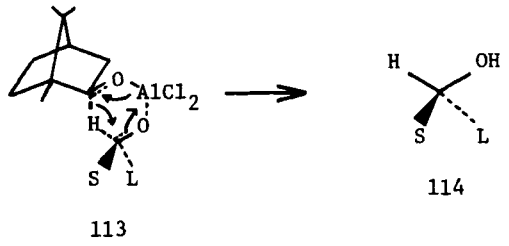
*Reduction of (+)-camphor with LAH gives a mixture of (−)-isoborneol (90%) and (+)-borneol (10%) (129). The complex with borneol reacts much slower with ketones.

†For a discussion of the effective size of the phenyl group, see ref. 1, pages 36–37.



Scheme 15

in Table 14. From a synthetic viewpoint, the reagent is not as effective as several of the tetracoordinate aluminum hydride reagents described in Sect. II. However, there are aspects of considerable theoretical interest embodied in the data. In common with other reagents, optical yields are higher for the phenyl alkyl series



than for methyl alkyl ketones. The optical yields also increased with branching at the α carbon of the alkyl group. The total absence of stereoselectivity in the reduction of methyl benzyl ketone could not be explained. Reduction of phenylglyoxylic acid and its ethyl ester (Table 14, entries 15 to 18) to (*S*)-(+)-mandelic acid is consistent with the preferred transition state **113** (Ph larger than CO_2H or CO_2Et), but reduction of the acid with the (−)-borneol complex inexplicably gave (*R*)-carbinol (Table 14, entry 16).

The stereochemical trend in the phenyl alkyl ketone series (Table 14, entries 6 to 11) is of considerable interest. The cyclic transition state model **113** correctly predicts the observed *R* configuration of the products, assuming the phenyl group is the bulkiest group (i.e., Ph = L). However, this model does not correctly predict the trend in the series since one would expect that *lower* asymmetric

Table 14

Asymmetric Reductions with (−)-Isobornyloxyaluminum Dichloride (**111**)

$$R{-}\overset{\overset{O}{\|}}{C}{-}R' + \mathbf{111} \longrightarrow R{-}CHOH{-}R'$$

	Ketone		Carbinol		
Entry	R	R′	Optical purity (%)	Configuration	Reference
1	Me	Et	2.8	*R*	131a
2	Me	Bu^i	5.0	*R*	133
3	Me	Pr^i	15.0	*R*	133
4	Me	Bu^t	18.0	*R*	133
5	Me	$PhCH_2$—	0.0	—	131a,b
6	Ph	Me	27.0	*R*	133
7	Ph	Et	38.0	*R*	133
8	Ph	Pr^n	44.0	*R*	133
9	Ph	Bu^i	66.0	*R*	133
10	Ph	Pr^i	84.0	*R*	133
11	Ph	Bu^t	35	*R*	136
12	Ph	*c*-C_6H_{11}[a]	40.0	*R*	133
13	Ph	D	10.4	*R*[b]	134
14	Ph	CF_3	8.4[c]	*S*	138
15	Ph	CO_2H	8[d]	*S*	132
16	Ph	CO_2H	52[d,e]	*R*[e]	132
17	Ph	CO_2Et	17[d]	*S*	132
18	Ph	CO_2Et	9[d,e]	*S*[e]	132

[a] *c*-C_6H_{11} is cyclohexyl.

[b] (−)-Bornyloxyaluminum dichloride gave the (*S*)-carbinol in 32.7% optical purity.

[c] A 68% optical yield was obtained with the (−)-bornan-2-*endo*-ol complex, and a 77% optical yield was obtained with a (*R*)-(−)-*p*-menthan-3-ol complex.

[d] Product is mandelic acid.

[e] Reagent derived from (−)-borneol.

