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NUCLEAR MAGNETIC RESONANCE STUDIES OF AMIDES*

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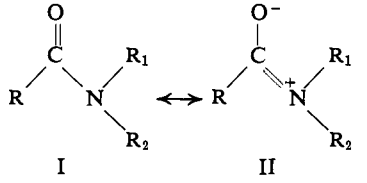
Contents

I. Introduction

Amides have been studied by nuclear magnetic resonance spectroscopy more extensively than any other class of compounds. Each of the 12 chapter headings in "High Resolution Nuclear Magnetic Resonance Spectroscopy"[1] can be directly connected with the study of amides. Application has ranged from "fingerprinting" and other qualitative analytical chemical uses at one extreme, to verification of valence-bond quantum mechanical predictions at the other.[2] Small molecules such as formamide and large molecules such as polypeptides and proteins have been examined. Structural features such as relative orientations of groups within an amide molecule have been revealed. One of the earliest applications of nmr spectroscopy to the study of hindered internal rotation was made with N,N-dimethylformamide.[3] This was followed rapidly by the earliest application of nmr signal shape analysis to the quantitative determination of the rate of internal rotation.[4] There have now been very many similar rate studies for a wide variety of amides.

Most of the nmr studies of amides are concerned with the partial double-bond character of the amide [C(O)–N] bond.[2] The double-bond character arises from the contribution of resonance structure II to the ground state of amides and



I II

leads to the following consequences: (1) the nonequivalence, geometrically and magnetically, of the nitrogen substituents even when $R_1 = R_2$; (2) long-range spin coupling from R to R_1 or R_2; (3) a stiff, approximately planar amide framework, which in turn is the key structural aspect of amides that determines many subsidiary structural aspects; and (4) a large barrier to rotation around the amide bond. All of these considerations are discussed in this review.

This review covers the manifold applications of nmr to amide chemistry. The coverage is, however, not always explicit and is at times more representative than complete. Also, as is natural in such circumstances, the authors' own

* This review was prepared as part of work under Contract AT(07-2)-1 with the U. S. Atomic Energy Commission.

(1) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, New York, N. Y., 1965.

(2) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 281.

(3) W. D. Phillips, *J. Chem. Phys.*, 23, 1363 (1955).

(4) H. S. Gutowsky and C. H. Holm, *ibid.*, 25, 1228 (1956).

interests are emphasized, *e.g.*, rotational barriers in amides. In general, the literature is reviewed up to October 1968. The review is, of course, less reliable with respect to completeness of coverage in the last few months prior to that date.

II. Diamagnetic Anisotropy of Amide and Thionamide Groups[5]

The occurrence of separate signal sets for identical N-substituted proton groups in N,N-disubstituted amides (under conditions such that rotation around the amide C–N bond is slow on the nmr time scale) is due to the anisotropy of the diamagnetic susceptibility of the carbonyl group. It has been suggested that a large diamagnetism (shielding) exists in conical regions extending above and below the plane of the amide group, while the regions in the plane of the amide group are paramagnetic (deshielding).[6,7] Using a dipolar approximation, McConnell[8] derived the following expression for the contribution to the shielding tensor of nucleus A, σ_A, arising from a distant electron group, G, within the molecule containing A.

$$\sigma_A{}^G = \frac{1}{N}\left[\frac{\chi^G}{R^3} - \frac{3\chi^G \cdot \mathbf{RR}}{R^5}\right] \quad (1)$$

In this expression N is Avogadro's number, χ^G is the molar magnetic susceptibility tensor, and **R** is the radius vector from the origin (chosen as the location of the induced dipole) to nucleus A. In principle, this relation could be used to predict the anisotropy shift for the different possible orientations of a proton with respect to the amide group. If this were possible, then the various amide proton resonances could be assigned. However, application of eq 1 is limited by the following factors:[5]

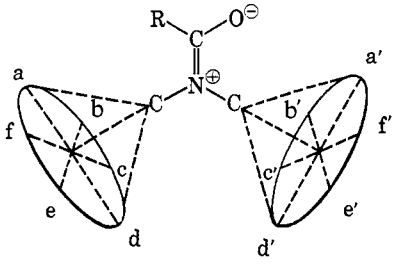
(1) The contributions to the shielding, σ_A, are small and significant essentially only with protons.

(2) The dipolar approximation is valid only if nucleus A is removed by about six bond lengths from the group G. Under such conditions, the contributions to the shielding are small and other effects, such as electric field effects, may give rise to shielding contributions of comparable, but uncertain magnitude.

(3) Reliable values for the magnitude of the anisotropy components of the carbonyl bond are lacking.

Narasimhan and Rogers[9] and Hooper and Kaiser[10] attempted to determine the magnetic susceptibility components of the C=O bond in amides from the observed differences in shielding constants for *cis* and *trans* protons in amides. (This approach has also been used for other-than-amide carbonyl compounds.[11]) The results obtained appear, however, to have only qualitative significance. One obvious shortcoming is the failure to treat the amide group as a whole. The electron delocalization is over at least three atoms and not just over the *two* atoms of the carbonyl groups.

Since theoretical treatments of the magnetic anisotropy of amides were not successful, experimental methods were sought. The most succinct and lucid account of an experimental approach is given by Paulsen and Todt.[12] These authors have amplified this short paper in full-length papers[13–15] and have developed a model for the anisotropic effect of the amide group[12] (III). The letters on the circles



III

indicate the possible proton positions. Two regions can be distinguished: the "plane region" (deshielded region), in the plane of the amide group with the positions aa′ and dd′ in which a experiences greater shielding than a′, and the "out-of-plane region" (shielded region) in which the c and c′ positions are opposed, with position c′ being shielded more strongly than c. The positions ee′ are equivalent to cc′. All available information (summarized in the following paragraphs) on sterically fixed protons is consistent with this model; *i.e.*, out-of-plane protons are more strongly shielded than in-plane protons. In N,N-dimethylamides, the protons of the N-methyl group *cis* to oxygen resonate at higher field than those *trans* to oxygen; thus the *cis*-methyl protons experience the greater shielding. This observation is consistent with the model given by Paulsen and Todt; the influence of dd′ is small owing to their greater distance from the carbonyl bond, and averaging of the effects of anisotropy on all positions a–f and a′–f′ leads to an average out-of-plane conformation for the methyl protons.[12]

Early and very important experimental observations and interpretations are to be found in the publications of Rae and coworkers.[16,17] The latest work contains an excellent review and an extensive bibliography.[17] The findings of these authors have been corroborated, and some qualitative and a few quantitative estimates of the effects of the anisotropy on chemical shifts have been published.[18–23] All of the quan-

(5) For a recent review of diamagnetic susceptibility studies see A. A. Bothner-By and J. A. Pople, *Annu. Rev. Phys. Chem.*, 16, 43 (1965).
(6) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p 124.
(7) J. A. Pople, *Discuss. Faraday Soc.*, 34, 7 (1962).
(8) H. M. McConnell, *J. Chem. Phys.*, 27, 226 (1957).
(9) P. T. Narasimhan and M. T. Rogers, *J. Phys. Chem.*, 63, 1388 (1959).
(10) D. L. Hooper and R. Kaiser, *Can. J. Chem.*, 43, 2363 (1965).
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(12) H. Paulsen and K. Todt, *Angew. Chem., Int. Ed. Engl.*, 5, 899 (1966).
(13) H. Paulsen and K. Todt, *Chem. Ber.*, 100, 3385 (1967).
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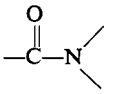
(16) R. F. C. Brown, I. D. Rae, and S. Sternhell, *Aust. J. Chem.*, 18, 1211 (1965).
(17) R. F. C. Brown, L. Radom, S. Sternhell, and I. D. Rae, *Can. J. Chem.*, 46, 2577 (1968), and references therein.
(18) R. E. Carter, *Acta Chem. Scand.*, 21, 75 (1967).
(19) T. H. Siddall, III, and W. E. Stewart, *J. Mol. Spectrosc.*, 24, 290 (1967).
(20) H. Baumann, N. C. Franklin, H. Moehrle, and U. Scheidegger, *Tetrahedron*, 24, 589 (1968).
(21) A. Ribera and M. Rico, *Tetrahedron Lett.*, 535 (1968).
(22) M. Zanger, W. W. Simons, and A. R. Gennaro, *J. Org. Chem.*, 33, 3673 (1968).
(23) G. J. Karabatsos, G. C. Sonnichsen, N. Hsi, and D. J. Fenoglio, *J. Amer. Chem. Soc.*, 89, 5067 (1967), and references therein. (Karabatsos has been concerned primarily with various anisotropic groups other than the amide group. However, his findings are quite relevant to the study of amides and amide isomerism.)
(24) K. Nagarajan, M. D. Nair, and P. M. Pillai, *Tetrahedron*, 23, 1683 (1967).

titative estimates are for positions that lie in the amide plane. There is also useful information in earlier reports.[29,30]

The general technique is to describe the anisotropic field by its effect on the shifts of protons that are in known orientations with respect to the amide framework



This requires that the proton(s) be fixed with respect to the framework or that some reliable model be available for averaging the proton position. The first alternative is simpler and has been the more fruitful line of investigation to date.

For this purpose C–H proton shifts in anilides, piperidones, piperidides, N-acetylindoline, hydroquinolines, and isoquinolines have been employed.[12,15–17,19–25,28] The chemical shifts of the N–H protons in N-unsubstituted amides could be especially useful, since they are always in the amide plane, but only when the measurements are extrapolated to infinite dilution. Otherwise, the strong intermolecular associations invalidate the use of shift data for the N–H protons.

The use of anilides for this kind of study depends on (a) knowing whether the benzene ring is *endo* (*cis* to oxygen) or *exo* (*trans* to oxygen); (b) knowing the angle between the ring plane and the approximate plane of the amide framework; (c) identifying the ring-proton signals as *ortho*, *meta*, or *para*. *endo–exo* assignment is dealt with in the section on isomer signal assignment. In N-substituted anilides, the ring is most definitely perpendicular to the amide plane when there is *ortho* substitution. Even in N-methylacetanilide the ring is perpendicular.[18] However, in acetanilide (unsubstituted on both ring and N) the ring is nearly coplanar with the amide plane.[18] In *ortho*-substituted anilides where the ring substituent is capable of hydrogen bonding to the N–H proton, the ring becomes closely fixed coplanar with the amide plane.[12,17,28–32] In this last situation averaging due to torsional or rotational motion is reduced to a minimum. The ring proton signals have been assigned by selective deuteration,[18] by analysis of the ring proton spectrum on the basis of unequal *ortho* (8–9 cps), *meta* (~2 cps), and *para* (~0) coupling constants, or by judicious substitution in the ring.[19] In *o*-nitroanilides, the 5-proton was identifiable as being the only ring proton coupled to the N–H proton.[28]

There is general agreement that in anilides, where the ring is coplanar with the amide plane, the ring protons are strongly deshielded (>1 ppm) in position 6 (see Figure 1), slightly deshielded (0.1 to 0.2 ppm) at positions 1 and 7, but essentially unaffected in other positions. The precise value for position 6 must vary from compound to compound. Very small distance and/or angle changes would greatly affect the shift in a steeply graded field.

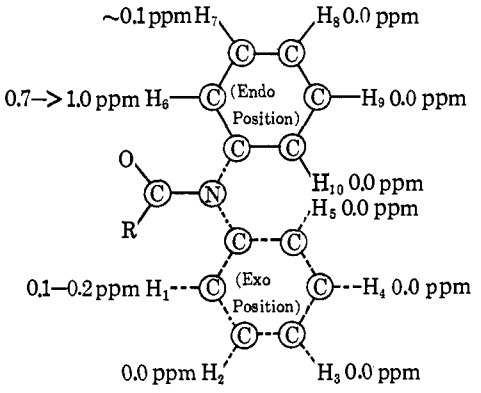
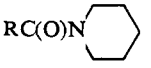


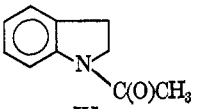
Figure 1. Secondary shieldings of aromatic protons in anilides.

Studies of piperidides



and related compounds have not thus far yielded quantitative data for deshielding or shielding. However, data for these compounds show that there is substantial shielding in the regions out of the amide plane.[12–15] Studies of out-of-plane positions have not been reported for anilides. N-Substituted anilides generally exist almost entirely as the *exo* isomer; thus the ring protons are too remote from the anisotropic source to show substantial effects. However, there are certain exceptions to the rule of *exo* isomer predominance. N-Substituted formanilides and trichloroacetanilides, Cl_3C–C(O)N-(R)(C_6H_5), often have significant populations of *endo* isomers.[38] These compounds may be useful for studies of the out-of-plane amide field.

N-Acetylindoline (IV) provides an additional opportunity for obtaining the downfield shift for a position analogous to 6 in anilides.[24] The only observed isomer is the *endo*



IV

isomer. The 7-proton shows a large downfield shift (8.22 ppm from TMS) from its position in indoline (6.45 ppm). The formyl derivative exhibits both amide isomers; the 7-proton signal for the *endo* isomer is at 8.05 ppm.[24]

All of the discussion above deals with the shifts due to amide anisotropy at positions occupied by protons on the nitrogen substituents; there has been little or no discussion of shifts of proton signals from the carbonyl substituent. Judging by the very low-field position of formyl proton signals in formamides, there is strong deshielding in the amide plane. Thionamide groups appear to have larger anisotropies than amide groups.[24,34–36]

(25) G. Fraenkel, M. P. Cava, and D. R. Dalton, *J. Amer. Chem. Soc.*, 89, 329 (1967).
(26) W. Walter and G. Maerten, *Justus Liebigs Ann. Chem.*, 712, 58 (1968).
(27) D. M. Lynch and W. Cole, *J. Org. Chem.*, 31, 3337 (1966).
(28) J. R. Bartels-Keith and R. F. W. Cleciuch, *Can. J. Chem.*, 46, 2593 (1968).
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(30) L. A. LaPlanche and M. T. Rogers, *J. Amer. Chem. Soc.*, 86, 337 (1964).
(31) I. D. Rae, *Can. J. Chem.*, 45, 1 (1967).
(32) I. D. Rae, *ibid.*, 46, 2589 (1968).
(33) T. H. Siddall, III, *J. Org. Chem.*, 31, 3719 (1966).
(34) P. L. Southwick, J. A. Fitzgerald, and G. E. Milliman, *Tetrahedron Lett.*, 1247 (1965).
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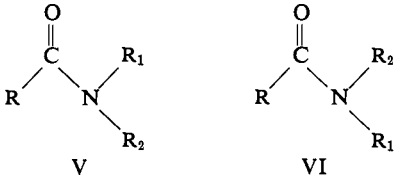
(36) H. Booth and A. H. Bostock, *Chem. Commun.*, 637 (1967).

III. Signal Assignments in Amides and Thionamides

Except in a few cases where there is chemical shift degeneracy, the *cis* (to oxygen) and *trans* substituents on nitrogen give well-separated nmr signals whenever rotation is slow around the carbonyl-to-nitrogen (amide) bond. The anisotropy of the magnetic susceptibility of the amide grouping is the principal cause of the chemical shift between *cis* and *trans* nmr signals. Hence the protons nearest the anisotropic group, the protons α to nitrogen, will usually be the most shifted with respect to each other. This shift is observed when substitution on nitrogen is symmetrical or unsymmetrical.

The proper assignment of the nmr signals is perhaps more important in the case of unsymmetrical substitution. In this case it serves to identify the isomers V and VI. However,



V VI

the assignment may still be critical with symmetrical substitution ($R_1 = R_2$). In particular, the relative *cis*/*trans* shifts may yield information on the structure of the amide molecule or the adducts and complexes that it forms with other molecules.

The assignment given to R_1 when $R_1 \neq R_2$ is commonly assumed to be at least qualitatively the same when $R_1 = R_2$. This assumption is valid when there are no other large anisotropic groups in or around the molecule. For example, if the carbonyl substituent (R) is a benzene ring, the assumption is obviously not valid.

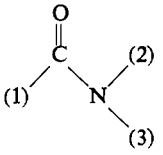
Six criteria have been used for nmr signal assignment. These are (1) inequality of *cis* and *trans* coupling constants; (2) differential solvent shifts; (3) the nuclear Overhauser effect; (4) shifts predicted from the probable shape of the anisotropic magnetic field of the amide group; (5) shifts induced by complexation with paramagnetic metal ions; (6) shifts produced by other anisotropic groups in the amide molecule.

Any single one of these criteria may not be absolutely conclusive. The assignments are usually based upon agreement between several of these criteria.

A. CRITERIA USED FOR MAKING SIGNAL ASSIGNMENTS

1. Inequality of cis and trans Coupling Constants

The coupling of protons in the carbonyl substituent (R) is greater to the protons in the nitrogen substituent that is *trans* to the R group (or that is *cis* to oxygen). (The following convention will be used for discussing this effect. The positions of attachment to the amide framework are numbered

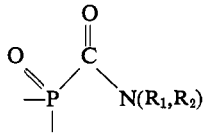


The *cis* coupling is $J_{1,3}$(H–H) and the *trans* is $J_{1,2}$(H–H).) As expected, the effect is greatest in formamide,[37–39] $J_{1,2}$(H–H) = 12.9 and $J_{1,3}$(H–H) = 2.1 Hz, and in monosubstituted formamides.[38,40] For formanilide $J_{1,2}$(H–H) = 11.0 and $J_{1,3}$(H–H) = 2.0 Hz.[41] Similar values are obtained for ring-substituted formanilides.[19]

The same effect, though of smaller magnitude, is noted for $J_{1,2}$(H–Me) *vs.* $J_{1,3}$(H–Me)[40–42] and for $J_{1,2}$(Me–Me) *vs.* $J_{1,3}$(Me–Me).[40] The effect is usually diminished or even disappears for substituents higher than methyl.

The theoretical basis for assuming that $J_{1,2} > J_{1,3}$ rests on the tenuous analogy of amides with ethylenes. Karplus predicts from valence-bond theory that for the ethylenic fragment $J(trans) > J(cis)$.[43] However, even for ethylenic molecules this relation is reversed in some cases.[44,45]

The coupling to phosphorus in carbamylphosphonates



and related compounds follows the relationship $J_{1,2}$(P–α-CH) > $J_{1,3}$(P–α-CH) when $R_{1,2}$ = Me, Et, but is reversed when $R_{1,2}$ = 2-Pr.[46,47] Also for dimethyltrifluoroacetamide it seems likely that $J_{1,3}$(F–Me) > $J_{1,2}$(F–Me).[48] Lewin reported what appears to be very long-range coupling through space to one N-methyl group, but not the other in N,N-dimethyl-*o*-fluorobenzamide.[49] $J_{1,3}$(F–Me) is probably greater than $J_{1,2}$-(F–Me) in this case also.

In spite of the reservations that must arise from the above discussion, the relationship $J_{1,2} > J_{1,3}$ has held, so far without exception, for proton–proton coupling. The relationship can be regarded as an empirical fact, whatever the theoretical justification. Even so, in truly critical situations, it would be better to support the assignment with additional evidence.

2. Differential Solvent Shifts

When the nmr spectrum of an N,N-dimethylamide in benzene is compared with the spectrum of the amide in a nonaromatic solvent, it is seen that the resonance peaks of both N-methyl groups are shifted upfield in benzene. However, one of the N-methyl group resonances usually exhibits a greater upfield shift than the other. Hatton and Richards proposed that the differential benzene shift was caused by a specific interaction between the π electrons of benzene and the positively charged amide nitrogen atom, with the negatively charged carbonyl oxygen being as far away from the center

(37) B. Sunners, L. H. Piette, and W. G. Schneider, *Can. J. Chem.*, 38, 681 (1960).
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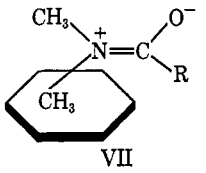
(46) T. H. Siddall, III, and C. A. Prohaska, *Appl. Spectros.*, 21, 9 (1967).
(47) T. H. Siddall, III, and W. E. Stewart, *Spectrochim. Acta, Part A*, 24, 81 (1968).
(48) M. T. Rogers and J. C. Woodbrey, *J. Phys. Chem.*, 66, 540 (1962).
(49) A. H. Lewin, *J. Amer. Chem. Soc.*, 86, 2303 (1964).

of the benzene ring as possible.[50,51] The proposed structure of the "complex" is VII. In this structure, both N-methyl



VII

groups are in the diamagnetic region of the benzene ring-current field and would thus undergo an upfield shift. However, the N-methyl group *trans* to oxygen is nearer the center of the benzene ring and its ^1H resonance would be shifted upfield by a greater amount than that of the N-methyl group *cis* to oxygen. The same effect has been observed for other N,N-dialkylamides, and it has become generally accepted that the resonance absorption belonging to the N-alkyl protons *trans* to the carbonyl oxygen is shifted farther upfield than the *cis* proton absorption in benzene solutions.

3. *Intramolecular Overhauser Effect*

In dilute solution in a magnetically inert solvent and with exclusion of molecular oxygen, the main mechanism for proton spin-lattice relaxation, T_1, is direct intramolecular dipole–dipole interaction.[52] The contribution to T_1 from the intramolecular dipole–dipole interaction of protons A and B is given by[52,53]

$$\frac{1}{T_1^{AB}} = \frac{\hbar^2\gamma_A^2\gamma_B^2\tau}{d^6} \qquad (2)$$

where T_1^{AB} is the contribution to T_1 for nucleus A or B, τ is the correlation time for random molecular rotation, d is the distance between protons A and B, and γ_H is the gyromagnetic ratio for protons. If $1/T_1^A = 1/T_1^{AB}$, complete saturation of the B nucleus will result in a 50% enhancement of the integrated intensity of the band of the A nucleus. This effect is known as the nuclear Overhauser effect (see ref 54 and references therein).

By observing the resonance of one proton or proton group while irradiating the other protons in the molecule, the protons responsible for the relaxation of any particular proton can be identified. Since T_1 shows a sixth power distance dependence, a given proton should be relaxed by the nearest proton or proton group. Anet and Bourn found that the formyl proton resonance intensity of N,N-dimethylformamide was slightly decreased upon irradiation of the high-field N-methyl group, but showed an 18% increase when the low-field N-methyl group was irradiated.[54] Thus the low-field N-methyl group is *cis* to the formyl proton.

