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Nuclear Magnetic Resonance Studies of the Intermolecular Interaction of Amides and Some Other Related Dipolar Molecules

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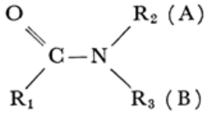
The chemical shifts for *N, N*-disubstituted amides and some other isoelectronic compounds as pure liquid and in dilute solutions in CCl_4 are reported. The characteristic shifts generally observed on going from a CCl_4 solution to pure liquid are explained in terms of specific self-association in the pure liquid.

Rotation about the central C–N bond of substituted amides is hindered, and two resonance peaks, those of protons of R_2 at site A and of R_3 at site B, are observed.



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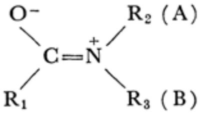


II

From the temperature dependence of the proton magnetic resonance spectra of substituted amides, the energy barriers restricting the internal rotation about the central C–N bond have been obtained.[1-5]

The barrier height strongly depends on the nature of the solvent and on the concentration when these substances are studied in solution.[4,5] This has been attributed to the changes of a partial double-bond character in the C–N bond arising from the intermolecular interactions. Whittaker and Siegel[5] showed evidence of the dipolar association of *N, N*-dimethylformamide (DMF) from their NMR study of solvent effects on the hindered internal rotation about the C–N bond.

However, there has been no dispute over the nature of the self-association which takes place between amide molecules in the pure liquid. Recently, there has been a considerable amount of work on the specific intermolecular interaction by the NMR method; for example, the solvent-solute interaction between benzene and amide.[6] the self-association of azabenzene[7] and of pyrrole[8] have been discussed, along with the configuration or the mode of the interacting molecules. Hence, in the present paper, a detailed investigation of dipolar interactions of highly-polar molecules, amides and some other related dipolar molecules will be made by examining the concentration effect on the proton chemical shifts of amide and some other carbonyl compounds.

It will be made clear that the dilution shift and the change in the proton-proton coupling constant in solution can be interpreted in terms of a "head-to-tail" type of association between amide molecules.

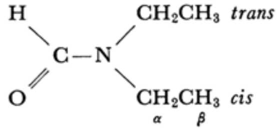
Experimental

Materials.—*N, N*-Dimethylformamide (DMF), *N, N*-dimethylacetamide (DMAC), *N, N*-diethylformamide (DEF), *N*-methyl-2-pyrrolidone, and some other carbonyl compounds listed in Table II were obtained from commercial sources. The remaining compounds were prepared as follows. *N*-Formylpiperidine was prepared from the reaction of piperidine with chloral.[9] *N, N*-Dimethylglycolamide (DGA) was prepared by the aminolysis of methyl glycolate. These compounds were so pure that they showed no impurity lines when the spectrometer gain was near its maximum; hence, no further purification of the samples was carried out.

NMR Spectra.—The chemical shifts were measured in c.p.s. from internal tetramethylsilane with a Varian A-60 analytical spectrometer operating at 60 Mc. at a temperature of about 35°C. The precision of the measurement of chemical shifts was within about ±0.3 c. p. s.

Results and Discussion

The Chemical Shift and the Proton-proton Coupling Constant.—The amides studied in this work are listed in Table I, together with the chemical shifts and the association shift, which is defined as the difference between the chemical shifts in the neat liquid and in the carbon tetrachloride solution $(\delta_{\text{in neat}}-\delta_{\text{in CCl}_4})$. The notations used to distinguish the various protons in the groups attached to the nitrogen atom are shown in III; each proton is referred to as *cis* or *trans* with respect to the carbonyl oxygen.



III

The NMR spectra of several amides are given in Fig. 1. The peaks in the NMR spectrum have been assigned by two different methods. The first one utilizes the difference in the long-range coupling constant between the protons of R_1 and R_2 or R_3; the *trans* coupling is believed to be larger than the *cis*.[10-12] The other method makes use of the change in the NMR spectrum of amides when they are diluted with benzene.[6,12] Hatton and Richards[6] proposed a specific interaction between benzene and the amide molecule in which the negatively-charged carbonyl oxygen was located as far away from the center of the benzene ring as possible.[12,13] We will now present our experimental results on the change in the proton-proton coupling constants and proton chemical shifts for each compound.