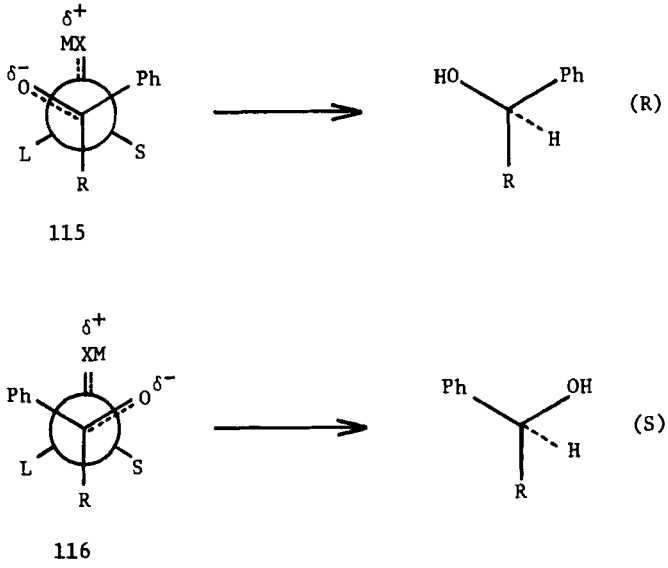
induction would occur as the bulk of the alkyl group increased. However, the results are the opposite, with the exception of the anomalously low degree of asymmetric induction with phenyl *t*-butyl ketone.

In order to explain this trend, Nasipuri and co-workers (135) adopted the essentially acyclic models **115** and **116** leading to the (*R*)- and (*S*)-carbinols respectively (Scheme 16). Models **115** and **116** are Newman-type formulas viewed along the C—H—C axis. The transition states are assumed to be reactant-like and involve loosely bound opposite dipoles $O^{\delta-}$ and $M^{\delta+}$.

In Scheme 16* (**115** and **116**), X = O and M = halogenated Al, while the

*The model is also meant to be applicable to reductions with Grignard reagents; X = CH_2 and M = halogenated Mg.

chiral carbon attached to X has the *R* configuration consistent with the (−)-isoborneol complex. Structures **115** and **116** are assumed to represent the most stable of several alternative conformations, with $XM^{\delta+}$ placed between the two negative dipoles, $O^{\delta-}$ and $C—Ph^{\delta-}$. The transition state **115** is favored over **116** on the basis of the unfavorable Ph ↔ L steric gauche interaction in the latter. With increasing bulk of R, rotation to separate L and R in **116** encounters a buttressing effect (increased Ph ↔ L interaction), which further favors **115**.



Scheme 16

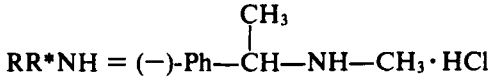
This explanation (135) rationalizes the stereoselectivity trend in the phenyl alkyl ketone series, but it does not explain the anomalous result with phenyl *t*-butyl ketone, which would be predicted to give the highest optical yield on the basis of this model.

A chiral aminoalane (**117**)* has been synthesized (eq. [30]) as well as a novel polymeric aminoalane (**118**) (139). Reduction of acetophenone by **117** in ether at −71°C gave the (*S*)-carbinol in an 85% optical yield (51% synthetic yield). Reduction of dialkyl ketones with **117** gave considerably lower optical yields, as did reductions with **118**.

*Compound **117** has specific rotation $[\alpha]_D^{23} = +27.5$ (c = 5, C_6H_6). It exists in benzene as a cis–trans mixture of a bridged dimer.

$$LiAlH_4 + RR^*NH \cdot HCl \longrightarrow RR^*N{-}AlH_2 + LiCl + H_2 \qquad [30]$$

117



118

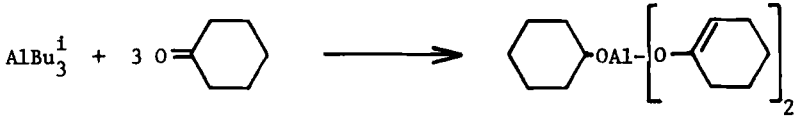
B. Organoaluminum Compounds

1. *Mechanism of Reduction of Ketones with Trialkylaluminum Reagents*

The reduction of carbonyl compounds with trialkyaluminum reagents has been known for several decades (140,141). Meerwein and co-workers observed that chloral is reduced to 2,2,2-trichloroethanol with triethylaluminum etherate (142). Organoaluminum reagents can function as reducing agents if they contain Al—H bonds or if they have hydrogen at a β (particularly a branched) position.

