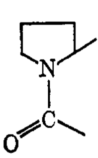
Nuclear Magnetic Resonance Studies of Several N-Acylisoindolines[1]

Kai-nan Fang and J. T. Gerig

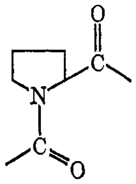
Contribution from the Department of Chemistry, University of California at Santa Barbara, Santa Barbara, California 93106. *Received September 30, 1968*

Abstract: The high-resolution pmr spectra of N-(N′,N′-dimethylcarbamyl)-, N-carbomethoxy-, N-acetyl-, N-benzoyl-, and N-trifluoroacetylisoindolines have been examined as a function of sample temperature. Hindered rotation of the acyl group is the only detectable kinetic process and it occurs in each compound with an activation energy that is larger than that found in the corresponding dimethylamides. An appreciable spin-coupling interaction across the five-membered ring was found in these compounds; the magnitude of this interaction appears to depend on the resonance effect of the substituent at the acyl carbon atom.

The presence of the amino acid proline in the backbone can have a profound effect on the conformational properties of a protein.[2] One important conformational influence that may result from inclusion of the proline structure in a polypeptide is a reversal of the screw sense of the helical secondary structure.[3,4] This effect is thought to derive from rotational *cis–trans* isomerism at the amide group of the proline, as shown in the partial structures Ia and Ib. Poly-L-proline, for example, can exist in two helical forms. One of these, poly-L-proline I, is a right-handed helix in which all the peptide bonds have the *cis* configuration (Ia),[5] while the other, poly-L-proline II, is a left-handed helix with all *trans* peptide linkages (Ib).[6] The kinetics of interconversion of these forms are consistent with the notion that the fundamental microscopic event involved is rotation about an amide bond.[4,7]

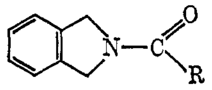


Ia



Ib

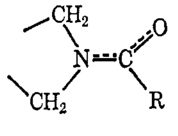
In order to provide a basis for a more detailed understanding of the effects of proline on the conformational properties of proteins, we have begun investigations with several series of compounds that should be reasonable models for some or all of the features of N-acylprolines. We seek additional information about the kinetics of rotational isomerism in these systems as well as the consequences of nonplanarity of the proline ring,[8] the possibility of trihedral nitrogen in the proline ring and the nature of nonbonded and hydrogen-bonded interactions between the proline system and its environment. Several N-acylisoindolines (II) form the first series that we have examined. Molecular models confirm one's impression that these molecules should be planar and essentially rigid as far as the five-membered heterocycle is concerned. They thus afford the opportunity to study the stereochemical attributes of the amide group in isolation. We describe here our experiments with these molecules.



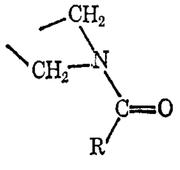
IIa, $R = (CH_3)_2N$
b, $R = OCH_3$
c, $R = CH_3$
d, $R = C_6H_6$
e, $R = CF_3$

Results

The ground state of an amide can be described as a structural hydrid of the two limiting forms shown below. In structure IIIa, the delocalization of π electrons in the amide bond is considered to be complete with the result that the atoms of the amide portion as well as the first atoms of the nitrogen substituents tend to lie in a common plane. If this delocalization can be minimized, a structure closer to IIIb results wherein the nitrogen atom is in a trihedral state. Each of these limiting structural forms has characteristic kinetic features; strongly restricted rotation about the acyl–nitrogen bond would be expected for IIIa and would result in *cis* and *trans* isomers in an appropriately constituted amide. This rotation is essentially free in IIIb. However, an appreciable barrier to inversion of the nitrogen lone pair would be expected for IIIb while the energy barrier to such inversion should be much smaller in IIIa.