4. *Shifts Predicted from the Shape of the Anisotropic Field*

If the shape and intensity of the amide magnetic field were known accurately, then many, if not all, problems in signal assignment would be solved. To a good approximation, the average proton positions in the contours of this field would be known. The accuracy of assignment would then be limited only by the choice of models for position averaging. Unfortunately, as discussed in another section, the description of this field has only somewhat dubious quantitative value to date. However, it is now certain that this field is deshielding over the amide plane, but becomes shielding at some angle out of the amide plane.[12,16,19,21]

5. *Shifts Induced by Complexation with Paramagnetic Metal Ions*

Complexation with paramagnetic metal ions can produce very large nmr shifts. These shifts may either be produced *via* the Fermi contact mechanism (contact shifts) or through space (pseudocontact shifts).[55] Only one effort to use these effects for amide signal assignment has been reported.[56] In this work it was observed that the signals for the N-α-CH_2 group in N-methyl lactams were shifted much more than the N-methyl signals when the lactams formed complexes with Ni(II). On that basis it was assumed that the *trans* (to oxygen) shift might generally be greater than the *cis* shift. This assumption led to the same assignments for dimethylformamide as made by criteria 1 and 2. These were assumed to be pure contact shifts. The validity of this assumption is, however, questionable. As a consequence it cannot be said that this technique has been established as a firm criterion for signal assignment. This technique may have considerable potential, however, and deserves more study. In most cases paramagnetic transition metals lead to complexes where there may be an unfortunate mixture of contact and pseudocontact terms. However, lanthanide complexes probably are subject only to pseudocontact effects.[57] The chief problem with the lanthanide complexes is to obtain the axially symmetric molecules necessary to allow a straightforward interpretation of the data.

6. *Shifts Induced by Other Anisotropic Groups in the Molecule*

The inclusion of aromatic rings in the molecule may lead to decisive information on signal assignment. The contours of the anisotropic magnetic field around the benzene ring are now well known.[58] If the ring is fairly well fixed in the amide molecule, then its effect on the shift of proton signals can be calculated.

Rae has used this method to make assignments in *ortho*-substituted formanilides.[59] The *ortho* substitution tends to force the benzene ring out of plane. In the *endo* isomer (ring *cis* to oxygen), the ring is remote from the formyl proton and has little effect on the formyl proton resonance. However, in the *exo* isomer, the ring is near the formyl proton. As *ortho* substitution forces the ring out of the amide plane, the formyl proton resonance of the *cis* isomer must be shifted upfield.

The benzene ring may also be rigidly fixed as part of a fused-ring system. Nagarajan, Nair, and Pillai made extensive

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(51) J. V. Hatton and R. E. Richards, *ibid.*, 5, 139 (1962).
(52) A. Abragam, "The Principles of Nuclear Magnetism," Clarendon Press, London, 1961, p 264.
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(56) B. B. Wayland, R. S. Drago, and H. F. Henneike, *J. Amer. Chem. Soc.*, 88, 2455 (1966).
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(59) I. D. Rae, *Can. J. Chem.*, 44, 1334 (1966).

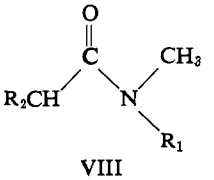
use of the ring field to assign signals in N-acylindolines and related compounds.[24] The R-group signals must be very much shifted downfield in the *exo* isomer as compared to the *endo* isomer because the R group in the *exo* isomer lies close to the benzene ring plane, producing a paramagnetic shift.

B. SIGNAL ASSIGNMENTS

1. N-Methyl Groups

The nmr spectrum of N,N-dimethylformamide (DMF) consists of one broad formyl proton absorption and two resonances for the N-methyl groups. The high-field methyl absorption shows a splitting of 0.8 Hz; the low-field methyl is split by 0.5 Hz. In addition, in benzene solution, the low-field N-methyl resonance is shifted to higher field than the high-field methyl resonance. From these results it was concluded, using criterion 1[60] and criterion 2,[50] that the high-field N-methyl resonance arose from the methyl group *cis* to oxygen. This assignment was later confirmed by Anet and Bourn's study of the nuclear Overhauser effect in DMF.[54] These assignments for *cis* and *trans* N-methyl groups also appear to be correct (by the same criteria) for N-methyl monosubstituted formamides and N-methyl-N-alkylformamides. That is, in the latter two types of amides, if both *cis* and *trans* isomers can be observed in solution, the *cis* N-methyl isomer resonance is at higher field.

In N-methylamides of type VIII, where R_1 = CH_3 or



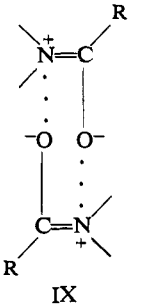
VIII

other alkyl group, the splitting of the N-methyl groups due to coupling with protons on the α-carbon is not always resolved, but the high-field N-methyl absorption is broader than the low-field N-methyl absorption, indicating that the high-field methyl is *trans* to R_2–CH or *cis* to carbonyl. In addition the low-field N-methyl shows a greater shift in benzene.

In most N,N-dimethylthionamides the relative shielding constants of the *cis* and *trans* N-methyl groups appear to be reversed. N,N-Dimethylthionformamide (DMTF) in the solvent formamide exhibits a typical amide spectrum; *i.e.*, the high-field N-methyl group is coupled more strongly with the formyl proton.[61] However, in the same solvent, coupling of the C–CH_3 protons in N,N-dimethylthionacetamide (DMTA) was found to be stronger with the N–CH_3 protons, giving rise to the lower field resonance of the $N(CH_3)_2$ doublet.[56,61] In addition, in benzene solution, the high-field N-methyl resonance was shifted farther upfield than the low-field N-methyl[61] Thus, the results for DMTA appear to be due to an inversion of N-methyl chemical shifts rather than a violation of criterion 1. Three possible explanations have been proposed for the reversal of the relative shifts of the N-methyl groups in DMTA.

(1) Paulsen and Todt have suggested that, in terms of their model, the plane region of thionamides has a larger cone of influence resulting in average "in-plane" shifts for freely rotating methyl groups.[12] This explanation does not, however, account for the relative N-methyl shifts in DMTF.

(2) It is known that N,N-disubstituted amides may exist in solution in either the monomeric form or the dimeric form IX and that the extent of dimerization depends upon



IX

such factors as nature of the solvent and amide concentration. It has been suggested by some workers that the relative shieldings of the N–CH_3 groups in N,N-dimethylamides and thionamides might be different in the same solvent depending on whether the compound was a monomer or self-association dimer.[62] Thus, the chemical shift reversal observed for DMTA could be due to a difference in the extent of dimerization of this compound as compared to other N,N-dimethylamides and thionamides. Molecular weight studies in carbon tetrachloride have shown that DMTF and DMTA exist as average molecular aggregates of 1.7 and 1.1 molecules/unit at formal concentrations of 0.03 and 0.05 *M*, respectively.[63] However, from a careful study of the chemical shifts of the NCH_3 groups of DMTF and DMTA in varying concentrations in CCl_4 and analysis of the data in terms of the monomer–dimer equilibrium, it has been concluded that the extent of aggregation of the amide or thionamide is not responsible for the shielding inversion observed for DMTA.[64]

(3) An alternative explanation by Neuman and Young attributes the reversal in DMTA to effects rising from increased steric interaction between the acetyl methyl group and the *trans* N–CH_3 group.[61] Neuman suggested that the higher barriers to rotation in thionamides as compared to the analogous amides could be explained by a greater contribution of the dipolar resonance form II to the ground states of thionamides than to those of amides. This in turn would lead to a shorter central C–N bond in thionamides, and steric interaction between the acetyl methyl group (R) and the *trans* N–CH_3 group would be increased (see ref 65 for a discussion of steric interactions in amides and for references to observed bond lengths in some amides and thionamides). Bond distortion or restricted rotation about the N–CH_3 bonds could then lead to the observed change in shielding.

Both the *cis* and *trans* isomers of N-methylthionformamide (NMTF) and N-methylthionacetamide (NMTA) have been observed in various solvents, and it appears that in both

(60) V. J. Kowalewski and D. G. deKowalewski, *J. Chem. Phys.*, 32, 1272 (1960).
(61) R. C. Neuman, Jr., and L. B. Young, *J. Phys. Chem.*, 69, 1777 (1965).
(62) R. C. Neuman, Jr., D. N. Roark, and V. Jonas, *J. Amer. Chem. Soc.*, 89, 3412 (1967).
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(64) R. C. Neuman, Jr., W. Snider, and V. Jonas, *J. Phys. Chem.*, 72, 2469 (1968).
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these compounds the N-methyl group *cis* to sulfur resonates at higher field than does the N-methyl group *trans* to sulfur.[66] Thus the inversion of the N-methyl shielding constants observed in DMTA is absent in NMTA. This observation is consistent with Neuman's second explanation if it is extended by including the effect of the *cis* N–CH_3 group in DMTA. That is, the *cis* N–CH_3 group in DMTA could cause crowding of the amide plane and force the *trans* N–CH_3 group closer to the acetyl methyl group, leading to bond distortion. In NMTA this secondary effect is absent, and the *trans* N–CH_3 group is not as sterically crowded; the bond distortion, or hindered rotation, is less, and "normal" amide behavior is observed. It must not be forgotten, however, that the solution behaviors of DMTA and NMTA are quite different; *i.e.*, whereas DMTA can be in the monomeric form or in a dimeric form held together by relatively weak dipolar forces, NMTA can exist as the strongly hydrogen bonded *cis* dimer or as a *trans* linear chain. The chemical shifts of *cis* and *trans* N-methyl protons in these two forms could be quite different from those in the DMTA monomers and dimers.

2. *N-Ethyl Groups*

In nonaromatic solvents at room temperature, the two N-methylene quartets of N,N-diethylalkylamides show very little chemical shift between them while the methyl triplets are separated by about 0.08 ppm. In benzene solution, the methylene proton absorptions are separated by about 0.59 ppm and the methyls by about 0.174 ppm.[51] The nmr spectrum of deuterium-decoupled methyl-deuterated N,N-diethylformamide-d_6 was observed at −40°, at which temperature the N–CH_2 resonances were separated, and it was found that the N–CH_2 *cis* to oxygen resonated at *lower* field than the N–CH_2 group *trans* to oxygen.[29] Thus the relative shielding constants of protons in the *cis* and *trans* sites are reversed in N,N-dimethylamides as compared to N,N-diethylamides. The *cis* N-ethyl methyl group, on the other hand, absorbs at *higher* field than the *trans* methyl group. In addition the chemical shifts between the N-methylene groups in diethylformamide (DEF) and diethylacetamide (DEA) show abnormal temperature and solvent behavior.[29,67] As the temperature is lowered, the chemical shifts might be expected to reach a limiting value and level off. This does not happen in the cases of DEF and DEA, however. Whittaker and Siegel suggested that steric interactions between the N-ethyl groups were responsible for the unusual chemical shift behavior.

3. *N-Isopropyl Groups*

The nmr spectrum of deuterium-decoupled methyl deuterated N,N-diisopropylformamide-d_{12} consists of two doublets for the N-methine protons.[29] The doublet splitting due to coupling with the formyl protons is 0.6 Hz for the low-field line and 0.4 Hz for the high-field line. Thus according to criterion 1, the methine proton *cis* to oxygen resonates at *lower* field than the *trans* methine proton. The high-field methyl groups are coupled to the low-field methine proton.[68] The methine proton chemical shift also exhibits the unusual temperature behavior noted for diethylamides.

Neuman and Young rationalized the inversion of the *cis* and *trans* chemical shifts in N,N-dimethylamides as compared to N,N-diethyl- and -diisopropylamides in terms of hindered rotation about the alkyl carbon–nitrogen bonds.[61] In the higher amides, the rotation need not be sufficiently hindered to freeze out the possible conformations; the presence of moderately hindered rotation can lead to differences in the relative populations of the possible conformations. In this case, the chemical shift for the α-protons will be a *weighted* mean of those corresponding to each of the conformations. On the other hand, the chemical shift of the N–CH_3 protons in N,N-dimethylamides will be an *arithmetic* mean of those shifts corresponding to each of the possible conformations. Recent work has tended to corroborate this line of reasoning.[69]

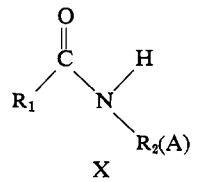
4. *N-t-Butyl Groups*

The methyl resonances of the *cis* *t*-butyl groups in both monosubstituted and unsymmetrically disubstituted N-*t*-butylamides occur at *lower* field than the *trans* methyl resonances.[70]

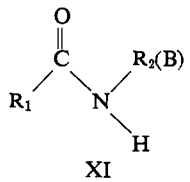
IV. Studies of cis–trans Isomer Ratios

A. N-MONOSUBSTITUTED AMIDES

N-Monosubstituted amides may exist as the *cis* (X) or *trans* isomers (XI).



X



XI

If an amide in solution occurs as a mixture of *cis* and *trans* isomers, separate *cis* and *trans* signals will be observed if rotation around the C–N bond is slow, *i.e.*, if $\tau_A \gg \sqrt{2}/2\pi(\nu_A - \nu_B)$, where τ_A is the mean lifetime at site A and ν_A and ν_B are the resonance frequencies at sites A and B, respectively. Thus, if *cis* and *trans* resonances can be assigned, *cis*/*trans* isomer ratios can be determined. (If only one set of signals is observed, however, it does not necessarily indicate that rapid rotation around the C–N bond is occurring, or that only one isomer is present, since other factors may cause chemical shift degeneracy of the *cis* and *trans* signals.)

There are wide variations in the relative abundance of the two isomers of unsymmetrically substituted amides. This variation occurs not only from amide to amide, but also for a given amide there may be considerable solvent and temperature dependence. For monosubstituted amides there may be a strong dependence on the amide concentration. Unfortunately the data for relative abundances were reported for a variety of experimental conditions. Sometimes the assignment of the more abundant isomer may be in doubt. For these reasons sweeping generalizations must be viewed with some caution. Also, the forces that determine abundance are often subtle and poorly understood. Rather minor considerations may easily shift the relative isomer free energies by a fraction of a kilocalorie/mole. At room temperature a change of

(66) J. Sandström and B. Uppström, *Acta Chem. Scand.*, **21**, 2254 (1967).
(67) A. G. Whittaker and S. Siegel, *J. Chem. Phys.*, **43**, 1575 (1965).
(68) Unpublished observations in this laboratory.
(69) T. H. Siddall, III, and W. E. Stewart, *J. Chem. Phys.*, **48**, 2928 (1968).
(70) L. A. LaPlanche and M. T. Rogers, *J. Amer. Chem. Soc.*, **85**, 3728 (1963).

Table I

Isomer Ratios in Secondary Amides, Carbamate Esters, Thionamides, and Thioncarbamate Esters

R	R_1	*Solvent*	% *trans*	*Ref*
		Alkylamides, $RC(O)NHR_1$		
H	Me	?	92	30
Me	Me	?	100	30
Me	Me	H_2O	97	71
Et	Me	?	100	30
Isobutyl	Me	?	100	30
H	Et	?	88	30
Me	Et	?	100	30
Et	Et	?	100	30
Isobutyl	Et	CCl_4	100	30
H	2-Propyl		80	30
H	2-Propyl	C_6H_6	84	26
Me	2-Propyl	?	100	30
Isobutyl	2-Propyl	CCl_4	100	30
H	*t*-Butyl	C_6H_6	82	30
H	*t*-Butyl	C_6H_6	70	26
Me	*t*-Butyl	CCl_4	100	30
Me	$CH(OOH)CH_3$	$(CD_3)_2CO$	100	72
Et	$CH(OOH)CH_2CH_3$	$(CD_3)_2CO$	100	72
H	Benzyl	C_6H_6	90	26
H	$CH(CH_3)C_6H_5$	C_6H_6	~87	26
		Anilides, RC(O)NH (Aromatic)		
	Aromatic substitution			
H	None	1.5 mol % in $CDCl_3$	45	41
H	None	2.9 mol % in $CDCl_3$	48	41
H	None	3.6 mol % in $CDCl_3$	49	41
H	None	5.1 mol % in $CDCl_3$	50	41
H	None	9.7 mol % in $CDCl_3$	58	41
H	None	23.3 mol % in $CDCl_3$	62	41
H	None	31.3 mol % in $CDCl_3$	64	41
H	None	38.6 mol % in $CDCl_3$	66	41
H	None	50.0 mol % in $CDCl_3$	70	41
H	None	52.5 mol % in $CDCl_3$	73	41
H	2-Me	$CDCl_3$ (−50°)	25	73
H	4-Me	100 mg/ml in $CDCl_3$	59	19
H	4-Me	250 mg/ml in $CDCl_3$	55	19
H	4-Me	250 mg/ml in CH_3OH	67	19
H	2-Cl-4-Me	250 mg/ml in $CDCl_3$	67	19
H	4-C_4H_9	100 mg/ml in $CDCl_3$ (0°)	42	19
H	4-C_4H_9	500 mg/ml in $CDCl_3$ (0°)	61	19
Me	None	C_5H_5N	99.9	74
Me	None	$CDCl_3$ (−20°)	>99	76
Me	2-Me	$CDCl_3$ (−20°)	94	75, 76
Me	2-(2-Propyl)	$CDCl_3$ (−20°)	85	76
Me	2-(*t*-Butyl)	$CDCl_3$ (−20°)	75	75, 76
Me	2,6-$(Me)_2$	$CDCl_3$ (37°)	74	76
Me	2,6-$(Me)_2$	$CDCl_3$	80	17
Me	2,6-$(Et)_2$	$CDCl_3$ (37°)	69	75, 76
Me	2,6-(2-Pr)$_2$	$CDCl_3$ (37°)	64	75, 76
Me	2-Cl-4-Me	$CDCl_3$ (37°)	100	19
Me	2-Cl-6-Me	$CDCl_3$ (37°)	80	17
Me	2,4,6-$(Et)_3$	$CDCl_3$ (37°)	69	75, 76
	2,4,6-(2-Pr)$_3$	$CDCl_3$ (37°)	63	76
	2,4,6-(*t*-Bu)$_2$	$CDCl_3$ (37°)	55	75, 76
		Alkylthionamides, $RC(S)NHR_1$		
	R_1			
H	Me	$CDCl_3$	88	66
H	Me	$(CD_3)_2CO$	88	66
H	Me	C_6H_6	86	66
H	Me	H_2O	86	66
H	2-Propyl	20 mol % in C_6H_6	70	26
H	*t*-Butyl	16.7 mol % in C_6H_6	4	26

Table I (Continued)

R	R_1	*Solvent*	*% trans*	*Ref*
H	$CH_2C_6H_5$	16.7 mol % in C_6H_6	84	26
H	$CH(CH_3)C_6H_5$	20 mol % in C_6H_6	74	26
H	$CH_2CH(CH_3)_2$	Neat	77	26
H	$CH_2CH(CH_3)_2$	25 mol % in NM	73	26
H	$CH_2CH(CH_3)_2$	33 mol % in C_6H_6	75	26
H	$CH_2CH(CH_3)_2$	20 mol % in C_6H_6	71	26
H	$CH_2CH(CH_3)_2$	5 mol % in C_6H_6	68	26
H	$CH_2CH(CH_3)_2$	10 mol % in C_6H_6	66	26
H	$CH_2CH(CH_3)_2$	5 mol % in C_6H_6	61	26
Me	Me	$CDCl_3$	100	66
Me	Me	CCl_4	98	66
Me	Me	C_6H_6	98	66
Et	Me	$CDCl_3$	100	66
Et	Me	CCl_4	100	66
Isobutyl	Me	$CDCl_3$	100	66
t-Butyl	Me	$CDCl_3$	100	66
	Thionanilides, RC(S)NH (Aromatic)			
	Aromatic substitution			
H	None	$CDCl_3$	0	31
Me	None	$CDCl_3$	60	31
Me	None	C_6H_6	27	31
Me	None	CCl_4	53	31
Me	None	dioxane	67	31
Me	None	CH_2Cl_2	69	31
Me	None	CH_3NO_2	86	31
Me	4-Me	C_6H_6	29	31
Me	4-Me	CCl_4	41	31
Me	4-Me	CH_2Cl_2	69	31
Me	4-Me	$MeNO_2$	80	31
Me	4-Me	10% in $CDCl_3$ (30°)	53	31
Me	4-Me	10% in $CDCl_3$ (60°)	51	31
Me	4-Me	2.5% in $CDCl_3$ (60°)	51	31
Me	4-Me	20% in $CDCl_3$ (60°)	47	31
t-Butyl	4-Me	$CDCl_3$	100	31
t-Butyl	2,5-$(Me)_2$	$CDCl_3$	100	31
	Thioncarbamate Esters, $R_1OC(S)NHR$			
	R_1			
Me	Me	$CDCl_3$	62	77
Me	Me	CCl_4	63	77
Me	Me	C_6D_6	66	77
Me	Me	C_5H_5N	73	77
Me	Et	$CDCl_3$	64	77
Me	Et	CCl_4	64	77
Me	Et	C_6D_6	67	77
Me	Et	C_5H_5N	76	77
Me	Isobutyl	$CDCl_3$	58	77
Me	Isobutyl	CCl_4	62	77
Me	Isobutyl	C_6D_6	66	77
Me	Isobutyl	C_5H_5N	75	77
Me	$CH_2CH_2CH(CH_3)_2$	$CDCl_3$	60	77
Me	$CH_2CH_2CH(CH_3)_2$	CCl_4	60	77
Me	$CH_2CH_2CH(CH_3)_2$	C_6D_6	65	77
Me	$CH_2CH_2CH(CH_3)_2$	C_5H_5N	80	77
Me	*t*-Butyl	$CDCl_3$	62	77
Me	*t*-Butyl	CCl_4	62	77
Me	*t*-Butyl	C_6D_6	70	77
Me	*t*-Butyl	C_5H_5N	66	77
t-Butyl	Me	C_6D_6	33	77
t-Butyl	Me	C_5H_5N	37	77
CH_3	$CH_2CH_2N(CH_3)_2$	$CDCl_3$	74	77
CH_3	$CH_2CH_2N(CH_3)_2$	CCl_4	75	77
CH_3	$CH_2CH_2N(CH_3)_2$	C_5H_5N	74	77
CH_3	$CH_2(CH_2)_2N(CH_3)_2$	$CDCl_3$	67	77
CH_3	$CH_2(CH_2)_2N(CH_3)_2$	CCl_4	67	77
CH_3	$CH_2(CH_2)_2N(CH_3)_2$	C_5H_5N	80	77

0.4 kcal/mol changes the isomer ratio by a factor of 2. The authors of this review suspect that small, *attractive* nonbonded interactions are more important than is generally recognized in determining isomer ratios. It also must be true that the exact shapes (beyond simple steric or size considerations) of the groups R, R_1, and R_2 are important. Any realistic molecular model shows how crowded the (approximate) plane of the amide molecule becomes as these groups become larger. For these reasons we have chosen to list certain general observations, but to limit the discussion of individual cases.