As to *N, N*-dimethylformamides, the magnitude of the long-range coupling constant between the formyl proton and the *N*-methyl protons decreases upon dilution with carbon tetrachloride (as is shown in Fig. 1). With higher concentrations,

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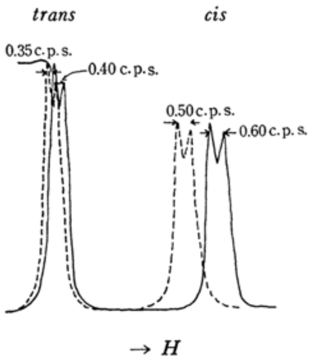

Fig. 1. *N*-Methyl signals of *N, N*-dimethylformamide ——: pure liquid, ----: 10% CCl_4 solution.

the polar structure, II, is favored by a dipolar-type interaction and a double-bond character between C and N serves to increase the long-range coupling constant between the formyl proton and the *cis* methyl proton J_{12}, or between the formyl proton and the *trans* methyl proton J_{13}. This may be seen obviously from the value of J_{12} or J_{13} given in Fig. 1. From the chemical shift data of DMF in Table I, it may be seen that the *cis* methyl signal shifts upfield as the concentration increases, while the *trans* methyl signal remains almost constant.

For *N, N*-dimethylacetamide, the two *N*-methyl signals are not equally sharp, with the higher field line being broader (as is shown in Fig. 2); the increased breadth of the high field line indicates that this line has a larger unresolved hyperfine interaction between *N*-methyl protons and *C*-methyl protons. When diluted with an inert solvent, carbon tetrachloride, the higher-field *N*-methyl signal line becomes sharp due to the diminution in the long-range coupling with *C*-methyl protons, as is also shown from the change in the H_{cis}/H_{trans} value given in Table I. Here, H_{cis} and H_{trans} indicate the height of the *cis* and *trans* methyl signals, and the H_{cis}/H_{trans} ratio is proportional to the ratio of the two long-range coupling constants, J_{12}/J_{13}. The large double-bond character of the C–N bond in the pure liquid makes J_{13} (*trans* coupling) larger, in turn resulting in a broad *cis* *N*-methyl signal line, that is, a decrease in the H_{cis}/H_{trans} value. This result also demonstrates the dipolar association for DMAC when the concentration increases. The *cis* *N*-methyl proton signal exhibits a larger upfield shift than the *trans* where there is a remarkable dipolar association of amide, as in the case of DMF. On the other hand, *C*-methyl protons show a downfield shift, much as that observed in the case of the formyl proton in DMF. In *N*-methyl-2-pyrolidone, in which rotation about the C–N bond is restricted, an upfield shift of the methyl proton resonance when the concentration is increased is also observed. On the other hand, α-methylene protons resonate downfield at higher concentrations; this is also attributed predominantly to the increment of the polar structure II, as is observed with the formyl proton in DMF and with the *C*-methyl protons in DMAC.

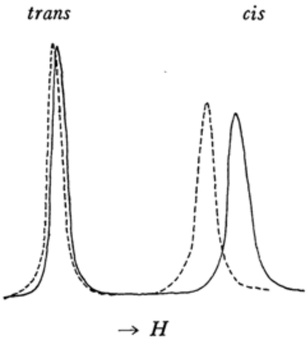

Fig. 2. *N*-Methyl signals of *N, N*-dimethylacetamide ——: pure liquid. ----: 10% CCl_4 solution.

N, N-Diethylformamide (DEF) and *N*-formylpiperidine are used to examine the concetration effect on the proton shift. In DEF and *N*-formyl piperidine, compared to DEF, it is very interesting that α-methylene protons exhibit shifts to a lower field in pure liquid than in a carbon tetrachloride solution, while β-methyl protons show an upfield shift in pure liquid, as is the case for *cis* methyl protons in DMF, DMAC, and *N*-methyl-2-pyrrolidone. It is also interesting to note that the β-methyl protons *trans* to the carbonyl bond show a larger downfield shift than the *cis* protons. These interesting results will be discussed below.