IIIa



IIIb

In all peptides investigated to date, structure IIIa is by far the dominant contributor to the ground state of the molecule.[9] However, a microwave study of form-

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(1) This work will form a portion of the Ph.D. thesis of K.-n. Fang at the University of California, Santa Barbara.

(2) B. Love and J. T. Edsall, "Currents in Biochemical Research," Interscience Publishers, New York, N. Y., 1956, p 378.

(3) H. Lindley, *Biochem. Biophys. Acta*, **18**, 194 (1955).

(4) I. Z. Steinberg, W. F. Harrington, A. Berger, M. Sela, and E. Katchalski, *J. Amer. Chem. Soc.*, **82**, 5263 (1960).

(5) W. Traub and U. Schmueli, *Nature*, **198**, 1165 (1963).

(6) P. M. Cowan and S. McGavin, *ibid.*, **176**, 501 (1953).

(7) G. N. Ramachandran, Ed., "Conformations of Biopolymers," Vol. II, Academic Press, New York, N. Y., 1967, pp 483, 499.

(8) J. Donohue and K. N. Trueblood, *Acta Cryst.*, **5**, 419 (1952).

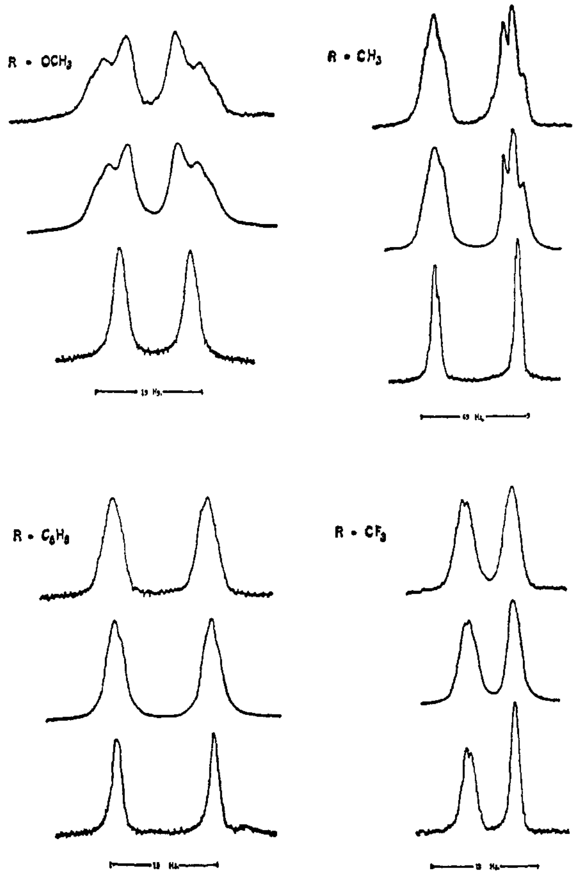

Figure 1. Slow-exchange pmr spectra of the benzylic region of several N-acylisoindolines. The spectrum of the carbomethoxy compound was recorded at −30° and 100 MHz, while the spectra of the remaining compounds were recorded at 21° and 60 MHz. The first trace in each series is the experimental spectrum, the second trace is the theoretical spectrum that results from the parameters listed in Table I, and the third trace is the experimental spectrum of the specifically dideuterated sample. In calculating the theoretical spectrum for the N-acetyl compound, a coupling constant of 0.5 Hz was assumed for the interaction between the acetyl methyl and one of the benzylic positions. In the N-trifluoroacetyl compound the analogous coupling was assumed to be 0.85 Hz.

amide shows that this molecule is slightly pyrimidal in the gaseous state.[10] Also, in three-membered rings (N-acylaziridines), the competition between the tendency toward electron delocalization and the unfavorable strain effects that accrue from incorporation of an sp^2 nitrogen atom into the ring leads to a compromise structure that is more similar to IIIb. An X-ray crystallographic study of N-benzoylaziridine shows that the nitrogen atom of this species is strongly trihedral while the analogous N,N-dimethylbenzamide is essentially planar.[11] Although inversion in N-benzoylaziridine could not be detected by nmr experiments,[12] Anet and Osyany have been able to determine the kinetics of inversion when the acyl group is N,N-dimethylcarbamyl or carbomethoxy.[13] Similar, but less pronounced, strain effects may be present in the N-acylisoindoline.