A tabulation of reported isomer ratios for various secondary amides and related compounds is given in Table I.[17,19,26,30,31,41,66,71-77] For N-alkylformamides the percentage of *cis* isomer increases as the size of the N-alkyl substituent increases.[30] This trend has been explained in terms of simple steric interactions between the N-alkyl substituent and the carbonyl oxygen.[30] The increase in the amount of the *cis* isomer of N-*t*-butylformamide from 18% in dilute benzene solution to 63% in sulfuric acid solution is consistent with this explanation, since the protonation of the carbonyl oxygen atom increases its effective size and leads to increased steric interaction between the carbonyl oxygen and the *t*-butyl group.[30]

As LaPlanche and Rogers point out, no satisfactory explanation has been given for the predominance of the *trans* isomer in N-alkylformamides such as N-methylformamide in which no steric interactions favoring the *trans* isomer are present, or in amides in which steric interaction would seem to favor the *cis* isomer, like N-*t*-butylformamide.[30]

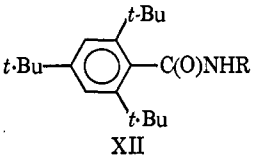
When the formyl hydrogen atom is replaced by an alkyl group, steric interaction between the group and the N-alkyl group leads to predominance of the *trans* isomer.[30]

Replacement of the N-alkyl group of an N-monosubstituted formamide by an aromatic group causes an increase in the stability of the *cis* isomer.[41,73] In addition, the isomer ratios show a strong concentration dependence as may be seen from results given in Table I. The N–H proton shift is concentration dependent, with high-field shifts of both the *cis* and *trans* N–H protons accompanying dilution with $CDCl_3$. As the $CDCl_3$ concentration is increased, both the *cis* and *trans* protons undergo a high-field shift, with the *trans* proton showing the larger shift.[41] The high-field shift with dilution was attributed to the decrease in amide–amide hydrogen bonding. The greater dilution shifts for the *trans* isomer presumably means that the hydrogen-bonded *trans* species dissociates to a greater extent with dilution than does the *cis* species. Two possible explanations have been offered for the observed concentration effects:[41] (1) the solvated *cis* form is thermodynamically more stable than the solvated *trans* form, or (2) the *cis* form even at high dilution is stabilized by hydrogen bonding and exists as ring dimers, whereas the *trans* form at the same concentration is hydrogen bonded to a lesser extent.

The effect of increasing the size of the substituent on the carbonyl carbon is shown by comparing formanilide and acetanilide. In acetanilide, in pyridine solution[74] and in $CDCl_3$ solution,[18] the *trans* form predominates (just as it does in the solid state).[78] Increasing the size or nature of the alkyl substituent on the carbonyl carbon has no effect on the isomer ratio.[17,18,21,22]

Substitution of bulky alkyl groups in the ring *ortho* positions in acetanilide increases the stability of the *cis* isomer.[17,75,76] The results given in Table I show that the amount of *cis* isomer is in direct proportion to the bulkiness of the *ortho* substituent. The amount of *cis* isomer is greatest when both *ortho* positions are occupied by *t*-butyl groups. These results were interpreted as follows.[76] In the *cis* form of acetanilide the benzene ring and amide group are nearly coplanar, and steric repulsion between the *ortho* proton and the acetyl methyl protons makes the *cis* isomer energetically less favored than the *trans*. When bulky groups are substituted in the *ortho* positions the dihedral angle between the aromatic and amide planes tends toward 90° in both the *cis* and *trans* isomers. Repulsive steric interactions in the *cis* and *trans* isomers become more nearly equal, and a statistical distribution of isomers is approached.

The N-monosubstituted amides XII exist as *trans* isomers exclusively.[79]



XII

The barrier to rotation around the C–N bond is greater in N,N-dimethylthionamides than in the corresponding amides.[80] From this behavior it has been concluded that the dipolar structure II makes a greater contribution to the ground state of thionamides than to that of amides, leading to a shorter C–N bond in the former case.[61] In addition the van der Waals radius of sulfur (1.85 Å) is larger than that of oxygen (1.40 Å), and hence any steric interactions involving these groups should be greater in thionamides and thereby shift the isomer ratio in favor of the *cis* configuration.[66] That this is the case is indicated by a study of the isomer ratios in some N-methylthionamides.[66]

The greater amount of *cis* isomer in NMTF as compared to NMF was attributed to the larger magnitude of the $S–CH_3$ steric repulsion in the *trans* isomer as compared to the $H–CH_3$ interaction in the *cis* amide. In the case of NMTA, the increased size of the S atom would be unfavorable to the *trans* isomer as compared to the amide, but the shortening of the thionamide C–N bond would also lead to an increase in the CH_3---CH_3 interaction in the *cis* thionamide. The latter effect is apparently slightly larger than the former. In the other C-alkyl, N-alkyl thionamides, the alkyl interaction apparently is predominant, since the *trans* isomer is observed exclusively.

For the other N-alkylthionformamides listed in Table I, the amount of *cis* isomer increases with the size of the N-

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(77) R. A. Bauman, *J. Org. Chem.*, 32, 4129 (1967).
(78) C. J. Brown and D. E. C. Corbridge, *Acta Cryst.*, 7, 711 (1954).
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alkyl substituent just as in the amide case. The effect of a given alkyl group is greater in the former than in the latter case, however.

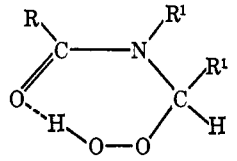
Thionformanilide exists as the *cis* isomer exclusively; the variable isomer ratios are observed with thionacetanilides.[31] Thus the S···aromatic interaction appears to be larger than the O···aromatic interaction. The thionacetanilide ratios varied with temperature and solvent in a fashion similar to formanilide. The observed increase of the amount of *trans* isomer with increasing polarity of the solvent was attributed to specific interactions between solute and solvent.[31]

When groups larger than methyl are present on the carbonyl carbon, the alkyl···aromatic interaction becomes larger than the S···aromatic interaction, and the *trans* isomer is observed exclusively.[31]

Methyl N-alkylcarbamates appear to exist as one isomer,[81] presumably the *trans* isomer. However, methyl N-alkylthioncarbamate and other alkylthioncarbamate esters exist as *both cis* and *trans* isomers[77] (see Table I). The increase in the alkyl···X interaction when X = S is the most likely reason for the increase in amount of *cis* isomer. For the alkyl N-methylthioncarbamates the amount of *cis* isomer shows a slight increase with increase in size of the O-alkyl substituent; when a *t*-butyl group is placed on nitrogen, the interaction between *t*-butyl and O-alkyl is apparently greater than the *t*-butyl–S interaction.

B. UNSYMMETRICAL N,N-DISUBSTITUTED AMIDES

The equilibrium distribution of *cis* and *trans* isomers of unsymmetrical N,N-disubstituted amides in solution appears to depend upon both steric and electronic factors. In alkylamides, in which electronic effects appear to be rather small, the most stable isomer seems in general to be that in which steric repulsion between the R group on the carbonyl carbon and the substituents on nitrogen are minimized. This conclusion follows from the study of isomer ratios of alkylamides by LaPlanche and Rogers.[70] The results of this study, summarized in Table II,[18,24,26,31,70,72,74,82–95] indicate that the preferred isomer in the formamides has the bulkier substituent *trans* to the carbonyl oxygen, in agreement with previous conclusions.[96,97] The other N-alkylformamides listed in Table II follow the same trend. When the R–C(O) substituent is larger than hydrogen, however, the bulkier group is *cis* to the carbonyl oxygen. These results were explained on the basis of the order of the size of the groups, *i.e.*, R (alkyl) > CH_3 > O > H.[70] (From the data obtained the authors were unable to establish whether the single sets of resonances for N-ethyl,N-methyltrimethylacetamide, N-butyl-N-methyltrimethylacetamide-N-methyl-N-*t*-butylacetamide, and N-acetyl-2-methylpiperidine arose from predominance of one isomer or rapid rotation around the amide bond [C(O)–N].[70]) In the hydroperoxides the preferred isomer is stabilized by intramolecular hydrogen-bonding[72] (XIII).

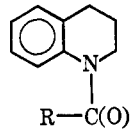


XIII

N-Methyl- and N-ethylformanilide in solution have the isomer distribution 95% *exo* (phenyl group *trans* to oxygen), 5% *endo* (phenyl group *cis* to oxygen).[88] On the basis of the results reported above, it might have been expected that the relative isomer stabilities would be reversed from those actually found. That is, the more sterically favored distribution would place the bulkier alkyl group next to the formyl hydrogen. However, some other factors which may also be important in determining the isomer distribution are (1) phenyl–amide group conjugation, (2) intramolecular hydrogen-bonding between the formyl proton and the phenyl π-cloud, and (3) π–π repulsion between the phenyl ring and the carbonyl group. Any of these effects, if present, could help stabilize the *exo* form over the *endo* form.

In general it appears that N-alkylacetanilides exist predominantly as the *exo* isomer.[17,18,74,89,91,98] However, in the case of 2′,6′-disubstituted acetanilides both *exo* and *endo* isomers exist in solution.[17,90,91] In only one class of compounds, N-methyl-2,6-dinitro- and 2,4,6-trinitroacetanilides, has a predominance of the *endo* form been observed.[91] The *endo*/*exo* ratio decreases as the polarity of the solvent increases.[91]

In N-acylindolines (IV) and tetrahydroquinolines (XIV) the benzene ring is preferentially *exo* unless steric or hydrogen-



XIV

bonding effects are important.[24] Thus N-formylindoline has predominantly the *exo* configuration, but in N-acetyl- or benzoylindolines the steric interaction between the C-7 proton and the R group makes the *endo* configuration the preferred one. In N-thionacetylindoline, interaction between the sulfur atom and the C-7 proton is apparently greater than C-7 to CH_3 interaction, leading to predominance of the *exo* isomer. In N-acetyltetrahydroquinolines, interaction between the acyl methyl group and the C-8 proton is reduced because of the flexibility of the tetrahydropyridine ring, and predominance of the *exo* configuration results.

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(93) W. Walter and G. Maerten, *Justus Liebigs Ann. Chem.*, **715**, 35 (1968).
(94) S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Chem. Commun.*, 480 (1966).
(95) L. Toldy and L. Radics, *Tetrahedron Lett.*, 4753 (1966).
(96) C. Franconi, *Z. Elektrochem.*, **65**, 645 (1961).
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Table II

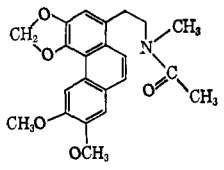
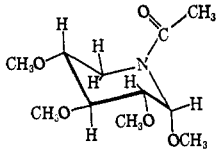
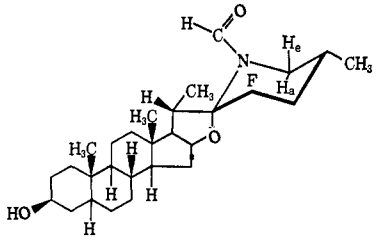
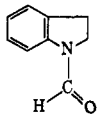
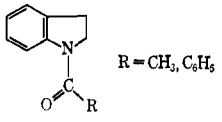
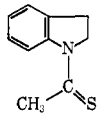
Isomer Ratios in Tertiary Amides and Thionamides

R	R_1	R_2	*Solvent*	*% isomer with R_1 cis to O*	*Ref*
		Alkylamides, $RC(O)NR_1R_2$			
H	Et	Me	?	40	70
H	*n*-Butyl	Me	?	39	70
H	Cyclohexyl	Me	?	34	70
H	2-Propyl	Me	?	33	70
H	*t*-Butyl	Me	?	11	70
Me	Et	Me	?	51	70
Me	*n*-Butyl	Me	?	53	70
Me	Cyclohexyl	Me	?	55	70
Me	2-Propyl	Me	?	58	70
Me	*t*-Butyl	Me	?		70
t-Butyl	Et	Me	?		70
t-Butyl	*n*-Butyl	Me	?		70
Isobutyl	*n*-Butyl	Me	?	50+	70
Me	Et	$CH(OOH)CH_3$	$CDCl_3$	26	72
Me	*n*-Propyl	$CH(OOH)CH_2CH_3$	$CDCl_3$	27	72
H	Me	$CH(CH_3)C_6H_5$	?	70, unassigned	82
H	Me	$CH(CH_3)C_6H_5$	?	54	26
H	Me	$CH_2C_6H_5$	?	52	82
H	Me	$CH_2C_6H_5$	?	56	83
H	Me	$CH_2C_6H_5$	?	54	26
H	Me	$CH(C_6H_5)_2$	?	67	82
H	2-Propyl	$CH_2C_6H_5$	?	54	26
$2,4,6\text{-}(Me)_3C_6H_2$	$CH_2C_6H_5$	Me	CCl_4 (38°)	73	84
$2,4,6\text{-}(Me)_3C_6H_2$	$CH_2C_6H_5$	Me	Chloronaphthalene–benzotrichloride	71	85
$2,4,6\text{-}(Me)_3C_6H_2$	$CH_2C_6H_5$	Me	Quinoline (40.6°)	72	84
$2,4,6\text{-}(Me)_3C_6H_2$	Cyclohexyl	Me	CCl_4 (38.8°)	70	84
$2,4,6\text{-}(Me)_3C_6H_2$	$-CH_2C_6H_5$	2-Propyl	Quinoline (38.8°)	79	84
$2,4,6\text{-}(t\text{-Butyl})_3C_6H_2$	$CH_2C_6H_5$	Me	Chloronaphthalene–benzotrichloride	89	86
$2,4,6\text{-}(Br)_3C_6H_2$	$CH_2C_6H_5$	Me	Quinoline	74	85
$2,6\text{-}(MeO)_2C_6H_3$	Me	$CH(CH_3)CH_2C_6H_5$	$CDCl_3$	50	224
$3,5\text{-}(NO_2)_2C_6H_3$	Me	$CH(CH_3)CH_2C_6H_5$	$(CH_3)_2CO$ (−10°)	25	87
		Anilides, $RC(O)NR_1$ (Aromatic)			
		Aromatic substitution			
H	Me	None	?	95	88
H	Et	None	?	95	88
Me	Me	None	C_5H_5N	95	74
Me	Me	$2,4,6\text{-}(NO_2)_3$	Dioxane-d_8 (37.5°)	25	89
Me	Me	$2,4,6\text{-}(NO_2)_3$	Acetic acid (37°)	32	89
Me	Me	$2,4\text{-}(NO_2)_2$	Dioxane-d_8 (18.4°)	37	89
Me	Me	$2,6\text{-}(NO_2)_2$	Dioxane-d_8 (39°)	44	89
Me	Me	$2,6\text{-}(NO_2)_2$	C_5H_5N (37.5°)	28	89
Me	Me	$2,6\text{-}(NO_2)_2$	$(CD_3)_2CO$ (35°)	33	89
Me	Me	$2,6\text{-}(NO_2)_2$	CH_2Cl (31°)	23	89
Me	Me	$2,6\text{-}(NO_2)_2$	C_6H_6 (32°)	17	89
α-Naphthyl	Me	$2,4\text{-}(Br)_2$, 6-Me	$CDCl_3$ (25°)	52, unassigned	90
			$C_2H_2Cl_4$ (100°)	63, unassigned	90
CH_2X X = Cl, Br, I	Me	2,6-R,R′ R,R′ = H, CH_3, *t*-C_4H_9, C_2H_5	$CDCl_3$	85–90	91
		Thionamides, $RC(S)NR_1R_2$			
		R_2			
Me	Me	$4\text{-}MeC_6H_4$	?	0	31
$2,4,6\text{-}(Me)_3C_6H_2$	Me	$CH_2C_6H_5$	$CDCl_3$ (50°)	32	92
H	Me	CH_2CH_2OH	25 mol % in C_6H_6	75	93
H	Me	CH_2CH_2OH	5 mol % in C_6H_6	73	93
H	Et	CH_2CH_2OH	25 mol % in C_6H_6	61	93
H	Et	CH_2CH_2OH	5 mol % in C_6H_6	60	93
H	2-Propyl	CH_2CH_2OH	25 mol % in C_6H_6	24	93
H	2-Propyl	CH_2CH_2OH	5 mol % in C_6H_6	28	93

Table II (Continued)

R	R_1	R_2	Solvent	% isomer with R_1 cis to O	Ref
H	*t*-Butyl	CH_2CH_2OH	25 mol % in C_6H_6	0	93
H	*t*-Butyl	CH_2CH_2OH	5 mol % in C_6H_6	0	93
H	Me	$CH_2C_6H_5$		61	26
H	Me	$CH(CH_3)C_6H_5$		73	26
H	2-Propyl	$CH_2C_6H_5$		20	26

Miscellaneous Amides

Amide	Solvent	% isomer shown	Ref
	$CDCl_3$ (40°)	46	94
	C_2Cl_4	47	13
	?	50	95
		75	24
		100	24
		100	24

At room temperature N-acylated pyrazoles, imidazoles, purines, and benzimidazoles apparently exist as single amide isomers, or else rotation is rapid, since only single signal sets were reported for these compounds.[99-102]

C. N-SUBSTITUTED LACTAMS

N-Methyl lactams with up to nine members are constrained to exist as the *cis* isomer XV[103-105] and exhibit only one N-CH_3 peak. The 11- and 13-membered lactams, however, show two N-CH_3 peaks. These two signals were assigned

(99) G. S. Reddy, L. Mandell, and J. H. Goldstein, *J. Chem. Soc.*, 1414 (1963).
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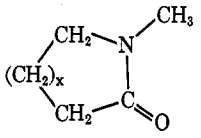
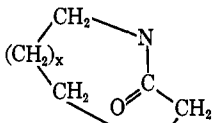


cis
XV



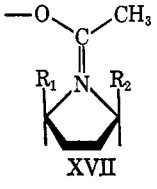
trans
XVI

to *cis* and *trans* methyl groups, and benzene solvent shifts indicated that the CH_3 peak at lower field was due to CH_3 in the *trans* configuration XVI. Room-temperature isomer ratios in CCl_4 were *cis*/*trans* 55/45 and 40/60 for the 11- and 13-membered lactams, respectively.[104,105] The isomer ratios show some solvent dependence.[108]

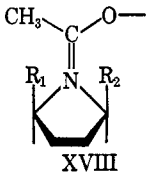
Other lactams have been studied and the configurations of the groups have been assigned.[106-108] These configurational assignments have been verified by X-ray analysis,[109] and by ultraviolet absorption studies.[108,109]

V. Conformational Studies of Amino Sugars

The amino group has been used as a probe to determine the structure and conformation of amino sugars. In the synthesis of amino sugars, it is sometimes difficult to determine whether ring closure has occurred on nitrogen or oxygen. However, it has been found that when a ring nitrogen is acetylated, the adjacent proton group resonances may be doubled at room temperature, becoming normal at elevated temperatures.[110-118] This effect is not observed upon N-acetylation when the nitrogen is not a part of the ring. The doubling in the former case is attributed to the presence of two conformers (XVII and XVIII) due to slow rotation around the amide [C(O)–N] bond; in the latter case, rotational averaging may occur by rotation around the N-ring C bond.

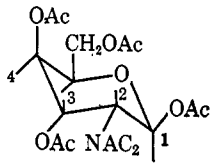


XVII



XVIII

In cases where the ring closes on the oxygen atom, chemical shifts of adjacent protons produced by acetylation of the amino group can be used to help make conformational assignments.[112,113] For example, in 1,3,4,6-tetra-O-acetyl-2-acylamino-2-deoxyhexoses (XIX), it was found that the deshielding influence of an equatorial diacylamino group upon an adjacent proton is much greater when the adjacent proton



XIX

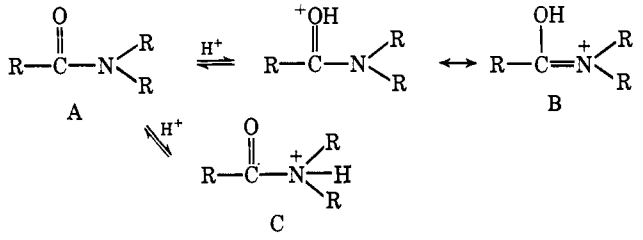
is axial than when it is equatorial.[114] Thus an equatorial diacylamino group at C_2 causes the H_1 axial proton (in the β anomer) to be shifted to a lower field than the H_1 equatorial proton (in the α anomer). This effect can be used to distinguish between anomers, and combined with the coupling constants can be used to determine the conformation of the amino sugar derivatives, assuming, of course, that no conformational changes occur upon acetylation.[114-117]

It has also been pointed out that the generalization that the methyl protons of axial acetoxy groups appear at lower field than the methyl protons of equatorial acetoxy groups[118] does not necessarily hold true when substituted groups other than acetoxy groups (particularly acylamino groups) are present.[114,119]

VI. Studies of Specific Interactions

A. LEWIS ACID COMPLEXES

When an amide (A) is placed in a protonating acid, protonation may occur on either the oxygen atom (B) or the nitrogen atom (C). Earlier workers, using other methods, were un-



decided as to whether O- or N-protonation occurred.[120] Recent nmr studies have shown that protonation on oxygen is predominant. In the structures above it seem that O-protonation should lead to increased C–N double-bond character, whereas N-protonation would destroy the double-bond character. Thus the retention of two N-methyl peaks and the increased barrier to rotation around the C–N bond of DMA in strong acid solution and the increased proton–proton coupling across the C–N bond have been cited as evidence for O-protonation.[121-123] Also the increase of the amide ^{14}N quadrupole coupling constant of DMF upon

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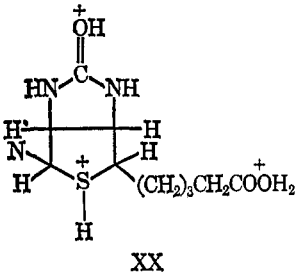
protonation indicates that O-protonation occurs.[124] Hampson and Mathias have explained the 8-ppm low-field shift of the resonance of the ^{14}N nucleus of DMF in TFA as being due to O-protonation.[125] More direct evidence was given by Gillespie and Birchall who showed that in fluorosulfuric acid at $\sim -80°$, many amides and thionamides exhibit a peak which may be definitely assigned to the C=O$^+$H or C=S$^+$H groups.[123,126]

Recent work, in which FSO_3H–S_6F_5–SO_2 mixtures were used, has shown that resonances from protonated oxygen and protonated nitrogen may be observed. Alkylcarbamates were found to be protonated only on oxygen, but urea and alkylureas were shown to be protonated on both oxygen and one of the nitrogen atoms.[127,128] D-Biotin (XX) was found to be triprotonated.



