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Configurations in Unsymmetrically N,N-Disubstituted Amides[1]

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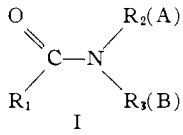
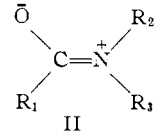
The nuclear magnetic resonance (n.m.r.) spectra of a series of unsymmetrically N,N-disubstituted amides have been studied and the peaks have been assigned in each case to the two possible conformational isomers. It is found that the bulkier substituent on nitrogen is *cis* to the formyl hydrogen in formamides and *trans* to the acetyl methyl group of acetamides, in the preferred isomer. These results are accounted for on the basis of steric interactions between substituent groups.

Introduction

Rotation about the central C–N bond of substituted amides is hindered, and at sufficiently low temperatures two resonance peaks will be observed for protons on group R_2 (I) arising from a chemical shift difference between protons of R_2 at site A and at site B. As the



I

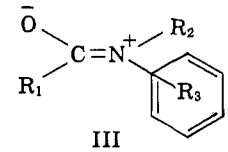


II

temperature is raised the mean lifetime τ_A of protons at site A decreases and becomes comparable with the reciprocal of the chemical shift ($\nu_B - \nu_A$) between protons of the group at site B and at site A. In this region the line shape is a function of temperature, and a study of the line shape[3,4] provides an estimate of the energy barrier hindering internal rotation (7–18 kcal./mole for most substituents R_1 when $R_2 = R_3 = CH_3$). The barrier is attributed to partial double-bond character in the C–N bond due to some contribution from resonance structures such as II. When $R_2 \neq R_3$ and $\tau_A \gg \sqrt{2}/2\pi(\nu_A - \nu_B)$, separate peaks may be observed for R_2 and R_3 in each isomer and the ratio of their intensities will then give the relative abundance of the rotational isomers.

From a study of the n.m.r. spectra, the preferred configurations for three unsymmetrically disubstituted formamides were assigned by Franconi[5] to the isomer in which the bulkier substituent occurs *cis* to the formyl hydrogen. These assignments were based on the assumption that the formyl hydrogen chemically shifted to lower field belongs to the isomer with the bulkier group *cis* to the formyl proton.

Two other methods of assigning the peaks in the n.m.r. spectrum of dimethylamides result in the assignment of the methyl resonance at higher magnetic field to the group which is in a position *cis* to the carbonyl oxygen (R_2 of I). One method depends on the difference in the long-range coupling constant between the protons of R_1 (I) and R_2 or R_3; the *trans* coupling is believed to be larger than the *cis*.[6–8] The other makes use of the change in the n.m.r. spectrum of amides upon dilution with benzene.[8] Hatton and Richards[8] proposed a specific interaction (III) between the benzene π-electrons and the nitrogen atom (with partial positive formal charge through resonance with structures such as II) in which the negatively charged carbonyl oxygen was as far away from the center of the benzene ring as possible. In an N,N-dimethylamide this would result in an enhanced shift to high field of the N-methyl



III

group *trans* to the carbonyl oxygen as benzene is added.

The same specific solvent effects with benzene are observed with ethyl,[8,9] isopropyl,[9] and *t*-butyl[9] substituents on the nitrogen and may therefore be used as a check for peak assignments in various aliphatic substituted amides.

In the present work, the n.m.r. spectra of unsymmetrically disubstituted amides have been studied, and the peaks assigned to the rotational isomers on the basis of coupling constants and behavior upon dilution with benzene.

Experimental

Chemical shifts were measured in c.p.s. from internal tetramethylsilane using a Varian A-60 analytical spectrometer. The temperature of the probe was approximately 35°. The precision of measurement of chemical shifts is about ±0.5 c.p.s. N-Butyl-N-methylformamide was obtained from Eastman Organic Chemicals, Rochester, N. Y. The remaining amides were prepared in this Laboratory and are listed in Table I.

Results and Discussion

The amides studied in this work are listed in Table II, together with the chemical shifts (c.p.s. from internal tetramethylsilane) and the *cis* and *trans* long-range coupling constants for the formamides. The designation (A) is given to the peaks which have been associated with groups which are in a position *cis* to the carbonyl oxygen (R_2 in I), while (B) refers to those n.m.r. resonances which we believe arise from groups *trans* to the carbonyl oxygen (R_3 in I). The percentage of the more abundant isomer present in the equilibrium mixture, as determined from the relative peak areas, has also been given in Table I. The n.m.r. spectra of several of the amides are given in Fig. 1–3.

In each case, except for the piperidines, the assignment was made first for the formamide in question on the basis of the magnitude of the long-range coupling constant between the formyl proton and the N-methyl protons. This is believed to be larger *trans* than *cis*[6–8]; thus the N-methyl resonance which is more strongly coupled may be tentatively assigned to the group which is in a position *cis* to the carbonyl oxygen. For each formamide in Table II, the N-methyl resonance to higher magnetic field has the larger value of $J_{H-CO-N-CH_3}$.

