TOPICS IN

STEREOCHEMISTRY

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VOLUME 14

AN INTERSCIENCE ® PUBLICATION
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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 As a result, many of the details found in these texts are already inadequate or out of date, although the student in stereochemistry and conformational analysis may still learn the basic concepts of the subject from them.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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S. H. WILEN

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 ^{1}H 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:

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

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

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

Temperature (K)	$\Delta G^{\ddagger}$ (kcal/mol)	
	$K = 1.0$	$K = 10$[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)	10	20	50	100
T_c (K)	$\Delta G^{\ddagger}$ (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 (τ = 30 ~ 90°), the conformation is called sc (see Fig. 1). If the angle corresponds to ap (τ = 180 ± 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.

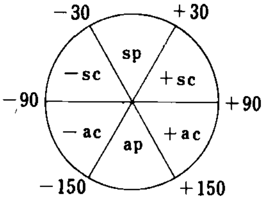
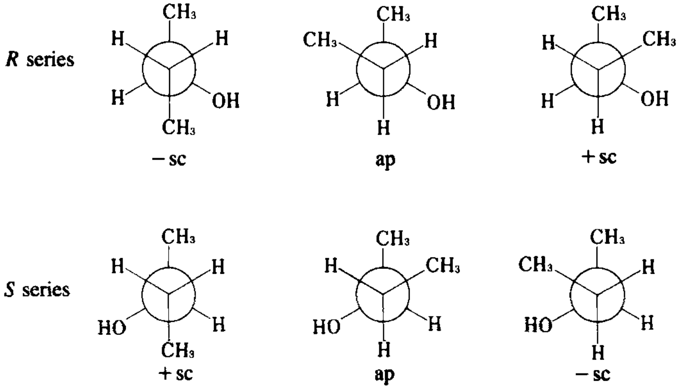


Figure 1

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.

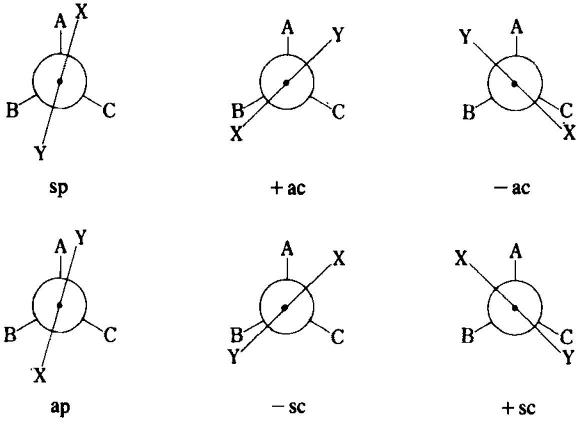
It is recommended in rule E of the IUPAC nomenclature that *RS* be used when the compound in question is a racemate. Then the conformations −sc(*R*)



Scheme 1

and +sc(*S*) may be written as ∓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).



sp +ac −ac

ap −sc +sc

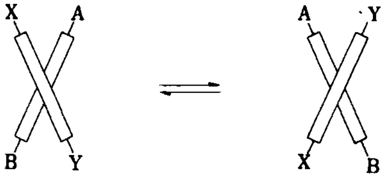
Scheme 2 (*R* series)

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

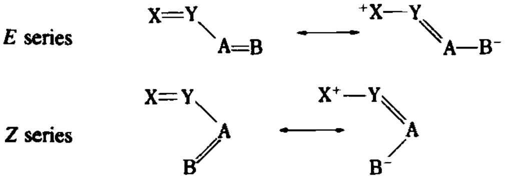
The most classical examples of atropisomerism, biphenyls, fall into this category. They form enantiomers because the two benzene rings are not coplanar and both rings are substituted unsymmetrically so that the plane passing through the pivot bond and one of the benzene rings cannot be a σ plane. If 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 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.



Scheme 3

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.