In *N, N*-dimethylglycolamide (DGA), anomalous[14] chemical shifts of methyl protons have been observed, the methyl signal line at lower field being broader (Fig. 3). When we assumed that the *trans* coupling is larger than the *cis*, as is the case for DMF and DMAC, it follows that the resonance of *cis* methyl protons occurs at a lower field in DGA.

This larger breadth of the lower-field resonance line may be expected to arise from the larger long-range coupling between *cis* *N*-methyl protons and the methylene protons in the methylol group than that for *trans* methyl protons. This is justified from the spin-spin decoupling experiment. The methyl proton signal at a lower field is sharpened by methylene proton decoupling (Fig. 3-a and 3-b). In this compound, as is shown in Table I, the

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[14] Similar anomalous features are not observed for similar hydroxyl amides, *N, N*-dimethylhydracrylamide and *N, N*-dimethyllactamide. The details of the NMR spectra of these compounds, together with those of DGA, will be published elsewhere.

TABLE I. CHEMICAL SHIFTS[a)] OF AMIDES

	Compound	Solvent	$H_\alpha(CH_3)$		$H_\alpha(CH_2)$		$H_\beta(CH_3)$		H or CH_3 (α to C=O)	H_{cis}/H_{trans}
			cis	trans	cis	trans	cis	trans		
1	*N*, *N*-Dimethylformamide	Neat	167.5	177.5	—		—		—	—
		CCl_4[b)]	160.0	177.2	—		—		—	—
		CCl_4+ MeOH[c)]	171.2	179.2	—		—		—	—
2	*N*, *N*-Dimethylacetamide	Neat	170.0	180.2	—		—		119.5	0.75
		CCl_4[b)]	171.0	180.2	—		—		117.0	0.82
		CCl_4+ MeOH[c)]	175.1	181.6	—		—		—	—
3	*N*-Methyl-2-pyrrolidone	Neat	163.5	—	—		—		—	—
		CCl_4[b)]	165.0	—	—		—		—	—
4	*N*, *N*-Dimethylglycolamide	CCl_4 (30 w/v %)	176.0	172.0	—		—		—	0.71
		CCl_4 (5 w/v %)	179.0	173.0	—		—		—	0.87
5	*N*, *N*-Diethylformamide	Neat	—	—	201.0[d)]		64.0	68.5	484.0	—
		CCl_4[b)]	—	—	196.0[d)]		65.5	71.5	476.0	—
6	*N*-Formylpiperidine	Neat	206.0	210.0	—		95.0		480.0	—
		CCl_4[b)]	204.0	210.0	—		98.0		472.0	—

a) Chemical shifts are in c. p. s. from internal tetramethylsilane.
b) 10±1% solution.
c) Methanol is added to a CCl_4 solution.
d) *Cis* and *trans* signals are superposed.

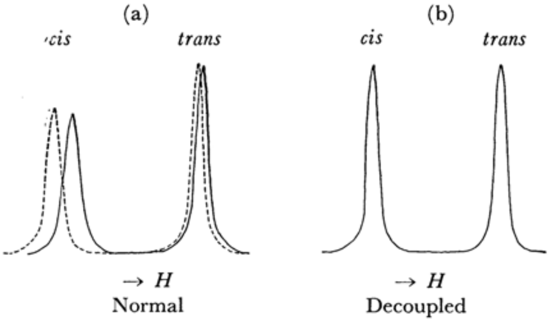


Fig. 3. *N*-Methyl signals of *N*, *N*-dimethylglycolamide, ——: 30% CCl_4 solution, ----: 5% CCl_4 solution.

proton signal of the *cis* methyl group also shifts upfield as the concentration increases.

The Nature of the Association of Amides.—The dilution of amides with CCl_4 may change the electronic distribution of the amide molecules, the diamagnetic anisotropy effect of the carbonyl bond, and the energy barrier of internal rotation about the C–N bond. All of these effects may cause a change in the proton chemical shift.