Once the N-methyl resonance has been assigned in the formamides, the preferred configuration may be found, and all other peaks in the spectrum may be as-

(1) This work was supported by grants from the National Science Foundation and the National Institutes of Health, Division of General Medical Sciences.

(2) National Institutes of Health Predoctoral Fellow, 1961–1963.

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TABLE I

METHOD OF PREPARATION AND BOILING POINTS FOR AMIDES

Amide	Method of prepn.	Obsd. b.p. °C.	Obsd. b.p. mm.	Lit. b.p. °C.	Lit. b.p. mm.	Ref
N-Ethyl-N-methylformamide	A[a]	82.0	44	...		..
N-Ethyl-N-methylacetamide	B[b]	45.0	33	180	760 (?)	[e]
N-Ethyl-N-methyltrimethylacetamide	B	62.0–63.0	5	...		..
N-Butyl-N-methylacetamide	C[c]	65.0	3	...		..
N-Butyl-N-methylisobutyramide	C	72.5–73.0	2.5	...		..
N-Butyl-N-methyltrimethylacetamide	C	75.0–76.0	2	...		..
N-Cyclohexyl-N-methylformamide	D[d]	111.0–112.0	6	250	760	[f]
N-Cyclohexyl-N-methylacetamide	C	130.0	13	249	740	[g]
N-Isopropyl-N-methylformamide	A	58.5	7	...		..
N-Isopropyl-N-methylacetamide	C	60.0	17	69–70	13	[h]
N-Formyl-2-methylpiperidine	D	70.5–71.5	2	...		..
N-Acetyl-2-methylpiperidine	C	86.5–87.5	3.5	...		..
N-Methyl-N-*t*-butylformamide	D	64.5	5	...		..
N-Methyl-N-*t*-butylacetamide	B	56.5	5	...		..

[a] Method A involved heating formamide with the appropriate amine hydrochloride: A. Galat and G. Elion, *J. Am. Chem. Soc.*, **65**, 1566 (1943). [b] Method B is the reaction of the amine hydrochloride with sodium hydroxide and then with an acyl chloride: S. M. McElvain and C. L. Stevens, *ibid.*, **69**, 2667 (1947). [c] Method C requires the addition of the amine to the acyl chloride: N. L. Drake, C. M. Eaker, and W. Shenk, *ibid.*, **70**, 677 (1948). [d] Method D is the reaction of formic acid and the amine in xylene: J. H. Robson and J. Reinhart, *ibid.*, **77**, 498 (1955). [e] A. W. Titherley, *J. Chem. Soc.*, **79**, 391 (1901). [f] R. Lukes and J. Jizba, *Chem. Listy*, **47**, 1366 (1953). [g] A. Skita and H. Rolfes, *Chem. Ber.*, **53**, 1249 (1920). [h] J. v. Braun, F. Jostes, and H. Wagner, *Ber.*, **61**, 1428 (1928).

TABLE II

CHEMICAL SHIFTS[a] AND COUPLING CONSTANTS IN UNSYMMETRICALLY DISUBSTITUTED AMIDES

Amide	Percentage of preferred configuration[b]	$\delta_{N-CH_3(A)}$	$\delta_{N-CH_3(B)}$	$\delta_{N-C-CH_3(A)}$	$\delta_{N-C-CH_3(B)}$	$J_{H-C(=O)-N-CH_3}$ *trans*[c]	$J_{H-C(=O)-N-CH_3}$ *cis*[c]
N-Ethyl-N-methylformamide	60	−169.5	−179.0	−63.2	−68.5	0.70	0.3
N-Ethyl-N-methylacetamide	51	−171.5	−181.7	−61.2	−68.5	...	...
N-Ethyl-N-methyltrimethylacetamide	..	−180.3	−180.3	−65.4	−65.4	...	...
N-Butyl-N-methylformamide	61	−168.5	177.5	....	....	0.65	0.3
N-Butyl-N-methylacetamide	53	−171.7	−181.0	....	....	...	...
N-Butyl-N-methylisobutyramide	50+[d]	−172.0	−183.2	....	....	..	...
N-Butyl-N-methyltrimethylacetamide	..	−181.5	−181.5	....	....	...	...
N-Cyclohexyl-N-methylformamide	66	−165.2	−172.0	....	....	0.60	0.4
N-Cyclohexyl-N-methylacetamide	55	−164.5	−172.0	....	....	...	...
N-Isopropyl-N-methylformamide[e]	67	−162.5	−170.0	−65.7	−71.2	0.65	0.5
N-Isopropyl-N-methylacetamide[f]	58	−162.0	−169.7	−62.0	−69.0	...	...
N-Formyl-2-methylpiperidine	53	.....	.....	−68.3	−75.8	...	...
N-Acetyl-2-methylpiperidine	..	.....	.....	−68.0	−68.0	...	...
N-Methyl-N-*t*-butylformamide	89	−166.5	−172.5	−80.1	−81.8	0.60	?
N-Methyl-N-*t*-butylacetamide	..	−173.5	−173.5	−87.0	−87.0	...	...