XX

Succinimide, maleimide, N-methylmaleimide, 3,3-dimethylglutarimide, 3-ethyl-3-methylglutarimide, N-methyldiacetamide, and phthalimide are O-diprotonated; barbituric acid is O-triprotonated; and pyromellitic diimide is O-tetraprotonated.[129]

The dimethylformamide·HCl and N-methylacetamide·HBr salts in nonaqueous solvents also show a peak due to the C=O$^+$H group.[130] Evidence for O-protonation has also been given for amides in trifluoroacetic acid and trifluoroacetic acid–$CDCl_3$ solutions[131] (see, however, ref 132).

Nmr evidence similar to that obtained for O-protonation indicates that complexation of other Lewis acids such as boron compounds and metal ions occurs through the oxygen atom.[130,133–151] For the 1:1 adducts formed by *m*-methoxy- and *p*-nitrobenzamides and various Lewis acids, a linear correlation between the N-H proton chemical shifts and the equilibrium constant for formation has been observed.[152] In the case of ureas and thionureas, evidence has been obtained that boron trihalides[153] and phosphorus pentachloride[154] coordinate on nitrogen.

B. PROTOLYSIS

The N-methyl absorptions of NMA and NMF are doublets in neutral aqueous solution due to spin coupling with the N-H proton. In basic or weakly acidic solutions the doublet collapses to a singlet but reappears in strongly acidic solution.[155,156] Similarly, the doublet structure of DMA due to restricted rotation around the C–N bond collapses at intermediate acid concentrations.[155] These observations have been explained in terms of the equilibria given above[155] (A, B, C).

The doublet collapse of both the N-monosubstituted and disubstituted amides is due to the equilibrium A $\rightleftharpoons$ C which occurs at intermediate acid concentration. The equilibrium A $\rightleftharpoons$ B is the predominant one at both high and low acid concentrations. (In $CDCl_3$–TFA solutions the same phenomena occur and can be explained in the same manner.[131])

Equilibrium A $\rightleftharpoons$ C allows for hydrogen exchange and free rotation around the C–N bond. (Bovey and Tiers, however, have studied proton exchange and restricted rotation of the amide group in aqueous polyacrylamide and concluded that proton exchange and free rotation do not proceed by way of a common intermediate.[157]) Rates of hydrogen exchange as a function of pH have been reported.[155] Klotz and Frank, using optical methods, studied the effects of various catalysts upon the exchange rate and also determined that the energy of activation of the exchange was about 20 kcal/mol.[158,159] The effect of added electrolytes upon the proton exchange rate has been studied.[160] The rate of the acid-catalyzed exchange was found to be markedly dependent upon the nature of the added cation, but insensitive to the nature of the supporting anion (with the exception of SCN^-).

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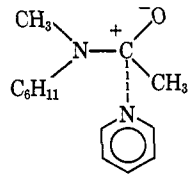
C. AMIDE–AMIDE AND AMIDE–SOLVENT INTERACTIONS

The relative contributions of the two resonance structures of amides depend to a certain extent upon the environment of the amide. Thus it has been reported that when the pure amide is diluted with a nonpolar solvent, coupling across the C–N bond decreases.[161] and E_a for rotation around the C–N bond decreases.[162] In N,N-dimethylamides, dilution produces a larger downfield shift of the *cis* resonance than the *trans*.[161] In DEF, the α-CH_2 protons shift to higher field with dilution while the β-methyl protons shift downfield, with the *trans* β-CH_3 showing the greater shift.[161] These results have been interpreted as indicating that in the pure liquid the dipolar resonance form is stabilized by head-to-tail dipolar associations.[161,162] In dilute CCl_4 solution, $\Delta H°$ and $\Delta S°$ values of -6 kcal/mol and -14.5 eu have been reported for the dimerization.[163]

Hydrogen-donating solvents also increase the contribution of the dipolar form by hydrogen-bonding through the amide oxygen.[87,61,164–166]

D. COMPLEXES WITH AROMATIC DONORS

Several workers have extended the studies of Hatton and Richards of the interaction between amides and aromatic solvents.[167–172] Moriarty studied the effects of the aromatic solvents benzene, pyridine, and collidine upon the proton chemical shifts of the *cis* and *trans* isomers of N-methylcyclohexylacetamide and proposed that the amide–pyridine complex has the structure XXI.[168]



XXI

Sandoval and Hanna studied the complexes of DMF with benzene, toluene, *p*-xylene, mesitylene, and durene and obtained equilibrium quotients for association and the chemical shifts of the N-methyl groups in the pure complex.[169] They found, in agreement with earlier work, that the N–CH_3 upfield shifts decreased as the number of aromatic methyl groups was increased. However, since the equilibrium quotients for association *increased* in the same direction, they concluded that the decrease in chemical shifts was due to a reduction in the aromatic ring current rather than to a weakening of the aromatic–amide complex, as had been proposed previously.

Matsuo has studied the effects of the solvents benzene, *n*-hexane, cyclohexane, carbon tetrachloride, acetonitrile, dioxane, triethylamine, acetone, and dimethyl sulfoxide upon the chemical shifts of the protons in some N-substituted imides.[170] A more detailed study of the complexes formed between N-substituted maleimide and benzene has been reported.[171]

When a protic substance such as trifluoroacetic acid or methanol is added to a benzene solution of an N,N-dimethylamide, all proton signals of the amide show an upfield shift.[172] The signal from the *cis* N–CH_3 group undergoes the largest upfield shift; this behavior may be due to insulation of the negative charge on the carbonyl oxygen by the acid proton allowing benzene solvent molecules to complex with the *cis* N–CH_3 and α-carbonyl groups.[172]

Stereospecific interactions between benzene and bis(N,N-dialkyldithiocarbamato)dimethyltin and bis(N,N-dimethyldithiocarbamato)methyltin halides have been studied.[173]

VII. ^{14}N Chemical Shifts

^{14}N chemical shifts vary over a range of 1000 ppm. The shielding constant can be separated into three components: σ_D, the diamagnetic shielding, σ_A, the long-range shielding, and σ_p, the paramagnetic shielding.[174] It has been argued that σ_D and σ_A are relatively unimportant in causing variations in ^{14}N shifts and that σ_p, which arises from asymmetries in the electronic structure produced by bonding, is the controlling factor.[175] When the nitrogen lone-pair electrons are involved in bonding, low-field shifts are observed.[174] It has been proposed that the magnitude of the shift is proportional to the extent of delocalization of the lone-pair electrons.[175] Thus in going from alkylamide to protonated alkylamide to alkylthionamide, low-field shifts of ~8 and ~40 ppm are observed.[125,175,176] Low-field shifts of 5–10 ppm have been observed for formamides in going from acetone to methanol solution, presumably because of the hydrogen-bonding stabilization of the polar structure by the methanol.[177] In selenoamides the ^{14}N shift is only about 4 ppm lower than that for the analogous thionamide, suggesting that the electron delocalization is only slightly greater in selenoamides than in thionamides.[176,178]

The shifts caused by the introduction of substituents capable of conjugation with the amide group can be rationalized in terms of the delocalization of the nitrogen lone-pair electrons.[176,178]

The effects of N-alkyl substitution are not so easily rationalized. N-Methylation of a primary amide produces a downfield shift of about 4 ppm; ethyl, propyl, or butyl substitution, however, produces a downfield shift of about 15 ppm.[125,178] From these results it has been concluded that N-alkyl substitution increases the electron delocalizations; from the greater shifts caused by the higher alkyl substituents as compared to methyl, it has been predicted that barriers to rotation around the amide C–N bond would increase as

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the size of the N-substituent increases.[125] However, the reverse situation appears to be true—increasing the size of the alkyl group decreases the barrier, presumably because of steric interactions present in the planar ground state.[179] Thus it appears that in cases where bond distortions can occur owing to steric interactions, the correlation between electron delocalization and chemical shift does not hold.

VIII. Studies of Hindered Rotations in Amides and Thionamides

A. METHODS USED TO MEASURE THE HEIGHTS OF ROTATIONAL BARRIERS

1. Signal Shape Analysis

Signal shape analysis is the most versatile method of determining exchange rates by nmr. It is the *only* widely applicable method for determining exchange rates for amides of the type $R_1C(O)N(R)_2$ where R_1 contains the same nuclear species as do the R groups. When applied with reasonable care in simple situations, it provides accurate rate values in the temperature range around the coalescence point of the separate signal sets (or the region of intermediate exchange). Fair accuracy is obtained in this range even with approximate or partial analyses.

The method becomes increasingly more difficult to apply accurately as either the slow or fast exchange limit is approached. It is quite feasible, in simple situations, to obtain good values of ΔF^*, the free energy of activation, but it is very difficult to obtain reliable rate data over a sufficient temperature range to give accurate values for the other rate quantities: E_a and A_0 or ΔH^* and ΔS^* (the energy of activation, frequency factor, enthalpy, and entropy of activation). The systematic error in determining these other rate quantities is generally much larger than random errors. None of the earlier determinations of these other quantities has any significance, except by chance. Even with the most sophisticated and careful of the recent experiments and analyses, there remains considerable risk of hidden errors.

Another largely unrecognized source of error is the minimum temperature variation of ±2° to be expected with currently available variable-temperature assemblies. If the rate study is extended over the typical 30–50° interval, the variance in E_a must be several per cent from this source of error alone. This error is smaller than the other systematic errors in many of the early studies, but is still often much larger than the errors quoted by the authors. An excellent and detailed discussion of these problems and many others discussed below is available.[180]

The recent work based on total line shape analysis probably gives values for E_a and A_0 that have quantitative significance. However, better values are obtained by combining signal shape analysis with equilibration (see section VIII.A.4).

a. The AB Uncoupled Case with Equal Populations

The simplest situation is that in which two protons are exchanging identity (chemical shifts) without being coupled to each other or to any other nuclei. No complication is added if groups of protons are treated, as long as the protons are identical within the group. This will be referred to below as the "AB Uncoupled Case with Equal Population." This will most obviously apply to amides of the type $XC(O)NMe_2$, where X either contains no protons or the protons in X are so far removed that there is no significant coupling to the methyl protons. N,N-Dimethylcarbamyl chloride ($ClC(O)NMe_2$) is an example of the first, and N,N-dimethylbenzamide is an example of the second. No coupling between the protons of the N-methyl groups has been reported for any N,N-dimethylamide. Even if coupling did occur, no complication of serious practical consequence would ensue as long as the coupling was small and did not significantly affect the Lorentzian shape of the signals. (However, for this reason even if for no other, the apparent signal width (or apparent T_2) would be a function of temperature.)

There are four papers that are vital to the discussion of the AB uncoupled case in general and of the case with equal population, in particular.[180-183] Nakagawa's formulation[183] of the Gutowsky–Holm equation[4] is the most comprehensive application of signal shape analysis to the AB uncoupled case. (The essential ideas are stated in nearly an identical fashion in another paper[182] and are easily derived from Gutowsky's paper.) Nakagawa's formulation is

$$v = Cx\{a^2rf(f-1) + r(1+ar)^2 + a(1+2ar)/4\}/$$
$$\{a^2f^2(f-1)^2 + (1+2ar+2a^2r^2)f(f-1) + r^2(1+ar)^2 + (1+2ar)^2/4\} \quad (3)$$

where $f = (\nu_A - \nu)/(\nu_A - \nu_B)$, $a = 2\pi p_B \tau_A/|\nu_A - \nu_B|$, v/C is normalized arbitrary intensity, $r = 1/2\pi T_2|\nu_A - \nu_B| = W_{1/2}/|\nu_A - \nu_B|$, $W_{1/2}$ is one-half the half-width at half-height in the absence of exchange, and the other symbols have their usual meaning.[184] The scale for f is fixed by the scale for $|\nu_A - \nu_B|$.

The variable v/C, in arbitrary or normalized units, an experimental quantity, is stated as a function of three independent variables. One of the independent variables, f, is experimental; the other two independent variables, r and a, are to be computed from the analysis. However, r and a together are functions of the three physical quantities τ, T_2, and $|\nu_A - \nu_B|$; one of these must be specified if the other two are to be determined. In practice the specified quantity is T_2 or $|\nu_A - \nu_B|$, since finding τ is the whole point of the undertaking. More often $|\nu_A - \nu_B|$ is left free to vary while T_2 is fixed. As long as T_2 is small compared to $|\nu_A - \nu_B|$, (Nakagawa's r is small), τ is insensitive to T_2 in the immediate neighborhood of signal coalescence, but depends linearly on the inverse of $|\nu_A - \nu_B|$.

An ideal situation for the determination of exchange rates by signal shape analysis is the AB uncoupled case (a) with equal population, (b) with a $|\nu_A - \nu_B|$ of at least several tenths of a part per million, and (c) in the center of the intermediate exchange region. This situation will be even better when (d) $|\nu_A - \nu_B|$ can be estimated at intermediate exchange by extrapolation from its temperature dependence over a considerable range where slow exchange obtains.

(179) Compare the barriers for various N,N-dialkylamides given in Tables III, IV, and VI.

(180) A. Allerhand, H. S. Gutowsky, J. Jonas, and R. A. Meinzer, *J. Amer. Chem. Soc.*, 88, 3185 (1966).

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(184) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959.

When this estimate agrees with $|\nu_A - \nu_B|$ obtained from the analysis, the error in the analysis may compare with the remaining uncertainties: (i) experimental and (ii) the assumptions inherent in Bloch's phenomenological equations. With a typical value of 20 kcal/mol for ΔF^* (transmission coefficient = 1) the reproducibility of the spectra and the temperature uncertainty of ±2° probably contribute equally (about 10% each) to the uncertainty in the exchange rate. A practical lower limit to the uncertainty in ΔF^* then may be as small as ±0.2 kcal/mol. By similar estimation, a 1% uncertainty in ΔF^* at 10 kcal/mol requires temperature control to about ±1°.

b. The AB Uncoupled Case with Unequal Populations

Unequal population can occur as an extra complication, and usually will, whenever the amide molecule is of the type $R_1C(O)NR_2R_3$. The R_2 group may either be *cis* or *trans* to the oxygen. The resulting *cis–trans* isomers can have the same population only by chance. Nakagawa's formulation in this case is

$$v = C[(1 + ar)\{-af(f - 1) + r(1 + ar)\} + a(f + p_B - 1)(f + 2arf - ar - p_B)]/[\{-af(f - 1) + r(1 + ar)\}^2 + (f + 2arf - ar - p_B)^2] \quad (4)$$

The signal shape is now described by four independent variables. In a purely mathematical way no complications ensue from the unequal populations since p_B does occur in the equation. The extra unknown is matched by the increased information content of the equation. In practice there is inevitably some loss in the information available for τ, T_2, and $|\nu_A - \nu_B|$. In general a more complex theoretical model that contains more variables must have less available information allotted to each variable when the physical experiment is the same as in the simpler case.

Fortunately, the additional demand for information can be met, at least in part, by additional experiments. The isomer population, p_B or p_A, can often be measured in the region of slow exchange and extrapolated into the region of intermediate exchange even as $|\nu_A - \nu_B|$ can be extrapolated. A further fortunate circumstance is that the width of the coalesced signal *at its maximum width* is a very sensitive function of p_B. Exchange rate determinations with unequal populations should always include measurements at the temperatures required to specify this maximum breadth.

As p_B becomes larger, the exchange region most sensitive to τ moves toward slow exchange. This follows, since the shape of the coalesced peak is less affected by a small component. The maximum signal breadth of the coalesced peak becomes less, and more similar to the breadth at fast exchange as p_B increases. In other words, the distinction between fast and intermediate exchange becomes less. On the other hand, the shape of the small peak is very sensitive to the exchange rate.

c. More Complex Cases

Rogers and Woodbrey have given the equation required to account for unequal T_2's for the two peaks.[48] Fraenkel and Franconi have taken unequal coupling to a third nucleus into account[122] (also see ref 185). The coupled AB case has been treated; the required computer programming can be done directly from the equation given.[186]

There are no reports of rigorous signal shape treatment for A_2X_3 (or A_2B_3) amides such as N,N-diethylamides or for AX_6 amides such as N,N-di-2-propylamides. The approximate treatments cited in the literature are difficult to judge on the basis of the descriptions given and may not have clear validity. It is possible to treat these cases with Alexander's density matrix method.[187,188] However, a good approximation is that in which the exchanging multiplets are treated as though they were superimpositions of exchanging doublets. For example, the two lowest field components of the methylene quartets of exchanging ethyl groups can be treated as one exchanging doublet, the two second lowest field components can be treated as another exchanging doublet, etc. To treat the data, a general computer program can be written based on the equation of Rogers and Woodbrey for an exchanging doublet.[48,188] This treatment appears to be valid even when second-order effects produce appreciable distortion of signal intensities.[189] The validity of the method is based upon the fact that the nuclear spin state of a given proton does not change during the course of an exchange operation. However, the true error situation will become increasingly obscured as the shapes to be analyzed become more complex.

d. Extracting the Exchange Rate Data

This discussion is largely restricted to the simplest situation, the AB case, without coupling and with equal population, but can be extended to other situations.

The most precise way to extract the exchange data is to obtain the best match of the entire experimental signal shape to a complete theoretical signal shape (total signal shape analysis). Computer programs for such matching have been written.[190] The discussion of the errors that may still remain, even with such a procedure, is beyond the capacity of these reviewers at this time. However, it should be pointed out that the problem of the weighting of the various data points on the signal shape remains. Intuitively it seems incorrect to give equal statistical weight to all data points. Improper weighting can itself lead to systematic errors. In the case of unequal population it would obviously be incorrect to give equal weight to the large and small peaks. The smaller peak is more sensitive to the exchange rate.

An alternative procedure is visual matching of the observed and calculated shapes. This can be aided by plots of various shape parameters such as the signal width (divided by $|\nu_A - \nu_B|$) at fractional (usually 1/2) height (*line broadening*), the ratio of the signal height at the maxima to the height of the trough between the maxima (*ratio method*), or *peak separation*. It is best to use two or more of these, or similar parameters at the same time.

(185) A. Pines and M. Rabinovitz, *Tetrahedron Lett.*, 3529 (1968).
(186) J. Heidberg, J. A. Weil, G. A. Janusonis, and J. K. Anderson, *J. Chem. Phys.*, 41, 1033 (1964).
(187) S. Alexander, *ibid.*, 37, 967 (1962).
(188) S. Alexander, *ibid.*, 37, 974 (1962).
(189) R. Munday and I. O. Sutherland, *J. Chem. Soc. B*, 80 (1968).
(190) J. Jonas, A. Allerhand, and H. S. Gutowsky, *J. Chem. Phys.*, 42, 3396 (1965).

2. Approximate Analysis

The various approximate analyses and their ranges of applicability have been thoroughly discussed by Gutowsky.[180] The basis of these methods is the reduction of the total signal shape equation to an approximation in which τ is expressed as a function of one of the signal shape parameters discussed above. Such procedures may be useful for estimating exchange rates in the course of an experiment. However, for an experimenter who is frequently involved in signal shape analysis, it is as easy, and may be much more accurate, to match observed and calculated curves. This can be done almost at a glance as suggested.[182] The ready availability of computer programs for total shape analysis and of precalculated shapes leaves little justification for the use of approximate procedures. However, at the coalescence temperature two useful relations may be used. For the AB uncoupled case with equal populations at the coalescence temperature, the exchange rate, k_c, is given by[180]

$$k_c = \frac{\pi|\nu_A - \nu_B|}{\sqrt{2}} \quad (5)$$

For small values of r ($W_{1/2}/|\nu_A - \nu_B|$), eq 5 gives a good k_c value. As r becomes greater than about 0.1, accurate determination of the coalescence temperature becomes more difficult. For the AB coupled case, k_c at the coalescence temperature is given by

$$k_c = \frac{\pi[|\nu_A - \nu_B|^2 + 6J_{AB}^2]^{1/2}}{\sqrt{2}} \quad (6)$$

where J_{AB} is the A–B coupling constant (see ref 191 and references therein).

3. Equilibration Method

The equilibration method is applicable, under favorable circumstances, to unsymmetrically substituted amides, $R_1C(O)NR_2R_3$, $R_2 \neq R_3$. If the mixture of *cis* and *trans* isomers can be displaced from its equilibrium value by any available method, it may be possible to observe the equilibration taking place. The chief additional requirement is that at least one signal from each isomer be unique for that isomer and well separated from all other signals. The data are analyzed in that case by applying eq 7, where R is the ratio

$$\ln\left[\frac{R - R_e}{R + 1}\right] = (k_1 + k_2)t + C \quad (7)$$

of signal intensities at time t, R_e is the equilibrium ratio or equilibrium constant, and k_1 and k_2 are the rate constants. A plot on semilog paper rapidly gives a half-time, $t_{1/2}$, from which $(k_1 + k_2)$ is obtained from the relation $(k_1 + k_2) = \ln 2/t_{1/2}$. In this ideal situation, errors in the rate constants may be kept as low as 10%.

Equilibrium displacement has been most commonly achieved by crystallizing out one isomer in substantially pure form. Many amides exist as good crystalline solids. Many of these, possibly nearly all, are in one isomeric form. With rotational barriers in excess of about 20 kcal/mol, it is not difficult to place the isomer in solution, transfer the solution, and begin the rate experiment before significant isomer purity is lost. With smaller barriers, the operation of sample preparation and transfer must be carried out at low temperature. This can be accomplished conveniently by operating through holes in a plastic cover of a deep, insulated box cooled with Dry Ice or liquid nitrogen.

Equilibrium displacement has been achieved by chromatography,[92] and also by stripping uranyl nitrate away from the amide–uranyl nitrate adduct at low temperature.[192]

4. Combined Signal Shape Analysis and Equilibration

In favorable cases it is possible to apply the signal shape and equilibration methods to the same compound. Mannschreck first pointed out that this makes rate determinations possible over a range of at least 10^7 in the rate and more than 100° in temperature.[85] The signal shape data need be used only in the neighborhood of coalescence or wherever they are most easily and accurately obtained. For a 100° temperature and 10^7 rate span and 10% variance in the rates, the variance in E_a is about 1% if the temperature can be controlled to ±0.5°. A method for measuring the sample temperature to ±0.3° has been reported.[193] However, it has been pointed out that a temperature gradient of 2–3° occurs over the 1 cm of effective sample length in an nmr tube in the sample probe of the Varian V-6040 variable-temperature assembly.[182] This gradient must contribute both to an averaging of the rate process over this temperature interval, and to broadening of the signal itself. Without better temperature control the controlling error is the error in temperature. With the typical performance (±2°) of the usual temperature accessory the variance in E_a is 3%. This analysis of variance is very crude and does not include replication; a detailed error analysis would be worthwhile but quite involved.