We examined the pmr spectrum of N-(N′,N′-dimethylcarbamyl)isoindoline (IIa) in toluene-d_8 or toluene-d_8/Freon-11 solutions as a function of temperature. Given the results with the corresponding aziridine[12,13] and the effect of aromatic solvents on the chemical-shift differences that is discussed below, this system should provide optimum conditions for detection of nitrogen inversion in this model of the proline ring. The benzylic and dimethylamino resonances appeared as sharp singlets at room temperature. No fundamental change occurred in the spectrum until sample temperatures below −70° were reached. Both singlets grew progressively broader as the temperature was lowered beyond this point but the width of the benzylic signals increased considerably more rapidly than those for the dimethylamino group and, at −115°, appeared as a band about 60 Hz wide (at 100 MHz). The dimethylamino peak was about 5 Hz wide at this temperature. No significant loss of resolution was indicated from the appearance of the aromatic region of the spectrum. Experiments below this temperature, however, were precluded by the limited solubility of this material.

The pmr spectra of the benzylic protons of the remaining four N-acyldihydroisoindoles were of the AA′BB′ type and are shown in Figure 1. No changes were observed in these spectra upon cooling the samples to −60° and each spectrum evolved to a singlet when the sample was heated to a sufficiently high temperature. Following the approach used by Anet and Osyany in their study of N-acylaziridines,[13] we attempted to extract the appropriate chemical shift and coupling constant parameters from these spectra in order to ascertain whether the temperature-dependent rate process observed was due to restricted rotation or to hindered nitrogen inversion. The Swalen–Reilly method was used in analyzing the spectra of IIb and IIc,[14] while the coupling constants for IId and IIe could only be crudely estimated by consideration of the observed line shapes at high and low temperatures. In all cases, the criterion for the acceptability of a set of spin-coupling parameters was that it lead to a calculated spectrum in acceptable agreement with the experimental spectrum. Enough information was contained in the spectra of IIb and IIc to strongly suggest that J_{AB} and $J_{AB'}$ must be both positive or both negative in sign but a clear-cut choice between these two alternatives was not possible. The geminal couplings, $J_{AA'}$ and $J_{BB'}$ were not well determined by the spectra and were assumed to be negative. The coupling constant and chemical shift data are given in Table I.

Table I. Nmr Parameters for N-Acylisoindolines

Substituent	δ_{AB}, ppm	J_{AB}, Hz	$J_{AB'}$, Hz
OCH$_3$^{a,c}	0.071	0.9	2.6
CH$_3$^{b,c}	0.203	1.1	1.7
C$_6$H$_6$^{a}	0.252	~1.0	~1.2
CF$_3$^{a}	0.115	~0.6	~0.8

^{a} Sample was a 10% solution in CDCl$_3$. ^{b} Sample was a 10% solution in 20% C$_6$H$_6$-CDCl$_3$. ^{c} $J_{AA'}$ and $J_{BB'}$ are about −12.5 Hz.

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[9] R. E. Marsh and J. Donohue, *Advan. Protein Chem.*, 22, 235 (1967).

[10] C. C. Costain and J. M. Dowling, *J. Chem. Phys.*, 32, 158 (1960).

[11] R. P. Shihaeva, L. O. Atovmyan, and R. G. Kostyanoviski, *Dokl. Akad. Nauk SSSR*, 175 (3), 536 (1967).

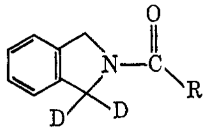
[12] G. R. Boggs and J. T. Gerig, *J. Org. Chem.*, in press.