[a] Chemical shifts are in c.p.s. from internal tetramethylsilane. Resonance peaks which are believed to arise from groups located *cis* to the carbonyl oxygen are labeled (A), while those *trans* are labeled (B). [b] The preferred configuration in the formamides is the isomer in which the bulkier group is located *cis* to the formyl proton; however, in the acetamides and in N-butyl-N-methylisobutyramide the bulkier group is *cis* to the carbonyl oxygen atom. [c] In dimethylformamide, it is believed that the *trans* coupling constant is larger than the *cis*.[6-8] [d] The percentage could not be determined due to the partial overlapping of the N-methyl and C-methine resonances. [e] $\delta_{N-CH(A)} = -287.0$ c.p.s.; $\delta_{N-CH(B)} = -247.5$ c.p.s. [f] $\delta_{N-CH(A)} = -271.0$ c.p.s.; $\delta_{N-CH(B)} = -235.0$ c.p.s.

signed on the basis of the relative peak areas. Then the assignments may be checked by benzene dilution studies. Peaks which have been associated with groups *trans* to the carbonyl oxygen should show the greatest chemical shift to high field upon dilution with benzene[8] (III), as is observed in each case (Fig. 2).

The resonance peaks of the other amides listed in Table I may then be assigned on the basis of chemical shifts by comparison with the corresponding formamide, since replacing a formyl proton with an alkyl group has only a small effect on the chemical shift of N-alkyl resonances. Confirmation of these assignments, as listed in Table I, was also obtained by benzene dilution studies.

In the unsymmetrically disubstituted amides studied in this work, the groups whose resonances appear to higher magnetic field when located *cis* to the carbonyl oxygen are: N–C*H*$_3$, N–CH$_2$C*H*$_3$, and N–CH–(C*H*$_3$)$_2$. The peaks due to N–C*H*–(CH$_3$)$_2$ and N–C–(C*H*$_3$)$_3$ groups, however, will occur at *lower* magnetic field when the group is *cis* to the carbonyl oxygen. The N–C*H*$_2$–R resonances occur at almost the same field and cannot be distinguished.

The methyl resonance of N-formyl-2-methylpiperidine (Fig. 3) is an apparent triplet due to partial overlapping of the two doublets which are a result of the spin coupling with the 2-proton. The doublet to higher field was assigned to the group *cis* to the carbonyl oxygen by comparison with the N–CH$_2$–C*H*$_3$ resonances of diethylamides.[9] Benzene solution studies were consistent with this assignment.

In agreement with Franconi,[5] we find that the preferred isomer in the formamides has the bulkier substituent *trans* to the carbonyl oxygen. However, in the acetamides the bulkier group is *cis* to the carbonyl oxygen. If the relative stabilities depend on simple steric factors and the order of size of the groups is R (alkyl) > CH$_3$ > O > H, then the above results are easily understood. Since a small rotation of the groups about the C–N bond, to take the atoms attached to

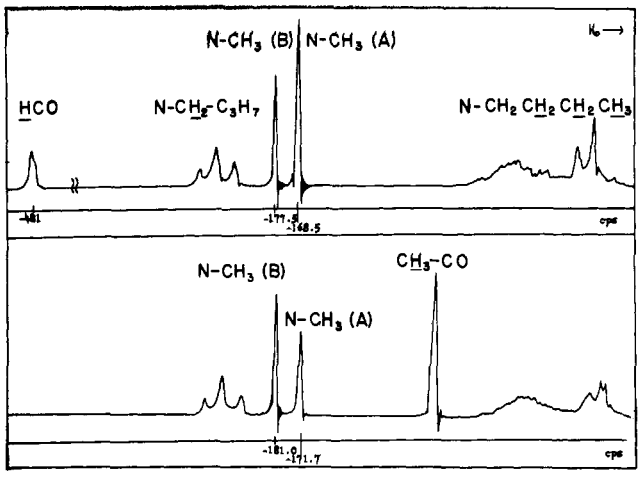

Fig. 1.—N.m.r. spectra (ν_0 = 60 Mc.) of (top) N-butyl-N-methylformamide and (bottom) N-butyl-N-methylacetamide. The two formyl proton resonances (at −481 c.p.s. relative to internal tetramethylsilane) could not be resolved. The N–CH_3 peak at higher field (A), arising from the methyl group *cis* to the carbonyl oxygen, is more intense in the formamide and less intense in the acetamide than the peak (B) from the other isomer. Relative integrated intensities of these peaks gave the isomer ratio in each case.