5. Spin-Echo Method

A rather specialized method of determining exchange rates is the use of the echo amplitudes in Carr–Purcell pulse sequences.[194,195] The advantage of this method is that it allows rate determinations over a wider range of rates than does conventional steady-state nmr. A further benefit is that it gives a second, quite different method for determining rotation rates. A disadvantage is that rather specialized equipment and technique are required. The most serious limitation is that the instrumentation must respond to *all* nuclei of a given species. Therefore, the method is applicable only to such molecules as $(CH_3)_2NC(=O)X$ where X contains no protons.

B. BARRIER HEIGHTS

1. Basis for Correlating the Data

Tables III–X summarize some quantitative data for rotation around the amide bond in N,N-disubstituted amides. Tabulations for other internal motions are given in the various sections. ΔF^*, the free energy of activation, was chosen as the rate parameter. When the results were obtained by

(191) G. J. Bishop, B. J. Price, and I. O. Sutherland, *Chem. Commun.*, 672 (1967).

(192) T. H. Siddall, III, *Inorg. Nucl. Chem. Lett.*, 1, 155 (1965).

(193) G. Isaksson and J. Sandström, *Acta Chem. Scand.*, 21, 1605 (1967).

(194) K. H. Abramson, P. T. Inglefield, E. Krakower, and L. W. Reeves, *Can. J. Chem.*, 44, 1685 (1966).

(195) A. Allerhand and H. S. Gutowsky, *J. Chem. Phys.*, 41, 2115 (1964).

signal shape analysis, ΔF^* is given at the signal coalescence temperature if the temperature is *not* italicized, or when italicized, at what appears to be the approximate midpoint of the temperature range covered by the authors. Whatever the method, ΔF^* is given in kilocalories/mole; however, these units are often omitted in the discussion. It is also assumed that the transmission coefficient is unity. This is common practice even though a coefficient of 0.50 may be indicated—certainly for $RC(O)N(R_1)(R_2)$ where $R_1 = R_2$.

Under Method is listed the experimental method used to obtain the data. Three general methods have been used: signal shape (s.s., a.s.s., or v.a.s.s.), pulse echo analysis, and equilibration of a separated isomer or isomer mixture that was initially displaced from equilibrium (E). The symbol s.s. has been given to an entry when calculated and experimental signal shapes were matched with more than one shape parameter. The symbol a.s.s. indicates that the authors used an approximate signal shape analysis, usually based on only one shape parameter. The symbol v.a.s.s. indicates that there may not be enough information to say that the shape analysis method is entirely valid.

Wherever available, the composition of the solution that was employed is given after the name of the amide. Unfortunately the solution composition is often not given in the original work.

The choice of ΔF^* as the *sole* rate parameter may be questioned. The choice is a matter of necessity since in many cases ΔF^* is the only parameter given. In many cases where E_a, ΔS^*, and/or ΔH^* are given, they probably have little significance (see section VIII.A). However, in the mid-range of exchange, around the signal coalescence temperature, the exchange rate can be obtained with moderate error (a few tenths of a kilocalorie/mole for ΔF^*) even with approximate methods.

Fortunately that which is necessary may also be sufficient. The evidence is overwhelming that the magnitude of the entropy of activation is small, perhaps always less than 10 eu or even 5 eu, for *all* rotations in N,N-disubstituted amides. (This may also be true for a wide range of molecular types and a variety of internal motions.) With ΔF^* almost independent of temperature, comparisons for different compounds or sets of conditions, each with its own coalescence temperature, will be valid to a few tenths of a kilocalorie/mole. This also happens to be the typical experimental error in ΔF^*.

The evidence for small entropies of activation is obtained in part from the more rigorous signal shape analyses now being used, spin-echo analysis with its wider useful temperature range, equilibration results, and especially from the limited number of experiments where signal shape analysis and equilibration experiments have been done for the same compound. The combined technique permits rate measurements over a range of up to 10^8. Small entropies of activation are also strongly indicated by absolute reaction rate theory. It is reasonable to assume that the dipolar contribution to the resonance description of an amide molecule goes to zero as the molecule goes into its activated state for rotation. This conclusion follows from the fact that in the activated state the plane formed by the nitrogen atom and its substituent bonds is perpendicular to the >C=O plane, and the delocalization of the nitrogen lone-pair electrons depends on $\cos^2 \phi$, where ϕ is the angle between planes. The activated molecule is therefore a less polar molecule and hence less associated with other amide or solvent molecules. However, the gain in entropy cannot be great since at most it is the difference in entropy associated with the vibrations of the weak association bond on the one hand, and the translationally free molecule on the other hand. Actually this would be an overestimate. Even in the activated state the amide carbonyl group must have about the same polarity as a ketone and therefore be capable of polar interactions. In respects other than association, the ground and activated states must be almost identical and therefore almost identical in entropy content. At most, small positive entropies of activation might then be expected for rotation around the amide bond in N,N-disubstituted amides.

2. *Slow Rotation around the Amide [C(O)–N] Bond*

a. Dimethylformamide

The first report of slow rotation in amides as detected by nmr[3] and the first measurement of the rotational barrier in amides were for N,N-dimethylformamide (DMF).[4] The measurement of the barrier height in this molecule is reported in at least 11 publications. Values for ΔF^* determined by different authors for DMF are given in Table III.[4,37,48,84,85,122,166,182,185,196,197]

Table III

Rotational Barriers Reported for Dimethylformamide

Solvent	*Method*[a]	ΔF^* (T_c)[b]	*Ref*
Neat	a.s.s.	22 (99)	4
Tetrachloroethane (0.04 mole fraction)	a.s.s.	20.9 (115)	37
Neat	s.s.	20 (113)	182
$NCCH_2CO_2Et$	s.s.	21 (114)	182
Acetone	s.s.	20 (113)	182
Sulfuric acid	s.s.	20 (99)	182
Neat	a.s.s.	22.4 (149)	48
Neat	a.s.s.	20.8 (*123*)	166
Formamide (0.12 mole fraction)	a.s.s.	21.2 (*108*)	166
α-Chloronaphthalene	a.s.s.	20.6 (128)	85
Hexachlorobutadiene	a.s.s.	20.4 (105)	84
Neat	a.s.s.	20.7 (*106*)	122
Sulfuric acid (0.4 *M*)	a.s.s.	21.1 (*100*)	122
Neat	a.s.s.[c]	20.9 (121)	196
Deuterioacetone (10%)	a.s.s.	21.1 (117)	196
$CFCl_3$ (10)	a.s.s.	21.2 (117)	196
Hexamethyldisiloxane (10%)	a.s.s.	20.9 (110)	196
Hexamethyldisiloxane (0.3%)	a.s.s.	21.6 (93)	196
Neat	s.s.	20.9 (119)	185
Neat[d]	s.s.	21.8 (116)	197
Neat[e]	s.s.	21.8 (126)	197
Trifluoroacetic acid (0.3 *M*)	s.s.	20.7 (99)	197
Trifluoroacetic acid (0.3 *M*)[e]	s.s.	20.7 (104)	197

[a] s.s. = signal shape analysis; a.s.s. = approximate signal shape analysis. [b] ΔF^*, kcal/mol at coalescence temperature (°C) except where temperature is italicized. Italicized temperatures are the approximate midpoints of the ranges studied. [c] Calculated from data given in ref 196. [d] Formyl proton decoupled. [e] $DC(O)N(CH_3)_2$ used; deuterium decoupled.

(196) A. G. Whittaker and S. Siegel, *J. Chem. Phys.*, 42, 3320 (1965).
(197) F. Conti and W. von Philipsborn, *Helv. Chim. Acta*, 50, 603 (1967).

For the neat liquid the mean value of ΔF^* from eight different reports is 21.1 kcal/mol at an average coalescence temperature, T_c = 118°. The most recent value is 20.9 at T_c = 119°.[185] For the closely related amide, N-methyl-N-benzylformamide (**18**, Table V), ΔF^* = 20.9 at 122° from signal shape, and 21.3 at 9° from reequilibration. A recent report[198] gives E_a = 20.5 ± 0.2 kcal/mol and A_0 = 5 ± 3 × 10^{12} for DMF; the entropy of activation is small as it is with **18**.[83] It now seems apparent that the barrier to rotation in DMF is 21 kcal/mol.

However, there is still some unexplained scatter of data from different laboratories. In particular, the values of 22.4 kcal/mol for ΔF^* with T_c = 149°[48] and 21.8 kcal/mol[197] stand out from the rest. The high value, 22.4, seems to be confirmed by the high value of T_c = 149°. The value 21.8 was obtained both with decoupling of the formyl proton at 100 MHz and with decoupling of deuterium at 60 MHz. It would be helpful if this scatter could be explained.

The effect of solvents may be very small—perhaps a few tenths of a kilocalorie/mole. In fact the scatter of ΔF^* that might be ascribed to solvent is smaller than the scatter obtained for the neat liquid. The small solvent effect is rather surprising. It would be expected that a polar solvent would stabilize the ground state by dipole–dipole interactions. Or in other words, the dipolar resonance form of the molecule should make a larger contribution to the molecular description in polar solvents. On the other hand, the activated state presumably has no dipolar contribution in its description and therefore should be less affected by the nature of the solvent. (Evidence of such an effect is clear from infrared spectra of amides. For example, there is a pronounced shift to higher frequency for the carbonyl stretching band when passing from polar to nonpolar solvents.[199])

It is especially surprising that H_2SO_4 and CF_3COOH as solvents have so little effect. If even a small fraction of the molecules were protonated at the nitrogen atom, the barrier to rotation would be reduced below detection by nmr, since this protonated form has no C–N double-bond character.

In aqueous acid solutions the barrier is reduced; T_c = 43° in 5 *N* HBr, HCl, or $HClO_4$.[122] (If the chemical shift between the methyl groups is about 10 Hz, then ΔF^* (43°) = 17 kcal/mol or the barrier is reduced by 4 kcal/mol.)

b. Other N,N-Dimethylamides

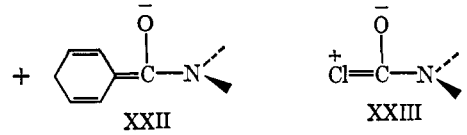
N,N-Dimethylamides have received a large share of the attention devoted to determination of rotational barriers in amides. This is, in part, due to the fact that the methyl signals at least approximate the AB uncoupled case. It is the only class of amides in which the spin-echo technique is generally applicable.

A summary of the barriers for various N,N-dimethylamides is given in Table IV.[4,48,62,84,85,162,166,170,182,193–195,200–202] Of the various values for **1**, R = Me, ΔF^* = 18.1 kcal/mol (75°) is probably the most accurate.[201] The experiment was performed with $CD_3C(O)NMe_2$ in order to circumvent the problem of unequal coupling of the acetyl methyl protons to the protons of the two N–Me groups. The data were treated by total line-shape analysis with a sophisticated computer program. The only departure from rigorous treatment was in the use of T_2 values derived from the line width of $CHCl_2CHCl_2$ at the experimental temperatures. It is probably more desirable, where feasible, to extrapolate T_2 values from the slow and fast exchange regions into the region of intermediate exchange. It is well known that T_2's vary from molecule to molecule (or even within a molecule for different nuclei). ΔF^* for the neat liquid **1** has been measured by several groups[4,48,182] and, ignoring the low value,[200] averages out to 19 kcal/mol. The data for solvents effects are sparse, but for the two reported studies the effect is small (even when the solvent is formamide).

For R = Et (**2**) the average of the reported results is 17.8 kcal/mol while for R = Pr (**3**) only one value, 18 kcal/mol, is available. With **2** there is evidence of a solvent effect. The average ΔF^* in CH_2Br_2 is 17.9 kcal/mol, while in CCl_4 it is 16.7 kcal/mol.

The steric effect in the series R = H (21 kcal/mol), Me (19 kcal/mol), Et (18 kcal/mol), Pr (18 kcal/mol), 2-Pr (16 kcal/mol) is due to the fact that the larger groups cannot be accommodated in the amide plane. The consequent loss of delocalization energy destabilizes the ground state and decreases the height of the rotational barrier. The ethyl group is the same "size" as propyl and may be only a little "larger" than methyl. It is always possible to rotate R in $R–CH_2$ in such a way as to avoid serious steric conflict. However, with $(R)_2CH$ (2-Pr), it is not possible to do so for both groups. With R = *t*-butyl the steric effect becomes acute. Qualitative observations in this laboratory suggest that the barrier for *t*-$BuC(O)NMe_2$ is 11–13 kcal/mol. When R is the cyclopropyl group, both steric and electronic effects are present. The cyclopropyl group may be "smaller" than the 2-Pr group, but the barrier may be decreased by competitive delocalization into the cyclopropyl ring.

With R = Cl (**14**), C_6H_5, phenyl with an alkyl substituent in any position except *ortho*, or CH_2=CH–, the decrease in barrier is clearly ascribable to competitive delocalization (cross conjugation). In particular it can be seen that the contribution of resonance structures XXII or XXIII would



XXII XXIII

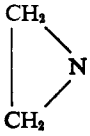
stabilize the activated state. With R = Cl, again there is some evidence of solvent effect. ΔF^* for **14** (neat) seems to be established at 17 kcal/mol. The several signal shape values agree well with each other and with the spin-echo value.

The barrier height lost to competitive delocalization is regained when the benzamide is *ortho* substituted (**7**, **9**) and further increased when there is di-*ortho* substitution (**11**, **12**). *ortho* substitution tends to force the benzene ring out-of-plane with respect to the carbonyl group, even in the activated state. This prevents stabilization of the activated state by competitive delocalization. Further, the ground state is stabilized by the out-of-plane ring, since steric interaction between the aromatic ring and the N-methyl group is decreased. This effect can become very large (see **22**).

(198) B. J. Price, J. A. Eggleston, and I. O. Sutherland, *J. Chem. Soc. B*, 922 (1967).
(199) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, Chapter 23.
(200) D. G. Gehring, W. A. Mosher, and G. S. Reddy, *J. Org. Chem.*, 31, 3436 (1966).
(201) R. C. Neuman, Jr., and V. Jonas, *J. Amer. Chem. Soc.*, 90, 1970 (1968).
(202) F. A. L. Anet and J. M. Osyany, *ibid.*, 89, 352 (1967).

Table IV

Barrier Heights for N,N-Dimethylamides, RC(O)NMe[a]

Compd	*R*	*Solvent*	*Method*	ΔF^* (T_c)[b]	*Ref*
1	Me	Neat	s.s.	19 (73)	182
	Me	Neat	a.s.s.	20.1 (87)	48
	Me	Neat	a.s.s.	19 (52)	4
	Me	Neat	a.s.s.	15.1 (70)	200
	Me	Neat	s.s.	18.1 (75)	201
	Me	$0.095X$[a] in $CD_3S(O)CD_3$	s.s.	18.3 (75)	201
	Me	$0.10X$ in $HC(O)NH_2$	a.s.s.	17.9 (75)	166
2	Et	Neat	a.s.s.	17.7 (61)	170
	Et	Neat	s.s.	18 (54)	182
	Et	Neat	a.s.s.	17.6 (62)	162
	Et	$0.85X$ in CH_2Br_2	a.s.s.	17.6 (62)	162
	Et	$0.69X$ in CH_2Br_2	a.s.s.	17.5 (61)	162
	Et	$0.58X$ in CH_2Br_2	a.s.s.	17.5 (61)	162
	Et	$0.41X$ in CH_2Br_2	a.s.s.	17.7 (60)	162
	Et	$0.22X$ in CH_2Br_2	a.s.s.	17.9 (60)	162
	Et	$0.10X$ in CH_2Br_2	a.s.s.	18.2 (66)	162
	Et	$0.69X$ in CCl_4	a.s.s.	17.4 (58)	162
	Et	$0.40X$ in CCl_4	a.s.s.	16.3 (39)	162
	Et	$0.11X$ in CCl_4	a.s.s.	16.6 (44)	162
3	*n*-Propyl	Neat	s.s.	18 (57)	182
4	2-Propyl	$0.33X$ in *o*-$C_6H_4Cl_2$	a.s.s.	16.2 (26)	193
5	Cyclopropyl	$0.33X$ in *o*-$C_6H_4Cl_2$	a.s.s.	16.4 (38)	193
	Cyclopropyl	Neat	a.s.s.	16.1 (47)	193
6	C_6H_5	$CHCl_3$	s.s.	16 (17)	182
	C_6H_5	EtC(O)Me	s.s.	15 (3)	182
	C_6H_5	CH_2Br_2	a.s.s.	15.0 (12)	48
7	*o*-$C_6H_4(NO_2)$	CCl_3CHCl_2	s.s.	20 (102)	182
8	*m*-$C_6H_4(NO_2)$	$CD_3C(O)CD_3$	s.s.	16 (16)	182
9	*o*-C_6H_4(OMe)	Neat	s.s.	19 (87)	182
10	*m*-C_6H_4(OMe)	$CD_3C(O)CO_3$	s.s.	15 (1)	182
11	2,4,6-Trimethylphenyl	0.6 *M* in 50:50 α-chloronaphthalene–benzotrichloride	a.s.s.	22.5 (168)	85
	2,4,6-Trimethylphenyl	CCl_2=CCl—CCl=CCl_2	a.s.s.	22.5 (160)	84
12	2,4,6-Tribromophenyl	0.6 *M* in 50:50 α-chloronaphthalene–benzotrichloride	a.s.s.	22.6 (171)	85
13		CCl_4	a.s.s.	16.4 (37)	202
14	Cl	Neat	s.s.	16.8 (*25*)	62
	Cl	Neat	a.s.s.	17.4 (53)	48
	Cl	Neat	a.s.s.	16.4 (*25*)	195
	Cl	Neat	a.s.s.	17.3 (59)	162
	Cl	$0.10X$ in CCl_4	s.s.	16.3 (25)	62
	Cl	$0.11X$ in CCl_4	s.s.	16.2 (?)	162
	Cl	$0.90X$ in CH_2Br_2	a.s.s.	17.5 (59)	162
	Cl	$0.63X$ in CH_2Br_2	a.s.s.	17.4 (58)	162
	Cl	$0.41X$ in CH_2Br_2	a.s.s.	17.4 (59)	162
	Cl	$0.11X$ in CH_2Br_2	a.s.s.	17.5 (59)	162
	Cl	$0.71X$ in CCl_4	a.s.s.	17.4 (60)	162
	Cl	$0.41X$ in CCl_4	a.s.s.	15.6 (51)	162
	Cl	$0.11X$ in CCl_4	a.s.s.	16.8 (45)	162
15	Cl_3C–	Neat	a.s.s.	14.7 (14)	48
	Cl_3C–	Neat	s.s.	14 (9)	182
	Cl_3C–	Neat	Pulse	15.0 (*25*)	195
	Cl_3C–	Neat	a.s.s.	15.0 (*25*)	195
	Cl_3C–	CH_2ClCH_2Cl	s.s.	14 (22)	182
	Cl_3C–	CH_2Cl_2	s.s.	14 (19)	182
	Cl_3C–	$CD_3C(O)CD_3$	s.s.	15 (13)	182
16	F_3C–	Neat	a.s.s.	19.5 (95)	48
	F_3C–	Neat	Pulse	18.5 (60)	194
17	CH_2=CH–	Neat	a.s.s.	16.8 (37)	48

[a] X = mole fraction. [b] See footnote *b*, Table III.

Table V

Barrier Heights for N-Methylamides, RC(O)N(Me)(R')

Compd	*R*	*R*$_1$	*Solvent*	*Method*	ΔF^* (T_c)[a]	*Ref*
18	H	$C_6H_5CH_2$	Neat	a.s.s.	23 (127)	82
18	H	$C_6H_5CH_2$	Neat	s.s.	20.9 (122)	83
18	H	$C_6H_5CH_2$	Neat	E	21.3 (*9*)	83
19	H	$(C_6H_5)(CH_3)CH$	Neat	a.s.s.	22 (*127*)	82
20	H	$(C_6H_5)_2CH$	Neat	a.s.s.	20 (*127*)	84
21	2,4,6-Trimethylphenyl	$C_6H_5CH_2$	0.8 *M* in CCl_4	E	22.6, 22.9 (*38*)	84
21	2,4,6-Trimethylphenyl	$C_6H_5CH_2$	0.8 *M* in quinoline	E	23.2, 23.4 (*41*)	84
21	2,4,6-Trimethylphenyl	$C_6H_5CH_2$	50:50 1-chloronaphthalene–benzotrichloride	E	22.4, 23.0 (*44*)	85
22	2,4,6-Tri-*t*-butylphenyl	$C_6H_5CH_2$	50:50 1-chloronaphthalene–benzotrichloride	E	30.3, 32.0 (*120*)	86
23	2,4,6-Trimethylphenyl	C_6H_{11}	0.8 *M* in CCl_4	E	23.0, 23.2 (*39*)	84
24	2,4,6-Trimethylphenyl	$(CH_3)_2CH$	0.8 *M* in quinoline	E	23.3, 23.9 (*39*)	84
25	CH_3, CD_3	2,4,6-Trinitrophenyl	Dioxane-d_8	s.s	18.2, 18.7 (*65*)	89
26	α-Naphthyl	2-Methyl-4,6-dibromophenyl	$CDCl_3$	E	22.5, 22.6 (*25*)	90
27	$ClCH_2$–	2-Methyl-6-*t*-butylphenyl	CCl_4	E	23.5, 25.0 (*25*)	91
28	$ClCH_2$–	2-Methyl-6-*t*-butylphenyl	$CDCl_3$	E	24.1, 25.9 (*25*)	91
28	$ClCH_2$–	2-Ethyl-6-*t*-butylphenyl	CCl_4	E	23.5, 25.0 (*25*)	91
28	$ClCH_2$–	2-Ethyl-6-*t*-butylphenyl	$CDCl_3$	E	24.2, 26.0 (*25*)	91
28	$ClCH_2$–	2-Ethyl-6-*t*-butylphenyl	85% $CD_3C(O)CD_3$–15% D_2O	E	24.6, 25.8 (*25*)	91
29	$BrCH_2$–	2-Ethyl-6-*t*-butylphenyl	CCl_4	E	24.0, 25.6 (*25*)	91
29	$BrCH_2$–	2-Ethyl-6-*t*-butylphenyl	$CDCl_3$	E	25.0, 26.3 (*25*)	91
29	$BrCH_2$–	2-Ethyl-6-*t*-butylphenyl	85% $CD_3C(O)CD_3$–15% D_2O	E	25.1, 26.2 (*25*)	91
30	ICH_2–	2-Ethyl-6-*t*-butylphenyl	CCl_4	E	24.6, 26.0 (*25*)	91
30	ICH_2–	2-Ethyl-6-*t*-butylphenyl	$CDCl_3$	E	25.6, 26.9 (*25*)	91
30	ICH_2–	2-Ethyl-6-*t*-butylphenyl	85% $CD_3C(O)CD_3$–15% D_2O	E	25.7, 26.7 (*25*)	91
31	$BrCH_2$–	2,6-Di-*t*-butylphenyl	CCl_4	E	28.8, 30.2 (*101*)	91
32	ICH_2–	2,6-Di-*t*-butylphenyl	CCl_4	E	28.8, 30.2 (111)	91
33	Lauryl lactam		CCl_4	a.s.s. (?)	19 (*70*)	105
34	H	$ClCH_2CH_2$	Neat	a.s.s.	21.7 (132)	200
35	H	CH_2=CH	Neat	a.s.s.	18.3 (99)	200
36	Me	$ClCH_2CH_2$	Neat	a.s.s.	17.5 (73)	200
37	Me	CH_2=CH	Neat	a.s.s.	13.4 (36)	200

[a] See footnote *b*, Table III.