The association shift of methyl protons of DMF, DMAC, *N*-methyl-2-pyrrolidone, and DGA, together with β-methyl and methylene protons of DEF and *N*-formylpiperidine, probably does not result from the changes in charge distribution, since, if so, the methyl signal would move to a lower field; this is in contrast with those experiments in which the concentration increases, whereupon the polar structure II is favored due to the dipolar interaction, and the positively-charged nitrogen atom withdraws the σ-electron in the C–H bond.

When the energy barrier restricting the hindered internal rotation about the C–N bond increases with the amide concentration,[4,5)] the separation between two methyl proton signals of DMF increases, and the symmetrical shift of two methyl proton signals can be observed. This internal rotation effect, however, will not contribute to the upfield shift of methyl protons of *N*, *N*-dimethylamides at high concentrations, because one of the two methyl proton signals at the higher field shifts upfield more than that of the lower-field methyl signal, resulting in an asymmetrical shift (Fig. 1). In fact, in *N*-methyl-2-pyrrolidone, which has a rigid structure and in which the methyl resonance is not affected by the internal rotation about the C–N bond, the upfield association shift is also observed for *N*-methyl protons. Thus, the upfield association shift is attributable to the long-range shielding effect of the carbonyl group. Two possible explanations of this behavior of chemical shifts come to mind; (1) a dipolar association may modify the magnetic anisotropy of the carbonyl bond, which in turn should change the chemical shift of the *N*-methyl protons. (2) This association may also decrease the average distances between amide molecules, and the proton resonances of one amide molecule may be affected by the magnetic anisotropy of the carbonyl bond of neighbouring amide molecules. These two effects are referred to as the intramolecular and the intermolecular long-range diamagnetic anisotropic shielding effect (abbreviated as the intra- and intermolecular anisotropic effects respectively). In fact, there may be a superposition of these two effects.

The intramolecular anisotropic effect of the carbonyl group can be ruled out as a main factor from the following considerations. First, a dipolar association like the hydrogen bonding at the carbonyl oxygen[15] enhances the charge polarization of the carbonyl bond. However, when the hydrogen bonding occurs, as is shown in Table I, the *cis* methyl proton resonance shows a larger downfield shift than does the *trans*. Therefore, the upfield shift of *cis* methyl protons as the concentration increases may be due to the intermolecular anisotropic effect. Second, α-methyl proton resonance of DEF and *N*-formylpiperidine show a downfield shift as the concentration of amides increases. If the intramolecular anisotropic effect is the main factor in the association shift, this contrary tendency of the association shift is in contrast to the shift for methyl protons of DMF and DMAC. Thus, not the intra- but the intermolecular anisotropic effect is believed to be mainly responsible for the concentration effect of the chemical shifts of protons neighboring the carbonyl bond.

The anisotropic shielding effect of the carbonyl double bond has been exhibited in amides,[15-17] α,β-unsaturated carbonyl compounds, a series of steroids,[18] and α-methylenecycloketones.[19] In each of these cases, the chemical shift data indicate that the resonance spectra of magnetic nuclei shift to a higher field when the nuclei are constrained to a position in a conical region above and below the carbonyl bond.[20]

In the qualitative sense, it then follows that the association shift to the higher field indicates that the methyl group is in a conical region above or below the carbonyl double bond of another amide molecule. Thus, the structure of the dipolar association of the type demonstrated in Fig. 4 (the "head-to-tail" type of dipolar interaction) is probably favored for DMF, DMAC, *N*-methyl-2-pyrolidone, and DGA.

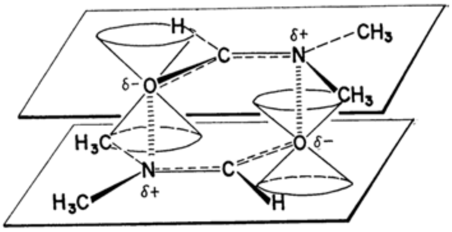


Fig. 4. The proposed model of the specific dipolar association of *N, N*-dimethylformamide.

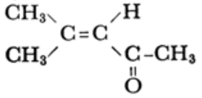
In order to investigate further this type of association for other, similar carbonyl compounds, we measured the association shift of mesityl oxide and phorone. The results are listed in Table II; also shown is the chemical shift change effected by the hydrogen bond. The association shifts of these two carbonyl compounds are also upfield for the *trans* methyl proton; this reveals the same type of dipolar association as when the amides exist.