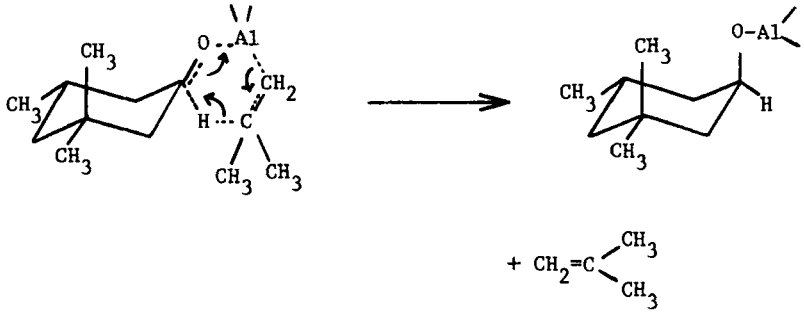
The reaction of $AlEt_3$ with carbonyl compounds gives a mixture of addition and reduction products (142–145). For example, the reaction of $AlEt_3$ with 3-pentanone gave addition, reduction, and enolization products, whereas reaction of diisopropyl ketone with the same reagent gave reduction and enolization, but no addition (145). The reduction of aldehydes with $AlEt_3$ was interpreted as a type of MPV reduction in which ethyl groups act as hydride donors (146).

Triisobutylaluminum (TIBA) is an effective reducing agent for ketones. However, in most cases only one isobutyl group is available for reduction. Enolization occurs after a rapid reduction involving the first isobutyl group (143,147). For example, an enolate is formed in the reaction of TIBA with cyclohexanone (143) (eq. [31]).



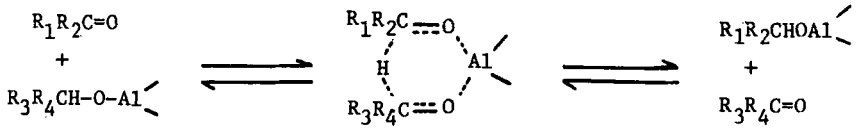
$$+ \text{i-}C_4H_8 + 2\ \text{i-}C_4H_{10} \qquad [31]$$

A study of the stereoselectivity of reduction of 3,3,5-trimethylcyclohexanone (**5**) with TIBA in benzene showed that under kinetically controlled conditions (excess reagent and short reaction time) 96% of *trans*-3,3,5-trimethylcyclohexanol (*trans*-**6**) was formed (148). This high degree of stereoselectivity was explained by proposing a cyclic 6-center transition state with hydride transfer occurring preferentially from the less hindered side (Scheme 17).



Scheme 17

In the presence of excess ketone, a slower equilibration occurred leading to *cis*-3,3,5-trimethylcyclohexanol (*cis*-**6**) almost exclusively (148). It was shown that aluminum 3,3,5-trimethylcyclohexyl alcoholate could be oxidized by the addition of cyclohexanone with corresponding reduction of the latter. These processes occur by a similar MPV oxidation–reduction mechanism, shown in a general form in Scheme 18.



Scheme 18

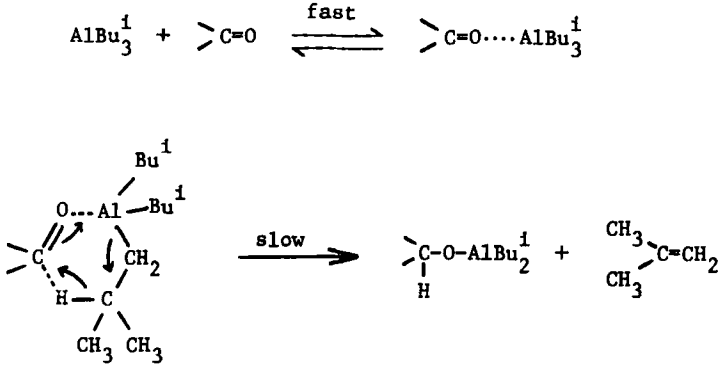
Teisseire and co-workers (149) have also shown that the reduction of several terpene ketones with excess TIBA involved preferential hydride transfer from the less hindered side of the substrate.

Heinsohn and Ashby (147) have suggested that a variation in the stereoselectivity of reduction with the TIBA : ketone ratio may be due in part to the

degree of association of TIBA,* in part to competitive reduction with a complex $R_2CHOAlBu^i_2 \cdot AlBu^i_3$, as well as to isomer equilibration.