This mutual locking of groups into position is very important in amides; it occurs frequently. For example, from qualitative observations in this laboratory, the barriers in oxalamides are higher than in acetamides or malonamides. Each half of the oxalamide has the same effect on the other half that the *ortho*-substituted ring has in benzamides.[203] To a certain extent these comparatively simple systems are models for the steric interdependence that must exist in biological molecules.

Compound **13** (R = aziridine ring) is an interesting case. The rotational barrier in tetrasubstituted ureas is too low to be observed by nmr. Each nitrogen tends to electronically stabilize the excited state of the other and to destabilize the ground state of the other sterically. However, the aziridine ring can be made coplanar with the –CO group only at the expense of considerable strain. As a consequence it is ineffective in stabilizing the activated state for the $-NMe_2$ grouping, leading to observable slow rotation around the amide bond in $-C(=O)N(Me)_2$.

When R = CCl_3 or CF_3, it appears that two or more effects are present. The electron-withdrawing power of both groups tends to stabilize the activated state relative to acetamides, and steric effects should destabilize the ground state. Yet the barrier for R = F_3C (**16**) is close to the value for the acetamide **1**. Possibly there are some weak intramolecular attractive interactions between the groups.

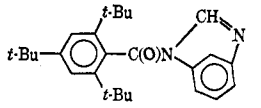
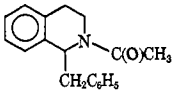
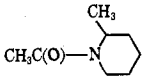
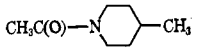
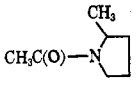
c. N-Methylamides

N,N-Disubstituted amides, where one group on nitrogen is a methyl group, have been especially useful in the study of slow rotation around the amide bond. Data are given in Table V.[82–86,89–91,105,200] Many of these compounds can be obtained, without any special effort, as one isomer in crystal form. Others can be separated into isomers by chromatography or by some other method. Often both isomers can be obtained in sufficient amounts to be studied separately. Thus the kinetics of rotation can be studied by allowing the separated isomers to equilibrate (method E in the tables). In favorable circumstances a kinetic study can be made at low temperature (typically <40°) by equilibration while making a kinetic study on the same compound by signal shape analysis at high temperature (typically >100°). Data for **18** were obtained in this way.[83] It can be seen that ΔF^* is almost independent of temperature. (The isomer ratio is near unity and is ignored.) Comparison of the data for **11** and **21** leads to the same conclusion.[85] Several interesting trends can be observed in the rotational barrier data for this group of amides.

(203) T. H. Siddall, III, and M. L. Good, *J. Inorg. Nucl. Chem.*, 29, 149 (1967).

Table VI

Barrier Heights for Various Amides

No.	*Compound*	*Solvent*	*Method*	ΔF^* (T_c)[a]	*Ref*
38	$HC(O)N(Et)_2$	Neat	v.a.s.s.	20.4 (*100*)	204
39	$CH_3C(O)N(Et)_2$	Neat	v.a.s.s.	16.9 (*25*)	204
40	$CH_3C(O)CH_2C(O)N(Et)$	Neat	v.a.s.s.	16.8 (*25*)	204
41	$CH_3C(O)N(n\text{-}Pr)_2$	Neat	v.a.s.s.	17.0 (*25*)	204
42	$CH_3C(O)N(2\text{-}Pr)_2$	Neat	v.a.s.s.	15.7 (*25*)	204
43		$CCl_2{=}CCl{-}CCl{=}CCl_2$	E	27.6, 28.7 (*80*)	94
44	$HC(O)N(CH_2C_6H_5)(2,6\text{-}(CH_3)_2C_6H_3$	$CDCl_3$	E	22.6, 23.7 (*35*)	205
45	$HC(O)N(CH_2C_6H_4\text{-}2\text{-}N(CH_3)_2\text{-}2,4,6\text{-}(CH_3)_3C_6H_2$	$CDCl_3$	E	23.1, 23.5 (*35*)	205
46	$HC(O)N(CH_2CH_3)(2,6\text{-}(CH_3)_2C_6H)$	100 mg in 0.75 ml of $CDCl_3$	E	22.1, 23.0 (*17*)	192
47	$(\alpha\text{-Naphthyl})C(O)N(CH_2CH_3)\text{-}(2,4,6\text{-}(Br)_3C_6H_2)$	$CDCl_3$	E	21.8, 22.0 (*25*)	90
48	$HC(O)N(CH{=}CH_2)(CH_2CH_2Cl)$	Neat	a.s.s.	18.3 (99)	200
49	$CH_3C(O)N(-CH_2C_6H_5)_2$	0.38*X* in CH_2Br_2	a.s.s.	18.0 (71)	162
	$CH_3C(O)N(-CH_2C_6H_5)_2$	0.38*X* in CCl_4	a.s.s.	17.6 (62)	162
50		$CDCl_3$	a.s.s.	19 (*70*) (Ring inversion ?)	25
51		Neat	a.s.s.	15.3 (15)	14
52		$CDCl_3$	a.s.s.	16.4 (~60)	27
53		Neat	a.s.s.	18.1 (55)	14
54	N-Acetyl-α-D-xylopiperidinose	D_2O	a.s.s.	17.2 (~70)	14
55	Methyl 2,3,4-tri-O-methyl-N-acetyl-α-D-xylopiperidinoside	$CCl_2{=}CCl_2$	a.s.s.	17.4 (~90)	14
56	N-Acetyl-1,6-anhydro-L-idopiperidinose	D_2O	v.a.s.s. v.a.s.s.	H(1) 16.1 (30) $CH_3C(O)$ 15.7 (5)	14
57	1,6-Acetimino-N-acetyl-1,6-didesoxy-L-idopiperidinose	D_2O	v.a.s.s.	16.4 (40)	14
58	1,6-Acetimino-1,6-didesoxy-L-idopyranose	D_2O	v.a.s.s. v.a.s.s.	H(1) 18.4 (75) $CH_3C(O)$ 18.3 (60)	14
59	1,6-Acetimino-N-acetyl-1,6-didesoxy-L-idopiperidinose	D_2O	v.a.s.s. v.a.s.s.	H(1) 19.2 (90) $CH_3(O)$ 19.0 (55)	14
59A	N-Ethoxycarbonylazepiniron tricarbonyl	$CDCl_3$	v.a.s.s.	13.1 (−28)	206

[a] See footnote *b*, Table III.

The effect of mutual locking in the ground state that was noted for N,N-dimethyl *ortho*-substituted benzamides is also observed in this group of amides (**21**–**24**). With **22** an extreme effect is obtained. The additional rotational barrier from this locking is at least 10 kcal/mol, or is 50% of the barrier due to electronic effects (if the barrier in DMF and in **18** can be taken as due solely to electronic effects). Comparison of **21**, **23**, and **24** shows that there may be other, though much smaller, locking effects. With R_1 = cyclohexyl or 2-Pr the barrier is larger than with R_1 = benzyl. The cyclohexyl and 2-Pr groups should crowd the amide plane and *reduce* the barrier. The barrier is certainly decreased in N,N-di-2-propylamides such as the acetamide. Qualitative observations in this laboratory show that tetra-2-propyloxalamide has a high barrier. Perhaps a similar locking occurs in this oxalamide.

This locking effect also extends to *ortho*-substituted anilides (**26**–**32**). The effect is substantially as large in anilides. However, the data for **26** (also **47**; see Table VI) suggest that *ortho* substitution in both rings does not produce an additive effect. Further experiments would be interesting.

An additional effect with anilides (**27**–**32**) is to make the *endo* isomer (benzene ring *cis* to the carbonyl group) occur in observable amounts. In most anilides, even with 2,6-dimethyl substitution, the *exo* isomer dominates to the exclusion of the *endo* isomer. However, with large *ortho*

substituents the *endo* isomer is present in observable amounts. It may be that the α-halogen atom in compounds **27–32** contributes to the increased thermodynamic stability of the *endo* form.[33]

The excellent study of the α-haloacetanilides[91] is the best evidence currently available for the occurrence of the expected solvent effect on barriers in amides (or at least these amides). Compounds **27–30**, consistently show an increase of about 1 kcal/mol in barrier height in the polar solvents. Rotational barriers were also measured for **29** and **32** at a second temperature. For **29** E_a = 26.3 kcal/mol and $\Delta S^* < \pm 1$ eu; for **32** E_a = 27.8 kcal/mol and $\Delta S^* < \pm 1$ eu.

The data for **25** result from an impressively thorough signal shape study. All of the reasonable variations in signal shape input parameters for the AB uncoupled case have been taken into account. This study is the most sophisticated model available for the AB uncoupled case. The kinetic quantities are E_a = 21.0, 19.2 kcal/mol; log A_0 = 14.3, 13.5; ΔH^* = 20.3, 18.5 kcal/mol; and ΔS^* = 4.7, 1.0; ΔF^* (65°) = 18.7, 18.2 kcal/mol. The ΔF^* values are very low compared to those for other disubstituted anilides, probably because of the stabilization of the activated state due to extensive conjugation with the nitro groups.

Compounds **34** and **35**, **36** and **37** in pairs show the expected effect of the vinyl group in diminishing the barrier through competitive delocalization. The lauryl lactam **33** has about the same barrier as a straight-chain compound.

d. Other Amides

Data for amides not listed in other sections are collected in Table VI.[14,25,27,90,94,162,192,200,204–206] One important question that could be answered from such data concerns the quantitative effect of large N-alkyl groups on the barrier. The data for **38–42** do suggest the expected trend—smaller barriers as the size of the alkyl group is increased. While this trend must be correct we are not certain that the data are derived from valid signal shape analysis. The authors used a peak separation and a ratio method of analysis but give no details.[204] These methods, as originally proposed, are approximations of the AB uncoupled case. Comparison of **47** with **26** does show that when an ethyl radical replaces a methyl radical the barrier is decreased. However, the results for **46** and **44** reflect very little difference between an ethyl radical and a benzyl radical. At the same time the data for **49** compared to data for **1** suggest little difference between methyl and benzyl radicals. These data show again that the effect of "size" of various N-alkyl groups on the rotation rate is not clearly understood.

The data for the monosaccharides and the simple piperidine and pyrrolidine compounds show that the five-membered ring systems consistently have barriers 2–3 kcal/mol larger than those of six-membered rings. The reasons for this relatively large effect are not obvious to the reviewers and are not discussed by the authors.[14]

e. Thionamides and Related Compounds

When the amide oxygen is replaced by sulfur or selenium, the amide rotational barriers increase.[207,208] For analogous amides and thionamides the increase may be as much as 5 kcal/mol, although a 2–3-kcal/mol increase is more typical. The increase is probably due to increased electron delocalization and increased size. The barriers in thionamides appear to show no solvent effect.[209]

A summary of thionamide barriers is given in Table VII,[62,80,92,166,193,207,209–212] and data comparing the barriers in amides and their thionamide analogs are collected in Table VIII. The typical increase (Δ) for the larger compounds is 2–3 kcal/mol; however, larger increases are observed for the N,N-dimethylthionformamide and N-methyl-N-benzylthionmesitamide. The 4-kcal/mol value for the mesitamide can be rationalized by assuming that the larger sulfur atom more firmly locks the mesityl ring out-of-plane, giving extra stability to the ground state of the thionamide. However, no ready rationale is available for $HC(X)NMe_2$.

An unexpected effect is observed in the comparison of $HC(S)NMe_2$ (**60**) with $HC(S)N2Pr_2$ (**61**); the reported barrier is *higher* for the N,N-di-2-propyl compound. This may indicate that some mutual locking occurs. However, qualitative observations in this laboratory indicate that the barrier in $HC(O)N2Pr_2$ is about the same as that in $HC(O)NMe_2$. Also the method of signal shape analysis for **61** is not clear. A further investigation of barriers in **60** and **61** may be in order.

The cyclopropylcarboxthionamide (**64**) shows a decreased barrier relative to the open-chain compound **63**. This is interpreted as evidence for competitive delocalization into the cyclopropyl ring.[193] It is interesting to note, however, that no difference exists for the oxygen analogs (**3** and **5**, Table IV).

A rather intricate interplay of competitive delocalization effects is to be noted for thioncarbamate (**71**, **76**) and dithioncarbamate derivatives (**72–75**). The thiol sulfur competes more effectively than the ester oxygen for electrons and the barrier is drastically reduced.

The data for **78** show that the barrier (around $-C(S)-NMe_2$) can be observed in a thiourea even though none has been reported for a urea. The data for **77** show that an acetylthiourea has a higher barrier than a thiourea. This inerease is probably due to electron delocalization (or competitive conjugation with C(O)), leading to more double-bond character for the $-C(S)-NMe_2$ bond.

The high barrier in $EtOC(O)C(S)NMe_2$ may be due in part to the same effect noted in this laboratory, qualitatively, for oxalamides. The ester plane is probably inclined to the amide plane; mutual locking may increase the amide barrier.

f. Monosubstituted Amides

Very few studies of the rates of rotation around the amide bond in monosubstituted amides have been reported. In part this has been due to the predominance of the *trans* form over the *cis* form (see ref 30, 41, and the references

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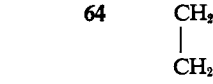
(206) H. Guenther and R. Wenzl, *Tetrahedron Lett.*, 4155 (1967).
(207) G. Schwenker and H. Rossway, *ibid.*, 4237 (1967).
(208) J. Sandström, personal communication.
(209) J. Sandström, *J. Phys. Chem.*, 71, 2318 (1967).
(210) W. Walter, G. Maerten, and H. Rose, *Justus Liebigs Ann. Chem.*, (1966).
(211) C. E. Holloway and M. H. Gitlitz, *Can. J. Chem.*, 45, 2659 (1967).
(212) T. H. Siddall, III, and W. E. Stewart, *J. Org. Chem.*, **32**, 3261 (1967).

Table VII

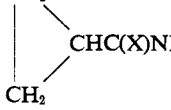
Barrier Heights for Thionamides and Related Compounds

No.	*Compound*	*Solvent*	*Method*	ΔF^* (T_c)[a]	*Ref*
60	$HC(S)N(CH_3)_2$	Neat	a.s.s.	26.5 (*185*)	80
	$HC(S)N(CH_3)_2$	40% in *o*-$C_6H_4Cl_2$	a.s.s.	24.1 (*160*)	80
61	$HC(S)N(CH(CH_3)_2)_2$	Neat	v.a.s.s.	27.7 (*174*)	80
		40% in *o*-$C_6H_4Cl_2$	v.a.s.s.	24.6 (*161*)	80
62	$CH_3C(S)N(CH_3)_2$	0.09*X* in $HC(O)NH_2$	a.s.s.	24.1 (151)	166
	$CH_3C(S)N(CH_3)_2$	0.33*X* in *o*-$C_6H_4Cl_2$	a.s.s.	21.6 (141)	209
63	$[(CH_3)_2CH]C(S)N(CH_3)_2$	0.33*X* in *o*-$C_6H_4Cl_2$	a.s.s.	19.3 (97)	193
64		0.33*X* in *o*-$C_6H_4Cl_2$	a.s.s.	18.4 (84)	193
65	$C_6H_5C(S)N(CH_3)_2$	0.33*X* in *o*-$C_6H_4Cl_2$	a.s.s.	18.4 (*92*)	209
	$C_6H_5C(S)N(CH_3)_2$	C_6H_5Cl	a.s.s.	17.5 (83)	207
66	$C_6H_5C(Se)N(CH_3)_2$	C_6H_5Cl	a.s.s.	18.9 (*107*)	207
67	$HC(S)N(CH_3)(CH_2C_6H_5)$	Neat	E	22.9, 23.3 (*55*)	210
68	$2,4,6\text{-}(Me)_3C_6H_2S)N(CH_3)(CH_2C_6H_5)$	$CDCl_3$	E	26.8, 27.3	92
69	$ClC(S)N(CH_3)_2$	CCl_4	a.s.s.	19 (*30*)	62
	$ClC(S)N(CH_3)_2$	0.33*X* in *o*-$C_6H_4Cl_2$	a.s.s.	19.1 (77)	209
70	$N{\equiv}C{-}C(S)N(CH_3)_2$	0.33*X* in *o*-$C_6H_4Cl_2$	a.s.s.	23.4 (171)	209
71	$CH_3OC(S)N(CH_3)_2$	Neat, also five measurements in *o*-$C_6H_4Cl_2$, *X* = 0.20, 0.33, 0.50, 0.64, 0.82	a.s.s.	17.8 ± 0.1 (68–70)	209
72	$CH_3SC(S)N(CH_3)_2$	0.33*X* in $C_6H_4Cl_2$ 0.33*X* in $CDCl_3$ 0.33*X* in CCl_4 0.20*X* in 2-PrOH	a.s.s.	15.7 ± 0.2 (21–30)	209
	$CH_3C(S)N(CH_3)_2$	Hexane	a.s.s.	14.7 (*25*)	211
73	$CH_3SC(S)N(-CH_2CH_2)_2$	Hexane	v.a.s.s.	15.0 (*25*)	211
74	$CH_3CH_2SC(S)NC{-}CH_2CH_3)_2$	Hexane	v.a.s.s.	15.2 (*25*)	211
75	$CH_3CH_2SC(S)N(CH_3)_2$	Hexane	a.s.s.	14.6 (*25*)	211
76	$CH_3CH_2OC(O)C(S)N(CH_3)_2$	0.33*X* in *o*-$C_6H_4Cl_2$	a.s.s.	23.4 (159)	209
77	$CH_2C(O)N(H)C(S)N(CH_3)_2$	0.33*X* in *o*-$C_6H_4Cl_2$	a.s.s.	16.1 (37)	209
78	$(C_6H_5)(H)NC(S)N(CH_3)_2$	160 mg/ml in $CDCl_3$	s.s.	10.7 (−40)	212
	$(C_6H_5)(H)NC(S)N(CH_3)_2$	$CDCl_3$	a.s.s.	11.5 (−43)	209

[a] See footnote *b*, Table III.

Table VIII

Comparison of Barriers in Amides and Thionamides

Compound type	ΔF^*, *kcal/mol* X = O	X = S	Δ
$HC(X)NMe_2$	21	26.5	5.5
$MeC(X)NMe_2$	19	21.6	2.6
$2\text{-}PrC(X)NMe_2$	16.2	19.3	3.1
$C_6H_5C(X)NMe_2$	16	18.4	2.4
$HC(X)N(Me)(CH_2C_6H_5)$	21	23	2
$2,4,6\text{-}(Me)_3C_6H_2C(X)N(Me)(CH_2C_6H_5)$	23	27	4
$ClC(X)NMe_2$	16.7	19	2.3
$MeOC(X)NMe_2$		17.8	1.9
$C_6H_5CH_2OC(X)NMe_2$	15.9		
	16.4	18.4	2

quoted therein). The signals from the *cis* form may either be absent entirely or be too weak to be very useful. However, with formamides, and most especially formanilides, the *cis* form is usually present in useful abundance.[19,21,41,59,73]

Isolation, by crystallization, of the pure isomers of *o*-methylformanilide (**79**) allowed study of the rotation rate by equilibration.[73] However, owing to the strong intermolecular association of monosubstituted amides, the overall process may involve making and breaking of hydrogen bonds as well as rotation. The data for individual equilibration experiments fit well to first-order kinetics and the dependence of rate on amide concentration is small. However, it is difficult to see how this apparent first-order behavior can extend over wide ranges of composition and temperature. For 70 mg of **79** in 1 ml of $CDCl_3$ "E_a" = 15.7 kcal/mol, "log A_0" = 11.0, and ΔF^* = 17.5 kcal/mol (at −30°) (the symbols are deliberately put in quotes since the meaning of the numbers is not clear). (Note the correction of a numerical error in calculating E_a and A_0 in the original article.)

The amount of the *cis* isomer increases for acetanilides as the bulk of *ortho* substitution increases. This increase is paralleled by an increase in the barrier to rotation.[75,76] Finally with 2,4,6-tri-*t*-butylacetanilide a 45:55 mixture of isomers is obtained; and isomer lifetimes are sufficiently long that pure *trans* isomer can be crystallized from ethanol and the isomers can be separated at +5° by thin layer chromatography.[75] Equilibrium isomer populations are repeated

in Table IX,[75,76] and kinetic data for 2,4,6-substituted anilides are given in Table X.[75] The authors recognized that they were dealing with a complex process that could, for example, be concentration dependent. By obtaining kinetic and equilibrium data at constant concentration of anilide (0.3 *M*) they hoped to be able to make significant comparisons between anilides.

Table IX

Isomer Population in Acetanilides[75,76]

Benzene ring substitution	*Temp, °C*	*cis/trans*[a]
Unsubstituted	−20	<1/>99
2-Me	−30	6/94
2-Et	−20	15/85
2-(2-Pr)	−20	25/75
2,6-$(Me)_2$	37	26/74
2,6-$(Et)_2$	37	31/69
2,6-$(2\text{-Pr})_2$	37	36/64
2,4,6-$(Et)_3$	37	31/69
2,4,6-$(2\text{-Pr})_3$	37	37/63
2,4,6-$(t\text{-Bu})_3$	37	45/55

[a] 0.3 *M* anilide in $CDCl_3$.