[13] F. A. L. Anet and J. M. Osyany, *J. Amer. Chem. Soc.*, 89, 352 (1967).

[14] J. D. Swalen and C. A. Reilly, *J. Chem. Phys.*, 37, 21 (1962).

Although of limited accuracy, these parameters do lead to theoretical spectra that agree with the experimental spectra, as shown in Figure 1.

The data in Table I are most consistent with the formulation of these molecules as planar and relatively rigid; the benzylic positions are made magnetically nonequivalent by slow rotation of the acyl portion of the molecule and nuclear spin–spin interactions between these two positions thus become observable. However, the four-bond cross-ring couplings that must account for the complexity of these spectra are of a magnitude unprecedented in noncyclic amides,[15] and to confirm this interpretation, N-acylisoindolines which were dideuterated at a single benzylic position were synthesized (IV). As shown in Figure 1, the pmr spectra of these molecules in the benzylic region are essentially two singlets.



IV

The line widths of the benzylic singlets in the spectra of the dideuterated compounds were 0.6–1.0 Hz broader than the line width of the tetramethylsilane reference peak. Excluding the possibility of some unexpectedly large difference in the relaxation mechanisms for the N-acylisoindolines and tetramethylsilane, this additional peak width must arise from other small couplings within the molecule. Double irradiation at either the nitrogen-14 or the deuterium frequency had no appreciable peak-sharpening effect. Couplings to either of these nuclei are not expected to be more than 0.3 Hz,[16] but perhaps a combination of small couplings to the amide nitrogen, the cross-ring deuterium atoms, and protons on the aromatic portion of the isoindoline skeleton account for these broadened signals.

The chemical-shift difference between the benzylic signals of the N-acetyl derivative (IIc) was quite solvent dependent.[17] In chloroform-d_1 these resonances appeared as a singlet but, in benzene, the separation was nearly 1 ppm. A solvent composed of 20% benzene in chloroform-d_1 was chosen for use in this work and this solvent effect was not further investigated. However, this observation signals the possibility that solute self-association and solute–solvent interactions can influence the kinetics of rotational isomerism in these molecules.[18]

The activation parameters for rotation of the N-acyl group were determined by the so-called total line-shape method[19] and are presented in Table II. Visual comparison of computer-generated spectra to the experimental spectra was used. Spectra of the undeuterated materials taken at 100 MHz were analyzed by the senior investigator and have been reported in preliminary form elsewhere.[20] The spectra of the specifically deuterated N-acylisoindolines, taken at 60 MHz, were analyzed independently by Fang.

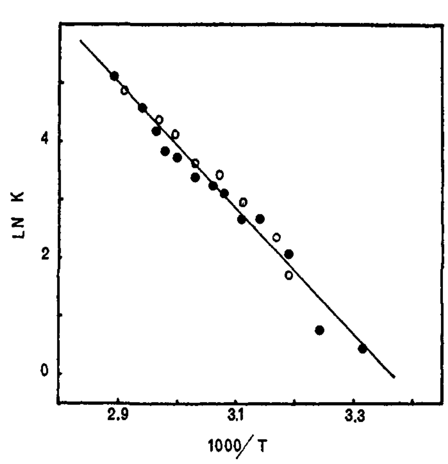


Figure 2. Arrhenius plot for rotation in N-benzoylisoindoline. The filled circles represent data obtained at 60 MHz while the open circles refer to the data obtained at 100 MHz.

Table II. Activation Parameters for Rotation in N-Acylisoindolines

Substituent	E_a, kcal/mol[a]	Log A	$\Delta F^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu[a]	T_c,[b] °C
OCH_3	20.9 ± 0.8	15.5	17.0	10 ± 2	39
CH_3[c]	23.4 ± 1.6	15.1	19.6	8 ± 4	101
C_6H_5	21.6 ± 0.9	15.9	17.0	12 ± 3	56
CF_3	31.9 ± 3.1	19.7	20.3	29 ± 8	106

[a] Root-mean-square errors appended. [b] The coalescence temperature at 60 MHz. [c] Solvent was 20% benzene in $CDCl_3$. For all other samples the solvent was $CDCl_3$.