Ashby and Yu have studied the kinetics of reduction of benzophenone with TIBA in ether and showed that the overall kinetic rate expression is second order, first order in TIBA and first order in ketone (151). The observed activation parameters were $\Delta G^{\ddagger} = 18.8$ kcal/mol; $\Delta H^{\ddagger} = 15.8$ kcal/mol; and $\Delta S^{\ddagger} = -10.1$ e.u. The negative entropy of activation is consistent with a cyclic transition state for the rate-determining hydride-transfer step. A Hammett study gave a value of $\rho = 0.362$, supporting nucleophilic attack by the aluminum alkyl on the carbonyl group in the rate-determining step.

In summary, the mechanism of reduction of ketones with TIBA may be formulated as involving (*a*) fast Lewis acid–base complexation between the reactants, and (*b*) slow hydride transfer (Scheme 19).



Scheme 19

2. *Chiral Trialkylaluminum Reagents*

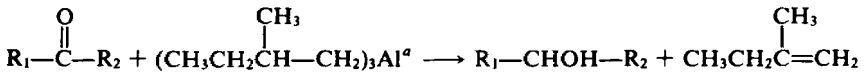
The chiral trialkylaluminum reagent used in the majority of asymmetric reduction studies is (+)-tris[(*S*)-2-methylbutyl]aluminum (**119**) or its etherates. This reagent is readily prepared from (*S*)-(+)-2-methyl-1-chlorobutane (152,153). Results of the reductions of prochiral ketones with these reagents and other chiral organoaluminum reagents are shown in Table 15.

Reductions of phenyl alkyl ketones with **119** or its diethyl or THF etherates

*Liquid TIBA exists as an equilibrium monomer–dimer mixture. For example, at 40° TIBA is 16% associated. In hydrocarbon solution, the dimer is more extensively dissociated with increasing dilution (150).

Table 15

Asymmetric Reduction of Ketones with Chiral Organoaluminum Reagents



119

Entry	Ketone		Reagent	Solvent (T, °C)	Carbinol		Reference
	R_1	R_2			Optical yield (%)[b]	Configuration	
1	Ph	Me	**119**	Pentane (0, −60)	6–8	*S*	157,159
2	Ph	Me	**119**-Et_2O	C_6H_6[c]	8	*S*	155
3	Ph	Me	**119**-Et_2O	Ether (0); pentane (0, −60)	6–9	*S*	157,159
4	Ph	Et	**119**	Pentane (0, −60)	13–15	*S*	154,157,159
5	Ph	Et	**119**-Et_2O	Pentane (0, −60); ether (0)	9–14	*S*	157,159
6	Ph	Et	**119**-THF	Pentane (0)	12	*S*	157
7	Ph	Et	**120**[d]	Pentane (0)[e]	12	*S*	156
8	Ph	Et	**121a**[f]	Pentane (0)	22	*R*	161
9	Ph	Et	**121b**[f]	Pentane (0)	23	*R*	161
10	Ph	Pr^n	**119**-Et_2O	C_6H_6[c]	7	*S*	155
11	Ph	Pr^i	**119**	Pentane (0 to −60)	32–44	*S*	154,159
12	Ph	Pr^i	**119**-Et_2O	Pentane (0 to −60); ether (0)	35–46	*S*	157,159
13	Ph	Pr^i	**119**-Et_2O	C_6H_6[c]	30	*S*	155
14	Ph	Pr^i	**119**-THF	Pentane (0)	43	*S*	157
15	Ph	Pr^i	**120**[d]	Neat; pentane (0)	18–19	*S*	156
16	Ph	Pr^i	**121a**[f]	Pentane (0)	56	*R*	161
17	Ph	Pr^i	**121b**[f]	Alkanes (0 to 98)	20–57	*R*	161