Table X

Kinetic Data for 2,4,6-Trialkylacetanilides[75]

Alkyl group	*Solution*	ΔF^* (T_c),[a] *kcal/mol*
Me	0.3 *M* in $CHBr_3$	18.3 (85)
Et	0.3 *M* in $CHBr_3$	18.8 (95)
2-Pr	0.3 *M* in $CHBr_3$	19.6 (15)
t-Bu	0.3 *M* in CHBr	24.2 (>150)
t-Bu	Saturated 1,2,4-trichlorobenzene	23.9 (~185)

[a] ΔF^* from very approximate signal shape analysis. The author's method of analysis is not clear to the reviewers. Presumably these are mean (for the two isomers) values.

The detailed explanation for the effects of varying the *ortho* substituents may be quite complicated; the rationale given below is, at best, incomplete. The basic factor determining both equilibrium and kinetic effects may be that the acetyl methyl group fits into a potential well provided by the benzene ring and its substituents. The *ortho*-substituted ring is out of the amide plane in its ground state. The out-of-plane ground state becomes more firmly locked as the bulk of the *ortho* substituent increases. Of course, to some extent the carbonyl oxygen is fitted into a deeper potential well in the *trans* isomers. There are electronic effects, as well; competitive electron delocalization into the benzene ring is decreased as the ring is held more out-of-plane. Similar explanations apply to the effects observed in N,N-disubstituted anilides and benzamides. A number of authors including these have expounded on this rationale.[76]

To date much more attention has been devoted to the nmr spectroscopy of N,N-disubstituted amides than to the nmr spectroscopy of monosubstituted amides. Because of biological significance the monosubstituted amides deserve more attention. Quantitative spectroscopy aimed at physicochemical measurements must be complicated by strong intermolecular effects. However, in a way this is itself an opportunity, since it should lead to increased knowledge of the structure of solutions of these compounds.

3. *Slow Rotation around Bonds Other Than the Amide Bond*

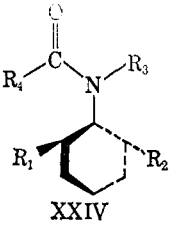
The rigidity of the planar (or near planar) amide framework leads to the possibility of other slow rotations in amides. A trigonal atom attached to any of the bonds projecting from the framework may lead to a biphenyl-like situation. The observations of slow rotation around these bonds are described in the following sections. In addition N,N-di-*sec*-alkylamides may exhibit slow rotation of tetrahedral groups against the trigonal nitrogen atom. It cannot be emphasized too strongly that the double-bond character of the amide bond plays a vital role in all these cases. If the amide bond lacked double-bond character and were easily deformed, cooperative rotation around the amide, or bond deformation, would greatly reduce the barrier to these other, biphenyl-like, rotations.

The isomers that may be produced by slow rotation around these other bonds are optical isomers. The ground state sets the trigonal rotor out-of-plane with respect to the amide framework. On the other hand, slow rotation around the amide bond may produce *cis–trans* isomers as in ethylenes; the ground state within the amide framework is planar.

a. Aryl–Nitrogen Bond in N-Substituted Anilides

It was early recognized by analogy with biphenyls that slow rotation around the aryl-to-nitrogen bond should be observable in *ortho*-substituted anilides. The earlier work in this area was reviewed by Adams.[213] Application of nmr spectroscopy has greatly facilitated these studies.[33,90,98,198,203,214–218] In general, whenever an anilide is *ortho* substituted in an unsymmetrical manner, slow rotation is detectable by nmr. Further, even with symmetrical substitution slow rotation may be detectable if an asymmetry center is included in the molecule.[218] Even without an asymmetry center the geminal species within the $R_1 = R_2$ groups in anilides are nonequivalent. The molecule as a whole has a symmetry plane but the slow rotation locks the geminal protons out of this plane.

The analogy with biphenyls is easily seen when the anilide is represented as XXIV. The nitrogen atom and its substituents



XXIV

(213) R. Adams, *Rec. Chem. Progr.*, 10, 91 (1949).
(214) T. H. Siddall, III, *Tetrahedron Lett.*, 4515 (1965).
(215) Y. Shvo, E. C. Taylor, K. Mislow, and M. Raban, *J. Amer. Chem. Soc.*, 89, 4910 (1967).
(216) T. H. Siddall, III, and W. E. Stewart, *J. Phys. Chem.*, 73, 40 (1969).
(217) T. H. Siddall, III, and W. E. Stewart, *Chem. Commun.*, 617 (1968).
(218) T. H. Siddall, III, *J. Phys. Chem.*, 70, 2249 (1966).

(R_3 and $R_4C(O)$) serve as the second benzene ring. When $R_1 \neq R_2$ the molecule has no symmetry plane. If the various R groups are sufficiently large there is a sufficiently high barrier to make rotation slow on the nmr time scale. Almost always the only amide isomer observable for the simple anilides (other than formanilides) is as drawn above with the benzene ring *trans* to oxygen, and the proposed ground state puts the benzene ring out of the approximate amide plane. The isomerism that may result produces enantiomers rather than *cis–trans* isomers.

It should be possible in principle to develop a general empiricism, as was done for biphenyls,[219] concerning the steric requirements of the R groups required to produce a given barrier to rotation. However, the necessary quantitative data are just beginning to accumulate. For that reason the discussion must be qualitative, even somewhat speculative in some respects at the present time.

Comparisons using the data now available are facilitated by the direct experimental observation that the temperature coefficient of ΔF^* is small for several anilides of α-chloro-α-phenylacetic acid.[216] Since the α carbon atom is asymmetric these anilides exist as diastereoisomers. Preferential crystallization of a diastereoisomer permitted the rotational barrier to be determined by equilibration at low temperature. In six cases (including one with $PhCH[OC(O)CH_3]C(O)$ as the acid moiety) the rotational barriers were obtained above 100° by signal shape analysis. The temperature coefficient of ΔF^* is small, almost insignificant (averaged over the six, $\Delta S^* = -3$ eu). Signal shape analysis showed also that ΔS^* is probably small for compounds **80**, **81**, **83**, and **84** (Table XI).[198] The average is $\Delta S^* = -6$ eu. Only compound **82** is assigned a relatively large value, $\Delta S^* = 15$ eu.

A small, negative entropy of activation may be the rule for this rotation. There is no obvious physical reason to expect a large ΔS^*. In the activated state the benzene ring is presumably approximately coplanar with the amide group. This arrangement could very well result in a small restraint of some internal motions but must leave many unaffected.

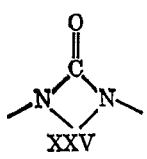
The data in Table XI[33,98,198,215,216,220] show that the rotation rate is insensitive (only about 1 kcal/mol variation) to the size of the R_3 group in the series R_3 = Me, $PhCH_2$–, Et, but that with R_3 = 2-Pr there is a large increase in the barrier. When R_3 = H or D no slow rotation is observed. Most of the data suggest that the rate is insensitive to the size of the R_4 group; however, experiments with R_4 = *t*-butyl would be most interesting in this connection. Also, the absence of slow rotation in most formanilides shows that rotation does respond to large changes in the size of R_4. When R_2 = H, there is a small effect for the series R_1 = Me, α-naphthyl, 2-Pr. The "size" of the naphthyl group may in part be due to its rigidity. Substitution in the 5 position has no effect when R_2 = H (**91** *vs.* **92**). Substitution in both the 2 and 6 positions causes a large increase (>9 kcal/mol) in the barrier. Comparison of **93** and **94** suggests that *meta* substitution may exert the same sort of buttressing effect as that observed in biphenyls.[219]

The small increase in barrier in passing from N-methyl to benzyl or ethyl as compared to the larger increase with 2-propyl may reflect the ability of benzyl or ethyl groups to rotate cooperatively. In the activated state the R group of R–CH_2– can be rotated completely out of the amide plane. It is not possible to rotate both β-methyl groups of the 2-propyl group out of the plane at the same time. However, such a simple explanation is certainly incomplete, as may be seen by comparing **91** with **88**. The interchange from R_1 = Me, R_3 = 2-Pr to R_1 = 2-Pr, R_3 = Mr decreases the barrier by about 4 kcal/mol. Evidently, and reasonably, cooperative rotation of the 2-propyl group can provide more steric relief to the activated state when 2-propyl = R_1 than when 2-propyl = R_3. The carbonyl oxygen atom produces a buttressing effect. It would be interesting to study a molecule with buttressing in the 3 position of the benzene ring. Compound **96** is of especial interest since the benzene ring is *cis* to the carbonyl oxygen. The smaller size of the oxygen atom as compared to R_4 = alkyl lowers the barrier.

Electronic effects must be important in biphenyl-like rotation in these anilides. It has been known for some time that the stiffness and resistance to distortion of other bonds nearby plays an important role in the rate of rotation around the pivot (or interannular) bond in biphenyls.[221] The double-bond character and, hence, stiffness of the amide bond, plays a key role in the biphenyl-like rotation of amides. Generally speaking, amines with their absence of double bond-to-nitrogen character do not show slow rotation. Compounds **84**, **97**, **98**, and **99** do show slow rotation, but presumably only because the very bulky groups provide enough steric hindrance to offset the loss of stiffness. In a similar way the barrier is less in sulfonamides (see compounds **82** and **83** and ref 33) and also less in ureas.[33] The smaller barrier in **81** as compared to **80** is probably due to this effect. There is competitive delocalization (or across conjugation) with the benzene ring that is attached directly to the carbonyl group in benzamides.[48] The loss of stiffness in the amide bond is reflected (according to the explanation) in the lower barrier in **81**. This particular effect must be unique to amides as compared to biphenyls. However, polarimetry studies have already shown the importance of other, more general electronic effects in amides.[213]

The electronic effects that lead to stiffness in the amide bond interact with and confuse any simple steric effect. An increase in size of R_3 and R_4 tends to increase the barrier to biphenyl-like rotation on a direct, simple steric basis. At the same time it tends to force the amide molecule more away from a planar structure. The double-bond character of the amide bond is diminished because of the decreased delocalization of electrons over this more nonplanar structure. In this way larger R_3 and R_4 groups *indirectly* tend to *reduce* the barrier to biphenyl-like rotation.

The importance of this steric-electronic interaction is even more apparent in ureas. Simultaneous maximum electron delocalization into both amide bonds of a urea is sterically impossible. This would require complete coplanarity of the urea framework, XXV, with impossible crowding in the



XXV

plane. Larger groups should force greater loss in stiffness. However, as in amides, larger groups should act directly

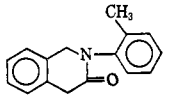
(219) R. Adams and H. C. Yuan, *Chem. Rev.*, 12, 261 (1933).

(220) A. Mannschreck and H. Muensch, *Tetrahedron Lett.*, 3227 (1968).

(221) F. H. Westheimer in "Steric Effects In Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter XII.

Table XI

Barriers to Rotation around the N–Aryl Bond in Anilides and Related Compounds

No.	*Compound*	*Solvent*	*Method*	ΔF^* (T_c)[a]	*Ref*
80	$CH_3C(O)N(CH_2C_6H_5)(2\text{-}CH_3C_6H_4)$	$C_6H_5NO_2$	s.s.	20.1 (142)	198
			a.s.s.	20 (135)	215
81	$C_6H_5C(O)N(CH_2C_6H_5)(2\text{-}CH_3C_6H_4)$	$C_6H_5NO_2$	a.s.s.	18.5 (99)	198
82	$p\text{-}CH_3C_6H_4S(O)_2N(CH_2C_6H_5)(2\text{-}CH_3C_6H_4)$	C_5H_5N	a.s.s.	16.0 (51)	198
83	$CH_3S(O)_2N(CH_2C_6H_5)(2\text{-}CH_3C_6H_4)$	C_5H_5N	a.s.s.	14.8 (21)	198
84	$[(CH_3)_3C]\text{-}N(CH_2C_6H_5)(2\text{-}CH_3C_6H_4)$	C_5H_5N	a.s.s.	16.1 (50)	198
85	$C_6H_5CH(Cl)C(O)N(CH_3)(2\text{-}CH_3C_6H_4)$	$CHCl_2\text{–}CHCl_2$	s.s.	20.3 (*25*)	216
		$CHCl_2\text{–}CHCl_2$	E	20.9 (*100*)	216
86	$C_6H_5CH[OC(O)CH_3]C(O)N(CH_3)(2\text{-}CH_3C_6H_4)$	$CHCl_2\text{–}CHCl_2$	s.s.	20.1 (*25*)	216
		$CHCl_2\text{–}CHCl_2$	E	20.5 (*100*)	216
87	$C_6H_5CH(Cl)C(O)N(CH_3)(\alpha\text{-naphthyl})$	$CHCl_2\text{–}CHCl_2$	s.s.	21.7 (*25*)	216
		$CHCl_2\text{–}CHCl_2$	E	21.6 (*100*)	216
88	$C_6H_5CH(Cl)C(O)N(CH_3)(2\text{-}PrC_6H_4)$	$CHCl_2\text{–}CHCl_2$	s.s.	22.3 (*25*)	216
		$CHCl_2\text{–}CHCl_2$	E	22.4 (*100*)	216
89	$C_6H_5CH(Cl)C(O)N(CH_2C_6H_5)(2\text{-}CH_3C_6H_4)$	$CHCl_2\text{–}CHCl_2$	s.s.	20.5 (*25*)	216
		$CHCl_2\text{–}CHCl_2$	E	21.4 (*100*)	216
90	$C_6H_5CH(Cl)C(O)N(\text{–}CH_2CH_3)(2\text{-}CH_3C_6H_4)$	$CHCl_2\text{–}CHCl_2$	s.s.	21.3 (*25*)	216
		$CHCl_2\text{–}CHCl_2$	E	21.6 (*100*)	216
91	$C_6H_5CH(Cl)C(O)N(2\text{-}Pr)(2\text{-}CH_3C_6H_4)$	$CHCl_2\text{–}CHCl_2$	E	25.4 (*25*); 26.0 (*100*)	216
92	$C_6H_5CH(Cl)C(O)N(2\text{-}Pr)(2,5\text{-}(CH_3)_2C_6H_3$	$CHCl_2\text{–}CHCl_2$	E	25.3 (*25*); 26.1 (*100*)	216
93	$C_6H_5CH(Cl)C(O)N(CH_3)(2,4\text{-}(Br)_2\text{-}6\text{-}CH_3C_6H_2)$	?	E	29.4 (*100*)	33
94	$C_6H_5OCH(CH_3)C(O)N(CH_3)(3\text{-}Br\text{-}2,4,6\text{-}(CH_3)_3C_6H)$	$CHCl_2\text{–}CHCl_2$	E	32.4 (100)	33
95	$[(CH_3)_2CH]C(O)N(CH_2C_6H_5)(\alpha\text{-naphthyl})$	Neat	v.a.s.s.	21 (140) (est)	98
96		?	a.s.s.	17.3 (73)	215
97	$(C_6H_5CH_2)(CH_3)N(2\text{-}Cl\text{-}3\text{-}CH_3C_6H_3)$	$CCl_2{=}CCl\text{–}CCl{=}CCl_2$	a.s.s.	15.1 (30)	220
98	$(C_6H_5CH_2)(CH_3)N(2\text{-}Br\text{-}3,5\text{-}(CH_3)_2C_6H_2)$	$CCl_2{=}CCl\text{–}CCl{=}CCl_2$	a.s.s.	15.8 (43)	220
99	$[(C_6H_5)(CH_3)CH](CH_3)N(2,6\text{-}(CH_3)_2C_6H_3)$	$CCl_2{=}CCl\text{–}CCl{=}CCl_2$	a.s.s.	17.6 (64)	220

[a] See footnote *b*, Table III.

to increase the barrier to biphenyl-like rotation. The data given in Table XII[217] are not absolute—the kinetic results are comparative only. They are based on the assumption that the same broadening of the methylene quartet of the ethyl group indicates the same rate in the fast exchange limit. However, it can be seen that the relative order of barriers by compound is independent of the true rotation rate.

The data in this table show that for ureas more is gained through increased stiffness in the amide bond than is lost by having smaller groups on the other nitrogen atom. The indirect effect is greater than the direct. The importance of stiffness in the amide bond is demonstrated in another way in the thiourea. Thionamides in general show greater stiffness in the amide bond than do the oxygen analogs.

Biphenyl-like rotation is also shown in other amide derivatives such as dialkyl N,N-dialkylcarbamylphosphonates $[(RO)_2P(O)C(O)N(R_1)_2]$[33] and such diamides as oxalamides and malonamides.[203] This phenomenon can lead to very complicated systems of isomers in diamides. For example, in an oxalamide such as $(Me)(OMeC_6H_4)NC(O)C(O)N(OMeC_6H_4)(Me)$ (**99A**) three isomers are possible due to slow rotation around the amide bonds (both N-methyl groups may be *cis* to oxygen, or both may be *trans*, or there may be one of each). Four sets of signals can arise—one each form the *cis–cis* and *trans–trans* isomers and two sets from the *cis–trans* isomer. Since there are two asymmetry centers each of these can in turn exist as a pair of diastereoisomers to give a total of eight signal sets. In the case of **99A** seven *o*-methyl signals are observable.[203]

b. Benzene–Nitrogen Bond in Acetanilides

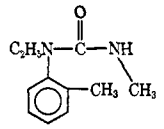
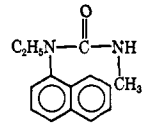
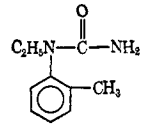
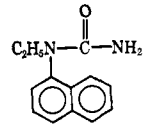
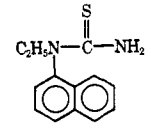
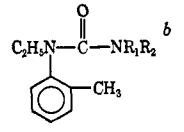
Slow rotation is observable for acetanilides when di-*o*-ethyl or 2-propyl groups are present.[222] This is true even though no evidence for such slow rotation could be obtained in this laboratory with $(Cl)(C_6H_5)CHC(O)N(H)(2,6\text{-}(CH_3)_2C_6H_3)$ or its deuterio derivative.[216] The symmetry requirements necessary to such observation are, of course, lacking in 2,6-dimethylacetanilide. However, when the *ortho* substituents are $-CHR_2$ or $-CH_2R$ and rotation is slow around the nitrogen-to-benzene bond, there is no symmetry element between the geminal species (Me or H, as the case may be) and they are nonequivalent. This is true even though the molecule itself is symmetric. As the temperature is raised the signals from nonequivalent species coalesce as a consequence of rapid rotation around this bond (since rotation around this bond amounts to a symmetry operation). These monosubstituted acetanilides have the interesting additional feature that there is an appreciable amount of both *endo* (benzene ring *cis* to carbonyl oxygen) and *exo isomers* present.

From approximate signal shape analysis the author obtained ΔF^*(rotation around the amide bond) = 19.3 kcal/mol (105°), ΔF^*(rotation around the benzene-to-nitrogen

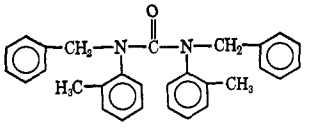
(222) H. Kessler, *Tetrahedron*, 24, 1857 (1968).

Table XII

Comparative Kinetic Data for Ureas[217]

No.	Compound	Comparison temp, °C	—ΔF*, kcal/mol[a]— k = 100 sec^{-1}	k = 1000 sec^{-1}
100		46	14.3	15.8
101		81	16.0	17.6
102		96	16.7	18.4
103		119	17.8	19.6
104		190	21.1	23.3
105	 [b]	≤ −50	<10	<10

[a] Assumes transmission coefficient of unity. 250 mg of compound diluted to 1 ml with *o*-dichlorobenzene. [b] Slow rotation is generally not observable for tetrasubstituted compounds dissolved n $CDCl_3$ above about −50°. Qualitative observation is reported for



bond in the *exo* isomer) = 18.9 kcal/mol (75°), and ΔF*(rotation around the benzene-to-nitrogen bond in the *endo* isomer) = 11.8 kcal/mol (−60°). The data are for 0.3 *M* MeC(O)-N(H)(2,6-(2-Pr)$_2$C$_6$H$_3$) in $CHBr_3$.

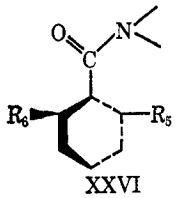
These observations are perhaps most important in that they allow a direct comparison of the barriers to rotation around the benzene-to-nitrogen bond in both *exo* and *endo* anilide isomers of the same compound. In most N-substituted anilides the *exo* isomer is the only readily observable isomer. The data of Kessler indicate, as the author suggested, that the rotation around the benzene-to-nitrogen bond in the *exo* isomer must take place *via* rotation around the amide bond.[222] This must be true whenever rotation around the amide bond and rotation around the benzene-to-nitrogen bond in the *endo* isomer are more rapid than direct rotation around the benzene-to-nitrogen bond in the *exo* isomer itself. This may be a general mechanism for the N-substituted anilides as well.

c. Nitrogen-to-Alkyl Group Bond

Slow rotation has also been observed around the bond between nitrogen and secondary alkyl groups in N,N-di-*sec*-alkylamides.[69] When both the substituents on nitrogen are *sec*-alkyl groups, the amide plane becomes so crowded that six significant potential minima develop for the *synchronous* rotation of the two alkyl groups. These minima occur as mirror pairs, the minima of a pair having the same energy. This leads to a three-site exchange situation with synchronous rotation as the exchange mechanism. The barrier to exchange is of the order of 10 kcal/mol in some cases, but no quantitative estimates are available.

d. Bond to the Carbonyl Group

Suitable trigonal arrays may rotate slowly around the bond that joins them to the carbonyl group. This behavior in *ortho*-substituted benzamides[90,223,224] is an obvious extension of the situation with *ortho*-substituted anilides as can be seen from XXVI. The chief difference is now that the carbonyl



XXVI

oxygen is much smaller than was the substituted carbonyl in the case of the anilides. As a consequence, for the same *ortho* substituents, rotation is more rapid in the case of the benzamides. No quantitative data are available, but from the data in ref 90 for singly substituted benzamides the barrier must lie in the range 8–14 kcal/mol. Very roughly the barrier is half as much as the barrier in anilides. With methoxy substitution in both *ortho* positions the barrier increases, possibly to about 20 kcal/mol.[224] Substitution in both *meta* positions by nitro groups also leads to slow rotation. However, the barrier is small, probably 10–12 kcal/mol.