The agreement between the two separate determinations was acceptable and is illustrated by Figure 2, where the combined data for the N-benzoyl derivative are presented graphically.

Discussion

In light of the results with the other N-acylisoindolines the change in the pmr spectrum of N-(N′,N′-dimethylcarbamyl)isoindoline at low temperatures may be due to slowing of rotation about the isoindoline–N,N-dimethylcarbamyl bond. If one takes 60 Hz as the slow-exchange chemical-shift difference, and −115° as the coalescence temperature, then the free energy barrier to rotation in this compound is estimated to be about 8 kcal/mol. Although in the expected relation to the barriers for the other N-acylisoindoles examined, the magnitude of this quantity does not firmly identify the nature of the rate process that becomes slow in this compound at low temperatures; nitrogen inversion would be expected to have a barrier less than 11 kcal/mol also.[13] This point cannot be clarified until we are able to obtain better resolved spectra of IIa at low temperatures, so that an analysis of the benzylic proton coupling pattern can be made.

Appreciable spin–spin couplings between nitrogen substituents have not been observed previously in

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(15) Such coupling constants are rather common in polycyclic hydrocarbons. For examples see: (a) K. B. Wiberg, B. R. Lowry, and B. J. Nist, *J. Amer. Chem. Soc.*, 84, 1594 (1962); (b) E. J. Corey and W. H. Pirkle, *Tetrahedron Lett.*, 5255 (1967); (c) V. F. Bystrov and O. P. Yablonsky, *J. Mol. Spectrosc.*, 20, 213 (1968). These references are illustrative but hardly exhaustive.

(16) Y. Terui, K. Aono, and K. Tori, *J. Amer. Chem. Soc.*, 90, 1069 (1968).

(17) For another example of this phenomenon in a similar system, see J. V. Hatton and R. E. Richards, *Mol. Phys.*, 5, 139 (1962).

(18) A. G. Wittaker and S. Siegel, *J. Chem. Phys.*, 43, 1575 (1965).

(19) R. C. Neuman, Jr., and V. Jonas, *J. Amer. Chem. Soc.*, 90, 1970 (1968).

(20) J. T. Gerig, *Tetrahedron Lett.*, 4625 (1967).

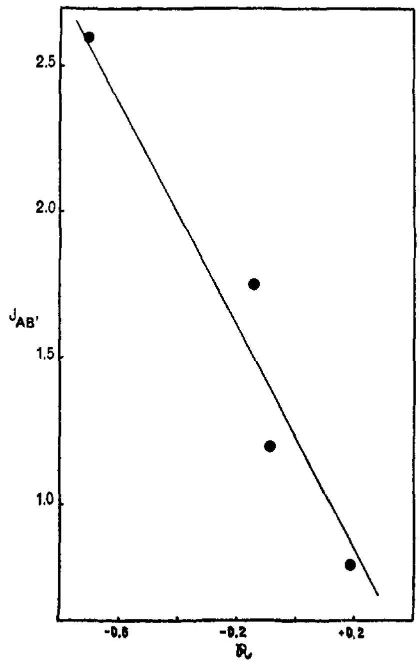


Figure 3. A plot of $J_{AB'}$ against the substituent parameter, R.

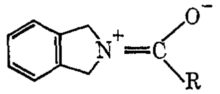
noncyclic amides. In particular, the dimethylamides corresponding to the N-acylisoindolines discussed above do not exhibit detectable spin coupling between the magnetically distinct N-methyl groups.[18,19] Annelation of the basic dimethylamide skeleton to a benzene ring to give the acylisoindolines conceivably could provide a favorable electronic pathway for coupling of one methylene group to another. However, it is difficult to see how this coupling mechanism, which must operate through five chemical bonds, could account for an increment in coupling constants between these nuclei of more than 1 Hz[21,22] and how it would respond to variations in the nature of the N-acyl substituent. Another possibility is that an appreciable part of this spin-spin interaction occurs through the amide nitrogen. This four-bond interaction should be numerically greater than the five-bond interaction and may be larger in these cyclic molecules than in the dimethylamides because of some subtle conformational effect.