TABLE II. CHEMICAL SHIFTS[a] OF α,β-UNSATURATED CARBONYL COMPOUNDS

	Compound	Solvent	Methyl protons	
1	Mesityl oxide[b,d]	Neat	125.2	110.7
		10% CCl_4	125.3	111.7
		10% CCl_4 +MeOH[e]	126.3	113.5
2	Phorone[c,d]	Neat	129.5	111.1
		10% CCl_4	128.8	112.9
		10% CCl_4 +MeOH	128.7	114.3

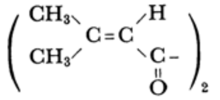
a) Chemical shifts are in c. p. s. from internal tetramethylsilane.

b)



$(\mathrm{CH_3})_2\mathrm{C{=}CH{-}C({=}O){-}CH_3}$

c)



$\left((\mathrm{CH_3})_2\mathrm{C{=}CH{-}C({=}O){-}}\right)_2$

d) S-cis form is favored for these compounds from the infrared spectra (Ref. 21), dipole moment measurements (Ref. 22) and carbon-13 magnetic resonance spectroscopy (Ref. 23).

e) The concentration of MeOH is about 5%.

From the above qualitative considerations as to the chemical shift change of the protons neighboring the carbonyl bond effected by the dipolar

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[15] More quantitative discussions on the hydrogen bonding effects on the proton chemical shifts of carbonyl compounds will be published in the near future.

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TABLE III. CHEMICAL SHIETS[a)] OF NITROSAMINES

Compound R_1R_2 NNO		Solvent	$H_\alpha(CH)$		$H_\alpha(CH_2)$		$H_\alpha(CH_3)$		$H_\beta(CH_3)$		Ref.
R_1	R_2		cis	trans	cis	trans	cis	trans	cis	trans	
C_2H_5	C_2H_5	Neat	—	—	271.0	251.5	—	—	62.0	82.0	Present work
		CCl_4	—	—	210.5	247.5	—	—	62.5	84.0	
CH_3	CH_2CH_3	Neat	—	—	215.4	250.2	180.0	223.2	61.2	79.8	24)
		CCl_4	—	—	211.2	249.0	175.8	222.6	63.0	82.8	
CH_3	$CH(CH_3)_2$	Neat	301.8	289.8	—	—	177.0	219.6	67.2	84.6	24)
		CCl_4	301.8	291.0	—	—	172.2	217.2	65.4	85.2	

a) Chemical shifts are in c. p. s. from internal T. M. S.

association mentioned above, we propose the dipolar association of the type given in Fig. 4 for amide and other carbonyl compounds. The structure of the dipolar association also indicates that *cis* methyl protons will show a large shielding effect of the carbonyl bond of neighboring amide molecule than those *trans* to the carbonyl bond; this finding is compatible with the experimental.

For *N*, *N*-diethyl amides and *N*-formylpiperidine the upfield shift of the β-proton and the downfield shift of α-protons by the association leads us to the inferences that β-protons may be in the conical region above or below the carbonyl bond and that the α-protons are nearly all in the remaining region of the carbonyl bond. If this model is valid, similar association shifts should be observed for the equimolecular and isoelectronic compounds, and *N*, *N*-diethylnitrosamine, in which the two methylene signals (for *cis* and *trans*) are well separated, unlike DMF. The experimental results are given in Table III for several nitrosamines. An inspection of the data will reveal that the chemical shift of β-protons goes upfield with an increase in the concentration of nitrosamine, while that of α-protons shows a downfield shift. The configuration of the dipolar-associated dimer of *N*, *N*-diethylnitrosamines is considered to be similar to that of *N*, *N*-diethylformamide.

We may summarize our conclusions as follows. In the pure liquid amides and some other isoelectronic compounds, i. e., α, β-unsaturated carbonyl compounds and nitrosamines, it is probable that the high-charge polarization of these molecules favors a structure of dipolar self-association in which the positively-charged nitrogen (or carbon) of one molecule is directly over the negative oxygen atom of the other.

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