18	Ph	Pr^i	**122a,b,c**[g]	Ether (0)	20–31	*S*	160
19	Ph	Pr^i	**123a,b**[h]	Ether (0)	19–20	*S*	160
20	Ph	Bu^t	**119**	Pentane (0 to −60)	29–30	*S*	154,159
21	Ph	Bu^t	**119**-Et_2O	Pentane (0 to −60), ether (0)	33–46	*S*	157,159
22	Ph	Bu^t	**119**-Et_2O	C_6H_6[c]	13	*R*	155
23	Ph	Bu^t	**119**-THF	Pentane (0)	38	*S*	157
24	Ph	Bu^t	**121a**[f]	Pentane (0)	26	*R*	161
25	Ph	Bu^t	**121b**[f]	Pentane (0)	13	*S*	161
26	Ph	Bu^t	**121b**[f]	Pentane (36)	0	—	161
27	Ph	Bu^t	**121b**[f]	Hexane (69)	14	*R*	161
28	Ph	CF_3	**119, 119**-Et_2O	Pentane (0 to −60)	5–12	*S*	157,159
29	Ph	CF_3	**119**-Et_2O	Toluene (110)	2	*R*	159
30	Me	Et	**119**	Pentane (0)	5	*S*	158
31	Me	Pr^i	**119**	Pentane (0)	16–17	*S*	158
32	Me	Bu^t	**119**	Pentane (0)	20	*S*	158
33	Me	Bu^t	**119**-Et_2O	Pentane (0), C_6H_6(25, 80)	10–14	*S*	158
34	Me	Bu^t	**120**[d]	Pentane (0)	11	*S*	156

[a]Except where indicated otherwise.

[b]The optical yields are generally corrected for the minimum optical purity of the organometallic reagent used.

[c]Reflux under N_2.

[d]**120** = tris[(*S*)-3-methylpentyl]aluminum.

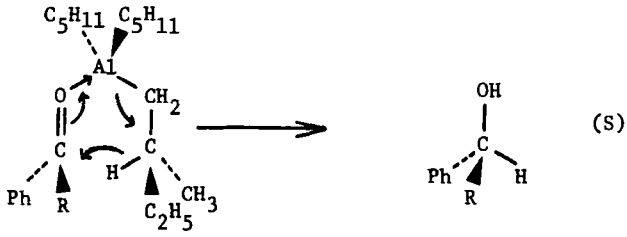
[e]Inverse addition.

[f]**121** $Al(-CH_2-\underset{\displaystyle H}{\overset{\displaystyle R}{\underset{|}{\overset{|}{C}}}}-Me)_3$: **a**, R = Pr^i; **b**, R = Bu^t.

[g]**122** R_2AlX, R = (*S*)-2-methylbutyl—: **a**, X = Cl; **b**, X = Br; **c**, X = I.

[h]**123** $R_3Al_2X_3$, R = (*S*)-2-methylbutyl: **a**, X = Cl; **b**, X = Br.

(**119**-Et_2O and **119**-THF, respectively) gave (*S*)-carbinols in low to moderate optical yields. The (*S*)-configuration of the predominant product is consistent with the previously proposed cyclic 6-center transition state for hydride transfer with TIBA (148). Scheme 20 illustrates this for **119**, assuming that Ph is larger



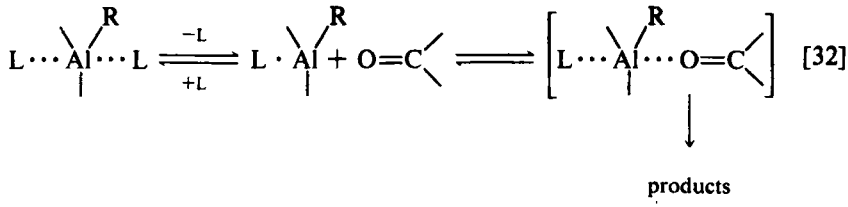
Scheme 20

than R. Kretchmer (155) noted an apparent discrepancy in the reduction of phenyl *t*-butyl ketone with **119**-Et_2O in refluxing benzene which gave the (*R*)-carbinol predominantly (Table 15, entry 22). However, when this reduction was repeated under the same conditions by Lardicci and co-workers (158), the (*S*)-carbinol was obtained.

Although solvent and temperature variations influence the optical yields in reductions with **119** and its etherates, the changes are not very large, and the results are not consistent. For example, lower temperatures increased optical yields to some extent, but in some cases had the reverse effect. Modifications of the structure of the chiral reagent did not provide uniformly significant improvements in optical yields. The use of tris[(*S*)-3-methylpentyl]aluminum (**120**) did not lead to improved optical yields (156). One would not expect greater stereoselectivity with this reagent, since the chiral center is further removed from the aluminum atom. The more bulky reagents tris[(*R*)-2,3-dimethylbutyl]aluminum (**121a**) and tris[(*R*)-2,3,3-trimethylbutyl]aluminum (**121b**) did show enhanced stereoselectivity in some reductions (Table 15, entries 8, 9, 16), but not in others (Table 15, entries 24 to 27).