Benzanilides with *ortho* substitution in both rings may produce very complex spectra. Contrary to the situation with simple anilides, both amide isomers (slow rotation around the amide bond) are usually observable. Since the bonds to the rings are both asymmetry centers there may also be diastereoisomers—or a total of four isomers for each compound, each with its own set of signals. In favorable cases it is possible to separate out rotation around the three bonds.[90] In very favorable cases separate quantitative studies may be possible.

An ethylenic group may replace the benzene ring of benzamides. Slow rotation was observed around the ethylene-to-carbonyl bond in *trans*-(C$_6$H$_5$)CH=C(C$_6$H$_5$)C(O)N-(2-Pr)$_2$.[225] However, the effect could only be observed at below −50°. The barrier is probably only about 8 kcal/mol.

The second amide group of an oxalamide may also take on the same role as the benzene ring of a benzamide on

(223) G. R. Bedford, D. Greatbanks, and D. B. Rogers, *Chem. Commun.*, 330 (1966).
(224) T. H. Siddall, III, and R. H. Garner, *Tetrahedron Lett.*, 3513 (1966).
(225) T. H. Siddall, III, and M. L. Good, *Naturwissenschaften*, 53, 502 (1966).

Table XIII

Free Energy Barriers to Rotation around the N–N Bond in Some Hydrazine Derivatives[191]

No.	*Compound*	*Solvent*	ΔF^* $(T_c)^a$
106	$(MeOC(O))(PhCH_2)N–N(CH_2Ph(O)COMe)$	Nitrobenzene	23.5 (142)
107	$(MeC(O))(PhCH_2)N–N(CH_2Ph)((O)CMe)$	Nitrobenzene	23.4 (188)
108	$(PhCH_2C(O))(PhCH_2)N–N(CH_2Ph)((O)CCH_2Ph)$	Nitrobenzene	23.3 (190)
109	$(PhCH_2C(O))(PhCH_2)N–N(H)((O)CCH_2Ph)$	$CDCl_3$	13.2 (4)

[a] See footnote *b*, Table III.

Table XIV

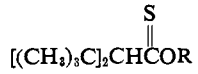
Barriers to Rotation in Diacylhydroxylamines[233]

No.	*Compound*	*Solvent*	ΔF^* (T_c),[a] *kcal/mole*
110	$(PhC(O))(PhCH_2)N–O–C(O)Ph$	$CDCl_3$–CS_2, 1:1	~9.8 (~−65)
111	$(MeC(O))(PhCH_2)N–O–C(O)Me$	$CDCl_3$–CS_2, 2:1	9.6 (−71)
112	$(PhCH_2C(O))(PhCH_2)N–O–C(O)CH_2Ph$	$CDCl_3$–CS_2, 2:1	9.6 (−61)
113	$(PhC(O))(Me)N–O–C(O)Ph$	$CDCl_3$–C_5H_5N, 1:5[b]	10.5 (−75)
114	$(MeC(O))(Me)N–O–C(O)Me$	$CDCl_3$	13.3,[c] 14.2 (−16)

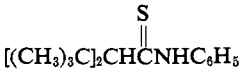
[a] From approximate signal shape analysis except **114**; see text for bonds involved. [b] Two amide isomers, 4:1 population, ΔF^* an average value. [c] Two amide isomers, 4.9:1, separate ΔF^*'s, complete signal shape analysis, E_a = 14.7, 15.1, log A_0 = 13.8, 13.4.

the ethylenic group above.[203,226] At −40° $(2\text{-Pr})_2NC(O)$–$C(O)N(2\text{-Pr})_2$ in $CD_3C(O)CD_3$ shows four sets of β-methyl signals. With one amide group the 2-propyl radicals are nonequivalent as entire radicals. Slow rotation locks the amide groups out-of-plane with respect to each other. Therefore, there is no molecular symmetry plane and the β-methyl groups are nonequivalent within the 2-propyl radical. There are then four different kinds of β-methyl groups, or four signals (the amide groups are themselves equivalent as entire amide groups). A similar effect is observed for the tetraisobutyl derivative, but not for the tetraethyl derivative.

Evidence for slow rotation around the C–C(S) bond in XXVII and XXVIII has been reported.[227]

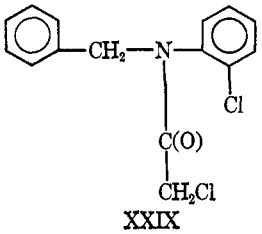


XXVII



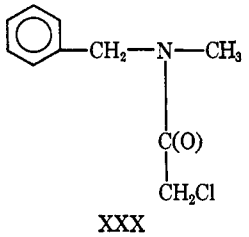
XXVIII

In benzene, toluene, or dimethyl sulfoxide solution the chloroacetyl methylene protons of XXIX are nonequivalent, but in several other solvents they are equivalent.[228] It has



XXIX

been proposed that the nonequivalence is due to slow rotation around the C(O)–CH_2Cl bond induced by complexation of XXIX with solvent molecules.[228] However an alternate and more plausible explanation is that the nonequivalence is due to slow rotation about the N-aryl bond. The benzyl methylene protons were found to be nonequivalent in *all* solvents, indicating that the N-aryl rotation was slow,[228] and thus the chloroacetyl methylene protons should be nonequivalent in *all* solvents. However, the observability of the nonequivalence depends upon the field gradients due to anisotropic groups in the molecule; in the solvents which gave no observable nonequivalence the methylene proton shifts could be accidentally degenerate. The three solvents in which nonequivalence was observed may, by their weak complexation with the amide group, destroy the degeneracy and lead to the expected AB pattern. In this case, an AB pattern would be observed for the methylene protons, even with rapid rotation around the $C(O)CH_2Cl$ bond. It was also reported that the chloroacetyl methylene protons in XXX were equivalent in benzene, toluene, and dimethyl



XXX

sulfoxide.[228] The latter explanation accounts for this observation better than the former.

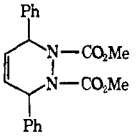
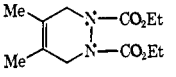
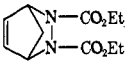
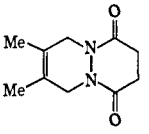
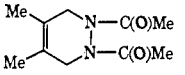
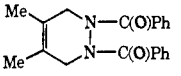
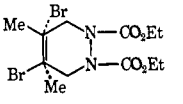
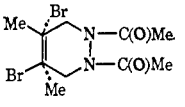
C. HINDERED ROTATIONS IN DI- AND TETRAACYLHYDRAZINES

Conti and Franconi observed and reported four sets of signals for N,N′-dimethyldiacetylhydrazide and the corresponding diformyl compound.[229] They correctly supposed that these signal sets arose from isomerism around the two

(226) T. H. Siddall, III, and M. L. Good, *Bull. Chem. Soc. Jap.*, 39, 1619 (1966).
(227) E. U. Elam, F. H. Rash, J. T. Dougherty, V. W. Goodlett, and K. C. Brannock, *J. Org. Chem.*, 33, 2738 (1968).
(228) R. J. Seymour and R. C. Jones, *Tetrahedron Lett.*, 2021 (1967).
(229) F. Conti and C. Franconi, *Ric. Sci.*, 36, 1205 (1966).

Table XV

Rate Data for Diacyltetrahydropyridazines, Related Compounds, and Urethans[a]

No.	*Compound*	*Solvent*	ΔF^* (T_c)[b]
115		Apparently these studies were all made in $CDCl_3$ or $CHCl_2CCl_3$	18.9 (97) 14.8 (−3)
116		However, the text is not absolutely clear on this point	20.7 (138) 14.7 (−8)
117			13.9 (−2)
118			<10.4 (no slow internal motion obsd)
119			>21.4
120			14.9 (8)
121			20.1 (102.5) 19.8 (81) 19.5 (*0*)
122			21.9 (20)

[a] For compound **121** data were obtained by approximate signal shape analysis (a.s.s.) at 102.5 and 81° on signals from different groups of protons. At 0° data were obtained by equilibration. For **122** data were obtained by equilibration. The remaining data were obtained by a.s.s. at coalescence (T_c). Data for **115** and **116** are from ref 231, **117–124** from ref 235, **125** and **126** from ref 239, and **127–129** from ref 245. All

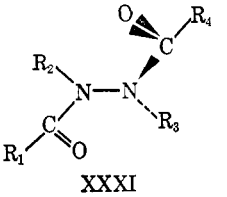
amide bonds (*cis–cis*, *cis–trans*, and *trans–trans* isomers—one set, two sets, and one set of signals). The temperature dependence of the spectrum of (MeOC)(O)($C_6H_5CH_2$)N–N(C_6H_5-CH_2)(O)(CoMe) was reported.[230]

The data in Table XIII were obtained by Bishop, Price, and Sutherland.[191] With **106** (as an example) four signal sets are obtained as were obtained by Conti and Franconi[229] for their compounds. These sets coalesce into a single set as the temperature is raised. The four sets arise from slow rotation around the amide bonds. However, the internal motion in these molecules is more complex than this. The methylene protons form four AB patterns; these coalesce into one AB pattern which then does not coalesce into a single line until 192°.

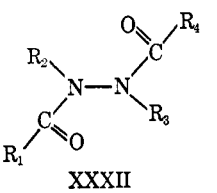
The AB behavior of the methylene protons indicates that there is no symmetry plane between the protons of a methylene pair and none for the molecule (except possibly perpendicular to and at the midpoint of the N–N bond). Either slow inversion of the nitrogen atoms or slow rotation around the N–N bond would eliminate the symmetry planes in question, on the nmr time scale. Slow inversion would produce diastereoisomers which in turn could lead to a further doubling of the number of signal sets (2 × 4 = 8). Slow rotation would allow only four sets.

The authors favor slow rotation. This appears to be the reasonable choice. However, it is possible that one diastereoisomer is so disfavored energetically that its signals are too weak to be observed.

Slow rotation around the N–N bond in tetraacylhydrazine derivatives has been reported (ΔF^*(120°) ~ 20–21 kcal/mol).[231,232] It has been proposed that the ground state of di- and tetraacylhydrazines has the twisted form XXXI and



XXXI



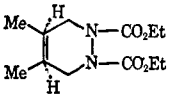
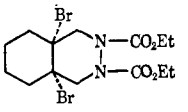
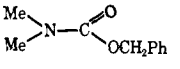
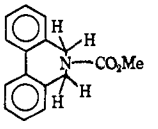
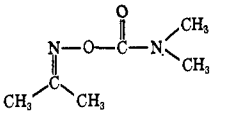
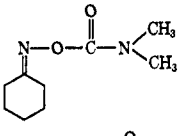
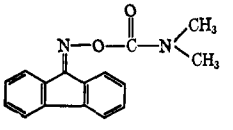
XXXII

that the high barrier to rotation around the N–N bond arises from steric and electronic repulsions in the eclipsed transition state XXXII.[191,231]

(230) R. M. Moriarty, Sr., M. R. Murphy, S. J. Druck, and L. May, *Tetrahedron Lett.*, 1603 (1967).

(231) B. M. Korsch and N. V. Riggs, *ibid.*, 5897 (1966).

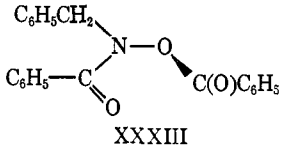
(232) A. Foucaud and R. Roudaut, *C. R. Acad. Sci., Ser. C*, 266, 726 (1968).

No.	Compound	Solvent	ΔF^* (T_c)[b]
123			~20 (*120*)
124			20.9 (116)
125		$CDCl_3$ Pyridine	15.9 (−3) 15.9 (−3)
126		$CDCl_3$	15.8 (−3)
127		CS_2	14.4 (−9)
128		CS_2	14.3 (−11)
129		CS_2	14.2 (−2)

the ΔF^* values in the range 13.9–15.9 kcal/mol are for rotation around the amide bond. The rest are for synchronous nitrogen inversion. These assignments do not necessarily agree with those of the original authors. They have been made on the basis of consistency in data not available to the authors at the time. [b] See footnote *b*, Table III.

D. HINDERED ROTATION IN DIACYLHYDROXYLAMINES

Price and Sutherland observed slow rotation around the amide bond and also the N–O bond in diacylhydroxylamines.[233] Their data are given in Table XIV. For **110**, as an example, at −80° they observed an AB quartet and a singlet (relative intensity 2.3:1). At about −65° these signals coalesced into a singlet. Slow rotation around the amide bond would produce two isomers each with its own signals (AB quartet for the one and singlet (by chance) for the other). The AB quartet requires the absence of a symmetry plane between the geminal (methylene) protons. The authors ascribed this to rotation of the C_6H_5–C(O) group out of the amide plane in the ground state (XXXIII). The two



XXXIII

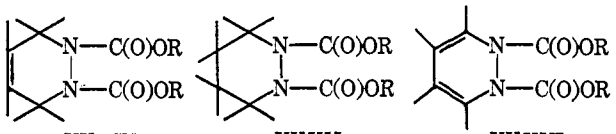
rotations were observably separated for **110**. For that reason ΔF^* is only approximate and not clearly assignable to a rotation. However, with **111** and **112** only one amide isomer was present and ΔF^* could be clearly assigned to hindered rotation around the N–O bond. On the other hand neither **113** nor **114** possesses geminal protons or groups and therefore cannot give any signal multiplicity due to rotation around the N–O bond. In these cases ΔF^* is clearly assignable to hindered rotation around the amide bond. This collection of compounds, and the discussion given by the authors, is an excellent demonstration of the use of nmr to obtain information about internal motions.

It should be noted that here and also with the diacylhydrazines there is a logical extension from the biphenyl-like rotation in amides. The rigid amide framework plays a vital role in establishing a high barrier to the internal motion that is present in addition to the barrier to rotation around the amide bond.

E. DIACYLTETRAHYDROPYRIDAZINES, RELATED COMPOUNDS, AND URETHANS

The nmr spectra of diacylated tetrahydropyridazines (XXXIV), hexahydropyridazines (XXXV), and dihydropyridazine (XXXVI) derivatives indicate that two rate processes occur in the accessible temperature range: a low-temperature process (spectral changes below 0–10°, $\Delta F^*_{270} \sim$ 14–15 kcal/mol) and a

(233) B. J. Price and I. O. Sutherland, *Chem. Commun.*, 1070 (1967).

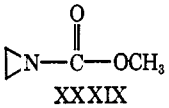


XXXIV XXXV XXXVI

high-temperature process (spectral changes above 30–50°, $\Delta F^*_{370-400} \sim$ 18–20 kcal/mol).[234–236] Contrary to earlier interpretations,[237,238] these processess appear to be due to hindered rotation about the amide C(O)–N bond (low-temperature process) and slow ring inversion (high-temperature process),[231,234–236,238,239] or slow "ring twisting" in the case of XXXVI. Bicyclo[2.2.2]octane derivatives, XXXVII, also exhibit two rate processes, but bicyclo[2.2.1]-, heptane derivatives, XXXVIII, exhibit only one process.[240]

XXXVII XXXVIII

The presence of two processes for XXXVII was attributed to slow amide rotation and a "bridge-flipping process. The absence of a second process in XXXVIII was taken as evidence that slow nitrogen inversion was not one of the two processes.[240] (Slow nitrogen inversion has been observed in N-carbomethoxyaziridine (XXXIX), but this



XXXIX

appears to be a special case arising from the unfavorable energetics involved in having an sp^2-hybridized nitrogen atom in a three-membered ring.[202]) The evidence suggests that the high barrier in the ring inversion processes arises from the necessity of rotation around the N–N bond.[231,234–236,239–241] Thus the magnitudes of the free energies of activation for the two processes are consistent with those measured for roation around the amide bond in acyclic urethans[236,239,242–244] and for rotation around the N–N bond in diacyl- and tetraacylhydrazines.[191,231,236]

Rate data are given in Table XV.[231,235,239,245] The data for **121** are of especial interest since this is the first case where rates were obtained for the same compound both by equilibration and signal shape analysis. It can be seen that the urethans have rotational barriers some 2–3 kcal/mol lower than the corresponding amides, presumably because of competitive electron delocalization in the former case.

Valega[244] presented evidence for slow rotation around the amide bond in carbamates, N–C(O)–O–R, and a further report was made by Lustig, *et al.*[243]

It can be seen that the carbamates have a barrier some 2–3 kcal/mol lower than for the corresponding amides. This is attributable to competitive electron delocalization. In the pyridazines it could be attributed in part to lost planarity in the N atoms.

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IX. Addendum

Since the completion of this manuscript, a number of important studies of amides have been reported. Of particular importance are the general exchange equations for more complex spin systems recently derived from the density matrix theory.[246–248] Also, several more studies using complete line-shape analysis have been reported. Some of the recently reported amide barriers are tabulated in Table XVI.[249–256] Other recently reported studies will be cited in the following paragraphs.

The amide rotational barriers (ΔF^*) of 18 substituted N,N-dimethylbenzamides have been determined by complete line-shape analysis.[257] Good correlations of the barriers were obtained with the substituent constants σ and σ^+. The effect of solvent upon the barriers and the mechanism of acid catalysis of rotation were also studied.[257]

Amide barrier studies of N-methylthiourea[258] and α-haloacetanilides,[259] the conformational equilibria between amide isomers of N-alkyl-N-picrylamides[260] and N-alkyl-2,4,6-trinitroacetanilides,[261] the barriers to rotation around the N–C(aromatic) bond in some substituted anilides,[262] and the $(CH_3)_2CH$–N bond in some N,N-diisopropylthionamides[263] were reported.

The effect of added phenol upon the amide rotational barriers in N-methyl-N-benzyl-*o*-chlorobenzamide and its thio analog was studied.[264]

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Table XVI

Activation Parameters for Various Amides

Amide	*Solvent*	E_a, *kcal/mol*	ΔH^*, *kcal/mol*	ΔS^*, *eu*	ΔF^* ($T°$, *C*), *kcal/mol*	*Method*[a]	*Ref*
^{15}N-Formamide	Diethylene glycol dimethyl ether	19.7 ± 0.4	19.0 ± 0.4	4.0 ± 2.0	17.8 ± 0.2 (25)	DM	248
^{15}N-Formamide	Methyl propyl ketone	19.2 ± 0.4	18.5 ± 0.4	2.7 ± 2.0	17.8 ± 0.2 (25)	DM	248
N,N-Dimethylformamide	CCl_4	20.5 ± 0.2	20.2 ± 0.2	−1.7	21.0 (128)	s.s.	249
N,N-Dimethylacetamide	Formamide (9.8 mol %)	21.3 ± 0.6			19.4 (25)	s.s.	250
N,N-Dimethylacetamide	Formamide (9.9 mol %)	20.9 ± 0.4			19.3 (25)	s.s.	250
N,N-Dimethylacetamide	Formamide (19.5 mol %)	19.6 ± 0.5			19.0 (25)	s.s.	250
N,N-Dimethylacetamide	Formamide (29.1 mol %)	19.5 ± 0.6			18.8 (25)	s.s.	250
N,N-Dimethylacetamide	Formamide (42.3 mol %)	19.5 ± 0.3			18.7 (25)	s.s.	250
N,N-Dimethylacetamide	H_2O	21.0 ± 0.9	20.3 ± 0.9	2.7	19.3 ± 0.9	s.s.	251
N,N-Dimethylacetamide·$AgNO_3$	H_2O	19.0 ± 0.7	18.4 ± 0.7	±1.4	17.9 ± 0.7	s.s.	251
N,N-Dimethyltrimethylacetamide	CH_2Cl_2	11.5 ± 0.3	10.9 ± 0.3	−4.3 ± 2	12.2 ± 0.3 (25)	s.s.	252
N,2,4,6-Tetramethyl-N-benzamide	1-Chloronaphthalene–benzotrichloride (1:1)	24.7 ± 1.6		1.7 ± 3.7	23.4 ± 0.3 (100)	s.s.	253
N,2,4,6-Tetramethyl-N-benzamide	1-Chloronaphthalene–benzotrichloride (1:1)	23.5 ± 1.1		−0.8 ± 3.6	23.1 ± 0.1 (100)	s.s.	253
N-Acetylpyrrole	CD_2Cl_2	12.55 ± 0.5	11.96 ± 0.5	−0.6 ± 2.3	12.14 ± 0.2 (25)	DM	247
N-Acetylpyrrole	$CDCl_3$				13 (−28)	a.s.s.	254
N-Formylpyrrole	$CDCl_3$				14 (5)	a.s.s.	254
N-Acetyl-3,4-dimethylpyrrole	$CDCl_3$				14 (−5)	a.s.s.	254
N-Methyl-N′,N′-dibenzylthiourea	$CDCl_3$				10.8 (−49)	a.s.s.	255
N-Phenyl-N′,N′-dibenzylthiourea	$CDCl_3$				11.3 (−42)	a.s.s.	255
$CH_3CH_2C(O)NHC(S)N(CH_2C_6H_5)_2$	$CDCl_3$				15 (27)	a.s.s.	255
N-Benzoyl-N′,N′-dibenzylthiourea	$CDCl_3$				15.5 (37)	a.s.s.	255
N,N-Dimethylselenoacetamide	*o*-Dichlorobenzene	26.0 ± 0.4	25.1 ± 0.4	5.1 ± 1.3	22.8 ± 0.1	s.s.	256
N,N-Dimethylselenobenzamide	*o*-Dichlorobenzene	19.5 ± 0.3	18.8 ± 0.3	−1.3 ± 1.2	19.3 ± 0.1	s.s.	256

[a] DM = density matrix method.

Further studies of the magnetic anisotropy of the carbonyl[265,266] and thiocarbonyl[266,267] groups were reported. The conformations of N-acylpiperidines[268] and N-acyl-1,2,3,4-tetrahydroquinolines[269] were investigated. Correlations of the N–H and formyl proton shifts of 23 *meta*- and *para*-substituted formanilides with the Hammett σ^0 constants were studied.[270]

Evidence for the protonation of poly-γ-benzyl-L-glutamate and some model amides in dichloracetic and trifluoroacetic acids[271] and some substituted acetamides in sulfuric acid[272] was presented, but N-benzoylglycine-*n*-propylamide was found to be nonprotonated in dichloroacetic acid.[273] Protonation of some 2-pyridones was shown to occur on oxygen and the effects of the protonation upon the nmr parameters of the ring protons were determined.[274]

Amide solvation of Fe(III),[275] Al(III),[276,277] Th(IV),[276] Mg(II),[276] and Li(I)[276,278] ions was reported. In ^{15}N-formamide, hydrogen-bonding between the bromide ion and the *trans* N–H proton was found to be favored over the *cis* by 0.7 kcal/mol.[279]

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