The coupling constants J_{AB} and $J_{AB'}$ have the dimensions of energy and it is reasonable to attempt a correlation of these quantities with the known effects of the substituents, R, on organic reactivity.[23] Swain and Lupton have recently demonstrated that the effect of a substituent on an energy quantity of interest can be expressed in terms of two substituent constants.[27] One of these constants, $\mathcal{F}$, represents the field and/or inductive effect of the substituent while the other, $\mathcal{R}$, portrays the resonance effect. These authors showed that most substituent constants that have been used in energy correlations can be expressed as a linear combination of $\mathcal{F}$ and $\mathcal{R}$. If we presume that $J_{AB'}$ observed in the N-acylisoindolines can be correlated with substituent constants, then the correlation will take the form of eq 1, where c_1 and c_2 are weighing coefficients and c_3 is a constant. (Correlations with J_{AB} were not undertaken because of the small spread in

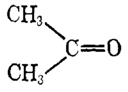
$$J_{AB'} = c_1\mathcal{F} + c_2\mathcal{R} + c_3 \qquad (1)$$

the data.) The limited number of values of $J_{AB'}$ were fit to equation 1 by a least-squares procedure.[28] The data were described by the equation $J_{AB'} = 0.1 \pm 0.3\mathcal{F} - 2.7 \pm 0.4\mathcal{R} + 1.16$ with a multiple correlation coefficient of 0.98. Thus, no reliable dependence of $J_{AB'}$ on $\mathcal{F}$ was found and, as the plot in Figure 3 shows, these coupling constants are smoothly correlated with $\mathcal{R}$, the resonance parameter. That the magnitude of $J_{AB'}$ can be correlated with the resonance effect of the acyl substituent on II seems to implicate the π electrons of the amide group in the transmission of "spin information" between the two groups of benzylic protons.

The high energy barriers to rotation of the acyl groups of N-acylisoindolines indicate substantial double-bond character in the acyl–nitrogen bonds as would obtain from a resonance structure such as V. This resonance structure could be considered analogous to acetone (VI). A type of long-range proton coupling



V



VI

that results from the interaction of the central π-electronic system with the carbon–hydrogen σ bonds has been postulated to account for the unusual four-bond proton–proton coupling constant in acetone.[29] The theoretical treatment of Holmes and Kivelson implies that this π contribution to the coupling is negative in sign. The contribution of the σ electronic framework to the coupling is probably positive in sign.[30-32] It is suggested, then, that as the resonance effect of R becomes smaller, the contribution of structures analogous to V becomes more important in the ground state of the acylisoindolines and, as this contribution becomes larger, the importance of the π-electronic coupling mechanism mentioned increases. Since this contribution is negative in sign, the observed coupling between the benzylic positions decreases. This suggestion does not take into account any angular dependence this coupling may have but we anticipate that this dependence will be qualitatively the same as observed in saturated systems and thus assign $J_{AB'}$ to the *trans* cross-ring coupling.[20,31]

It is interesting to compare the energetics of rotational isomerism in the N-acylisoindolines to the activation parameters for the corresponding dimethylamides (Table III). The entropies of activation for the N-

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(21) A. A. Bothner-By, *Advan. Magnetic Resonance*, **1**, 282, 291 (1965).

(22) S. Sternhell, *Rev. Pure Appl. Chem.*, 14, 15 (1964).