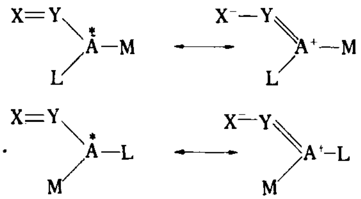
If two planar unsaturated groups are linked by a single bond (conjugated), the planar conformation is stabilized. In terms of valence bond theory, the planar structure is stabilized due to the contribution of resonance forms (Scheme 4).



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.)

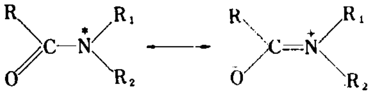


Scheme 5

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

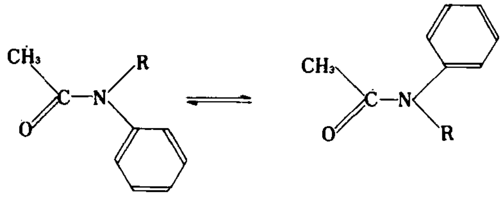
Effect of Substituents on Nitrogen on the Barrier to Rotation of Formamides and Acetamides ($RCONR'_2$)[a]

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*)

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

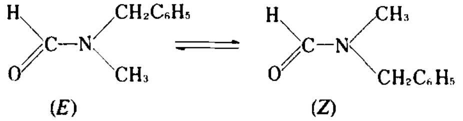
Barriers to rotation about the amide bond are expected to be affected by the electronic effect of the *R* substituent, because the electronic effect of the substituent should either stabilize or destabilize the canonical structure **2**. Rogers and Woodbrey (36) found that the barriers to rotation of *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:

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

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



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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

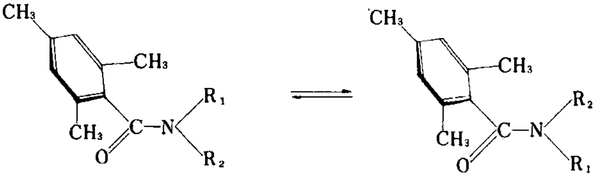

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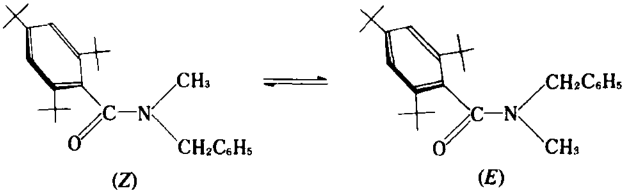
Table 6
Barriers to Rotation of Some Mesitamides (**5**)

R_1	R_2	Solvent	$\Delta G^‡$ (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 $\Delta G^‡_{393}$ 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 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.



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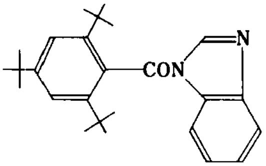
Mannschreck et al. (44) examined the effect of substituents on the barriers to rotation in 2,4,6-trisubstituted benzamides. In *N*-benzyl-*N*-methyl-2,4,6-tribromobenzamide, the rotational barrier ($\Delta G^‡$) is 23.8 kcal/mol at 35.8 to 40.6°C for the $Z \rightarrow E$ process in quinoline (44). This should be compared with $\Delta G^‡$ 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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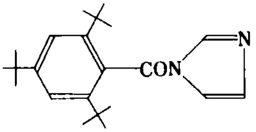

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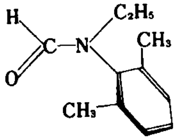
character of imidazole is stronger than that of benzimidazole, leading to less $^{-}O—C=N^{+}$ double-bond character. However, the steric effect, which will certainly raise the transition state energy for rotation, should not be forgotten. The benzimidazolyl group should give larger steric effects with 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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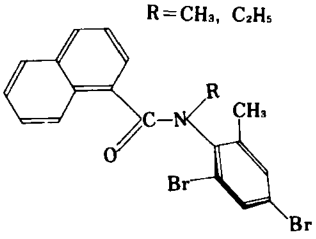

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