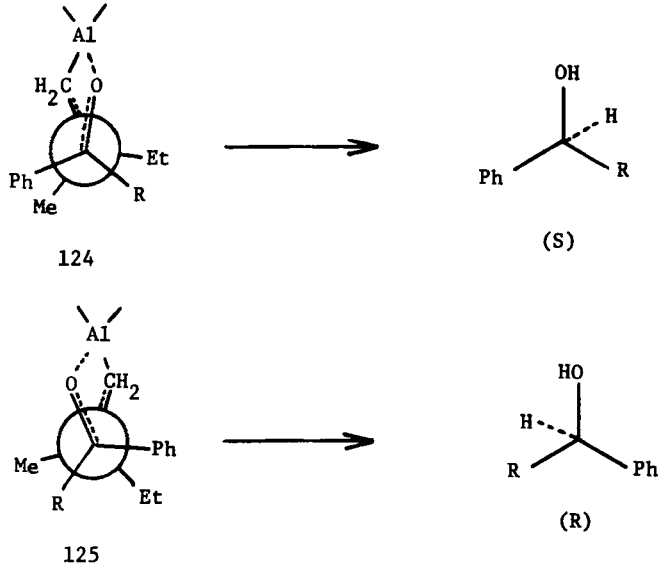
It should be mentioned in connection with the use of **119** and its etherates that conversions of alkyl phenyl ketones to the corresponding carbinols were approximately 90%, and addition and enolization were not significant. Rates of reductions were found to be lower in the ether solvents, particularly THF, than in pentane (157). The decrease has been attributed to competition between ether and ketone for the aluminum moiety (eq. [32]).

The degree of asymmetric induction with **119** increased in the order $CF_3 \simeq Me < Et < Bu^t < Pr^i$. As with the alkoxyaluminum dichloride reagent (Sect. III-A-2) the cyclic transition state model (Scheme 20) would predict a continuous



[32]

decrease in stereoselectivity with increasing bulk of the alkyl group. Lardicci and co-workers (157) have devised a transition state model for hydride transfer similar to that described by Nasipuri (135) and shown in Scheme 21. The favored transition states leading to (*S*)- and (*R*)-carbinols **124** and **125** are shown viewed along the C···H—C* axis. In these structures the aluminum atom (CH_2—$Al^{\delta+}$) is placed between the two negative dipoles (C—$O^{\delta-}$ and C—$Ph^{\delta-}$). Structure **124** is favored over **125** on the basis of steric interactions. Lardicci suggested



Scheme 21

that as R increases in bulk, the conformational mobility of Ph decreases, formally increasing its size, and that this steric effect is more pronounced in **125** than in **124** (157). This would predict the highest selectivity in favor of the (*S*)-carbinol for R = Bu^t, which is not observed. Possibly the unfavorable R ↔ Et interaction in **124** counters this trend for R = Bu^t. However, it appears that a truly satisfactory picture of the detailed mechanism of these reactions has not emerged.

Reduction of phenyl trifluoromethyl ketone by **119** generally leads to the (*S*)-carbinol* (Table 15, entry 28). One would expect that conformational changes in the favored transition states would occur. However, the degree of asymmetric induction in these cases is quite low, and the (*R*)-carbinol was in fact formed in toluene at 110°C (Table 15, entry 29), suggesting a rather delicate balance of competing interactions.

IV. SUMMARY

The modification of lithium aluminum hydride with chiral auxiliary reagents has resulted in several highly effective reagents, particularly for the reduction of aryl alkyl ketones and α,β-acetylenic ketones. Applications of several of these reagents to key reduction steps in more complex syntheses have been highly successful. Chiral tricoordinate aluminum reagents have given lower enantiomeric excesses of alcohols.

Further progress will undoubtedly involve the preparation of more generally applicable effective reagents, for example for the reduction of dialkyl ketones. Further systematic studies of promising reducing systems as well as increased knowledge of the actual species formed in the reaction of LAH with chiral reagents will be valuable.

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*Note that (*R*)-CF_3—CHOH—Ph is configurationally related to (*S*)-CH_3CHOH—Ph.

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