(23) It is well known that vicinal coupling constants can be correlated with the electronegativities of substituents[24,25] and that the various linear free energy substituent constants also depend on substituent electronegativity.[26]

(24) R. J. Abraham and K. G. R. Pachler, *Mol. Phys.*, **7**, 165 (1964).

(25) T. Schaefer, *Can. J. Chem.*, **40**, 1 (1962).

(26) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1955, p 613.

(27) C. G. Swain and E. C. Lupton, Jr., *J. Amer. Chem. Soc.*, **90**, 4328 (1968).

(28) W. A. Pavelich and R. W. Taft, Jr., *ibid.*, **79**, 4935 (1957).

(29) J. R. Holmes and D. Kivelson, *ibid.*, **83**, 2959 (1961).

(30) D. D. Elleman, S. L. Manatt, and C. D. Pearce, *J. Chem. Phys.*, **42**, 650 (1965).

(31) M. Barfield, *ibid.*, **41**, 3832 (1964).

(32) R. L. Vaulx, F. N. Jones, and C. R. Hauser, *J. Org. Chem.*, **29**, 505 (1964).

Table III. Activation Parameters for Rotation in N-Acyldimethylamines[a]

Substituent	E_a, kcal/mol	Log A	$\Delta F^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	Ref
CH_3[b]	20.6 ± 0.3	14.3	18.6	+4.7	19
C_6H_5[c]	16.8 ± 0.5	14.2	14.9	+4.5	*e*
CF_3[d]	20.6 ± 1.4	14.3	18.6	+4	*f*

[a] Large discrepancies in these quantities exist in the literature; the values quoted here are adjudged to be the most reliable. [b] Sample was 9.5% in dimethyl-d_6 sulfoxide. [c] Sample was 10% in chloroform-d_1. [d] Neat liquid. [e] J. T. Gerig, unpublished observations. [f] K. H. Abramson, P. T. Inglefield, E. Krakower, and L. W. Reeves, *Can. J. Chem.*, **44**, 1685 (1966).

acylisoindolines are somewhat larger than those for the dimethylamide and may be the result of some systematic error in the spectral analyses. It was hoped that the two-investigator–two-sample–two-frequency approach would minimize these errors. Solvent–solute or solute–solute association phenomenon could effect the chemical-shift differences needed for the spectral analyses at temperatures in the coalescence region; no significant changes in chemical-shift differences were noted at temperature well below coalescence, however. The energy barriers to rotation, either $\Delta F^{\ddagger}$ or E_a, tend to be larger than the barriers found in the corresponding dimethylamides, and are crudely in line with the resonance effect of the acyl substituent, R. The smallest barriers are found with substituents (N,N′-dimethylamino or methoxy) which can interact strongly in this manner and thus decrease the characteristics of structure V in the ground state. The largest barrier is found with trifluoroacetyl, the group with the smallest resonance effect as measured by $\mathcal{R}$. However, it is clear that barriers to rotation in these amides should also depend on the inductive and steric effects of these substituents.[19] Until these effects and the influence of solvent and self-association are better understood probably the only reliable conclusion that can be drawn from the activation parameters in the present work is that the barriers are higher than those found in acylic analogs. This conclusion can be understood in terms of a reduction of repulsive nonbonded (steric) interactions in the ground state of the N-acylisoindolines when the groups on nitrogen are retracted away from the acyl group upon incorporation into the five-membered ring.

Experimental Section

Isoindoline was prepared by the procedure of Bornstein, *et al.*[33]

General Procedure for Preparation of N-Acylisoindoles. Isoindoline was treated with the appropriate acylating agent (dimethylcarbamyl chloride, methyl chloroformate, acetyl chloride, benzoyl chloride, or trifluoroacetic anhydride), usually in the presence of aqueous base. The resulting crude solids were sublimed to afford colorless crystalline products. These materials rapidly darkened when exposed to air. The melting points and nmr spectral properties of these compounds are presented in Table IV. The mass spectrum of each compound showed a molecular ion at the appropriate m/e ratio and was interpretable in terms of the N-acylisoindole structure.