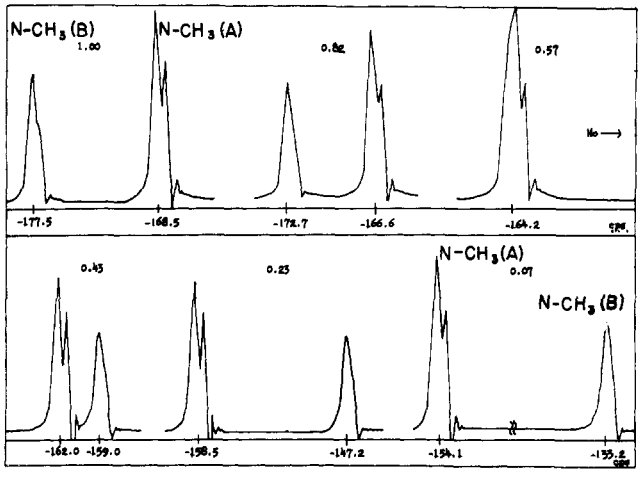

Fig. 2.—The behavior of the N-methyl peaks of the two isomers of N-butyl-N-methylformamide on dilution with benzene. The concentration is given above each peak in mole fraction amide. The chemical shift in c.p.s. relative to internal tetramethylsilane is given for each peak. The N–CH_3 peak at lower field moves rapidly to higher field on dilution in benzene crossing the second (B) peak at about 0.57 mole fraction amide. This behavior is expected for the N–CH_3 group *trans* to the carbonyl group and confirms the peak assignment made on the basis of spin splittings.

carbon out of the plane formed by the C–N bond and the atoms attached to nitrogen, would lead to a reduction in the contribution of resonance form II and so a loss in stability of the molecule, it is not surprising that the relative energies of the isomers are very sensitive to group size. The actual energy differences between isomers are small.

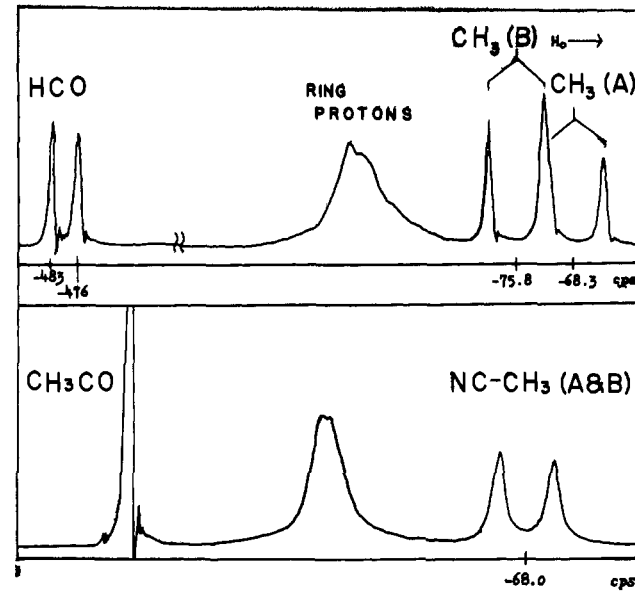

Fig. 3.—N.m.r. spectra (ν_0 = 60.0 Mc.) of (top) N-formyl-2-methylpiperidine and (bottom) N-acetyl-2-methylpiperidine. Two sets of resonance peaks occur in the spectrum of the formamide, while only one set is observed for the acetamide.

The n.m.r. spectra of N-ethyl-N-methyltrimethylacetamide, N-butyl-N-methyltrimethylacetamide, N-methyl-N-*t*-butylacetamide, and N-acetyl-2-methylpiperidine (Table II) differ from the spectra of the other amides in that only one set of resonances is observed. This may mean that (1) only one isomer is present in an appreciable amount, or (2) the rate of rotation about the C–N bond is fast enough that $\tau_A \ll \sqrt{2}/2\pi(\nu_A - \nu_B)$ and only an averaging of rotational isomers is observed in the n.m.r. spectrum. It is hoped that temperature measurements will help to determine the cause of this unusual behavior.

In certain cases it is possible to observe the formyl proton resonances of each rotational isomer (*ca.* −480 c.p.s.). The formyl and acetyl resonances of each isomer are clearly resolved in the N-cyclohexyl-N-methylamides, reflecting the difference between a cyclohexyl ring and a methyl group in their ability to produce long-range chemical shifts.

Further studies are under way to determine the effects of other substituents upon the isomer ratio. We plan to examine the spectra at various temperatures, to give a more quantitative estimate of the relative stability of the isomers.