Several synthetic routes to isoindoline specifically dideuterated at a single benzylic position were explored. The most satisfactory procedure incorporated a modification of a recently reported method for reduction of secondary and tertiary amides that involves reduction of the corresponding imino ethyl ether with sodium borohydride.[34] We followed this procedure but found that neither sodium borohydride nor lithium aluminum hydride could effect reduction of the intermediate imino ether. Finally, isoindoline-d_2 was obtained by reduction of the imino ether with a mixture of lithium aluminum deuteride and aluminum chloride.

Table IV. Physical Properties of N-Acylisoindole

Substituent	Mp, °C	Pmr spectrum, δ[a]
$N(CH_3)_2$	125.5–126.5	2.90 (s), 4.74 (s), 7.21 (s)
OCH_3	109–109.5	3.76 (s), 4.66 (m), 4.73 (m), 7.21 (s)
CH_3	84–85	1.92 (s), 4.42 (m), 4.65 (m), 7.18 (s)
C_6H_5	102–103 (lit.[b] 100°)	4.81 (s), 5.07 (s), 7.08–7.80 (m)
CF_3	77–78 (lit.[33] 81°)	4.93 (s), 5.05 (s), 7.26 (s)

[a] In parts per million (ppm) from internal tetramethylsilane, s = singlet, m = multiplet. [b] K. Frankel, *Ber.*, **33**, 2812 (1900).

General Procedure for Preparation of Deuterated N-Acylisoindoles. To prepare the imino ether of isoindoline, phthalimidine[35] (1 g, 7.5 mmol) was treated with triethyloxonium fluoroborate (2.5 g, 13 mmol), the mixture was stirred at room temperature for 18 hr, and the methylene chloride was then removed under reduced pressure. Distillation of the residue gave a colorless liquid, bp 96° (11 mm). The pmr and ir spectra data were consistent with formulation of this material as the imino ether. The distilled imino ether (0.8 g, 5 mmol) was dissolved in 10 ml of anhydrous ether (distilled from lithium aluminum hydride before use) and added to a mixture of lithium aluminum deuteride (0.5 g, 12.5 mmol) and aluminum chloride (0.15 g, 1 mmol) in 25 ml of dry ether. The mixture was heated to reflux under nitrogen for 24 hr. The excess hydrides were then destroyed by addition of saturated aqueous sodium chloride solution. The heterogeneous mixture was filtered. The ether layer was washed with water and dried over magnesium sulfate. Removal of the ether gave a crude black liquid (~0.6 g, ~75%) which was treated immediately with an acylating agent, as described above. The crude solids were sublimed to give materials whose physical properties did not differ significantly from those of the nondeuterated materials. Mass spectral analysis showed that the extent of deuteration was greater than 95% of the theoretical amount in each case.

Kinetic Studies. All nmr samples were approximately 10% solute by weight and were degassed and sealed under vacuum. The spectra were obtained with a JEOL C-60H and/or a Varian Associates HA-100 spectrometer equipped with standard variable-temperature probes. The temperature within the probe was determined by insertion of a Digitec Model 514 digital thermocouple into a sample tube containing a solvent; temperatures are believed to be accurate to at least 1°. Rate data were extracted from the experimental spectra by visual comparison of curves generated by an IBM 360/65 computer. The program used was based on a density-matrix treatment of the two-site exchange process.[36] An effective relaxation time at each site allowed one to simulate the line width effects of the differential coupling of the N-acetyl and N-trifluoroacetyl groups to the two groups of benzylic protons. For the nondeuterated compounds, a composite line shape, made up of three appropriately weighed two-site components, was used to approximate the observed spectrum. While admittedly crude, this procedure gave results in agreement with those obtained from the deuterated analog.

The rate data were fit to the linearized Arrhenius equation by least squares[37] and the activation parameters calculated by standard equations.[38]

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