HINDERED ROTATION IN N-METHYLFORMAMIDE. A PEPTIDE-BOND MODEL SYSTEM.*†

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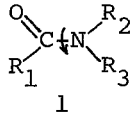
Summary. Barriers to rotation about the C-N bond in the cis and trans isomers of N-methylformamide have been determined by n.m.r. spectroscopy. Representative values are 20.7 and 22.0 kcal/mole. Arrhenius parameters have also been determined. These results are compared with C-N barriers for N,N-dimethylformamide and unsubstituted formamide. The data suggest that C-N rotational barriers for N-methyl amides may be similar to those for their N,N-dimethyl derivatives.

Energy requirements for rotation about the central C-N bond in amides (1) are of potential interest to those engaged in



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structural and physical-chemical studies of proteins. These barriers may often be determined by nuclear magnetic resonance (n.m.r.) spectroscopy and reliable data are now available for a variety of N,N-dimethyl (R_2=R_3=CH_3) and some N,N-dialkyl substituted amides.[1,2]

However, these data may not be representative of C-N rotational barriers in proteins since the latter are composed of N-monosubstituted rather than N,N-disubstituted amide groups.

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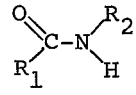
Monosubstituted amides (2) could have different barriers than



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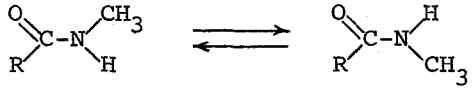
their disubstituted analogues (1) due to differences in steric effects, and hydrogen bonding interactions available to the N-H proton. For example, we have shown that hydrogen bonding to the carbonyl oxygen increases the C-N rotational barriers of N,N-dimethyl amides.[2a] It has also been recently reported that the C-N barrier for unsubstituted formamide is 3 kcal/mole lower than that for N,N-dimethylformamide.[3]

Virtually no rotational barrier data are available for monosubstituted amides (2).[1a] The requisite n.m.r. kinetic studies are complicated because the two rotational isomers (e.g., 3a and 3b) are present in different amounts and because in many cases



3a 3b

the minor isomer 3b is almost completely absent.[4] The spectra are further complicated by NH,NCH_3 and R,NCH_3 proton spin-coupling.[4]

We now report the results of a study of C-N rotational barriers in N-methylformamide (NMF) (3, R=H). This compound was chosen because the minor isomer 3b is present in sufficient concentration (ca. 10%). Spin-coupling was minimized by use of NMF-d_1 ($DCONHCH_3$) and NMF-d_2 ($DCONDCH_3$). The data are contrasted with those for formamide and for N,N-dimethylformamide, and suggest that barriers for N-methyl amides and their N,N-dimethyl derivatives may be similar.

Materials and Methods

N-Methylformamide-d_1 (DCONHMe) was synthesized from DCOOH and methylamine; b.p. 95°/20 mm; n.m.r. (ref. TMS) doublet (area 9) 2.78 δ (J = 5.0 Hz.), doublet (area 1) 2.92 δ (J = 5.0 Hz.). N-Methylformamide-d_2 (DCONDMe) was synthesized by treatment of DCONHMe with several portions of D_2O; b.p. 98.5°/20 mm; n.m.r. (ref. TMS) singlet (area 9) 2.79 δ, singlet (area 1) 2.92 δ. Undeuterated N-methylformamide samples obtained commercially or synthesized by reaction of methylamine and formic acid were identical; b.p. 96°/19 mm; n.m.r. (ref. TMS) multiplet (area 9) 2.77 δ (J = 5.0 Hz., J = 0.9 Hz.), doublet (area 1) 2.92 δ (J = 4.4 Hz.). Formamide-d_2 ($HCOND_2$) was obtained by treatment of formamide with several portions of D_2O; b.p. 90°/6 mm.

Variable temperature n.m.r. spectra were obtained using a Varian A-60D spectrometer. Temperatures were calibrated as previously described.[2] Kinetic analysis was performed using the complete two-site exchange equation of Gutowsky and Holm as modified by Rogers and Woodbrey to accommodate unequal values of T_2 for the two signals.[2] Final rate constants were selected by visual comparison of experimental and theoretical spectra in the same manner as in our earlier studies.[2] The resultant activation parameters (see Table I) were derived from an extensive collection of kinetic data: entry 1, 19 points, 60° range; entry 2, 11 points, 47° range; entry 3, 20 points, 60° range; entry 4, 7 points, 19° range.

Results and Discussion

N.m.r. spectra of N-methylformamide (NMF) and its deuterated derivatives NMF-d_1 and NMF-d_2 in neat solution and a variety of solvents show two NCH_3 resonance signals in the ratio 9 to 1.

Table I. Activation Parameters for C-N Rotation in N-Methylformamide (NMF), Formamide (F), and N,N-Dimethylformamide (DMF).[a]

No.	Amide	Solvent[b]	E_a (kcal/mole)	log A	ΔF^*_{298} (kcal/mole)	$\Delta\Delta F^*_{298}$[c] (kcal/mole)	ΔF^o_{298}[d] (kcal/mole)
1	NMF-d_1	neat[e]	23.6±0.6 23.7±0.5	14.0±0.4 15.0±0.3	22.0 20.7	1.3	1.4
2	NMF-d_2	neat[f]	25.0±1.2 24.3±0.8	14.9±0.7 15.4±0.5	22.1 20.7	1.4	1.4
3	NMF-d_2	f-d_2[f]	25.6±0.7 24.3±0.7	15.1±0.4 15.2±0.4	22.4 21.0	1.4	1.3
4	NMF-d_2	f-d_2[g]	22 26	13 16	22.2 21.6	0.6	1.3
	F	diglyme[h]	19.7±0.2	14.2	17.8		
	DMF	neat[i]	20.5±0.2	12.7	20.6		
		neat[j]	20.8±0.6	13.2	20.2		
		neat[j]	21.6±2.7	13.5	20.7		

(a) For NMF entries, first and second lines of data correspond to isomers 3a and 3b, respectively. (b) f-d_2 = formamide-d_2. (c) $\Delta\Delta F^* = \Delta F^*(3a) - \Delta F^*(3b)$. (d) Determined from isomer populations. (e) Contained trace amounts of methylamine. (f) Contained trace amounts of NaOD. (g) No base added. (h) Reference 3. (i) Reference 5a. (j) Reference 5b.

These correspond to isomers 3a and 3b respectively. On heating, they reversibly broaden and coalesce into a single NCH_3 resonance in a manner characteristic of rotational interconversion.

Deuterium substitution in NMF simplified the n.m.r. spectra, but broadened NCH_3 lines from unresolved ND,NCH_3 spin-coupling were still present. Kinetic analysis was facilitated by the introduction of trace amounts of base into the samples. The base catalyzed ND (or NH) exchange leading to sharp NCH_3 singlets. That it did not catalyze C-N rotation is implied by: (1) the independence of the activation parameters on the nature of the base (Table I, entries 1 and 2); (2) the observed independence of rate constants on concentration of base; and (3) the similarity of the activation parameters in the presence and absence of added base (Table I, compare entries 1, 2 and 3, with

4). The latter parameters (entry 4) possess relatively large errors due to the unresolved ND,NCH_3 coupling since base was not present.

The rotational free energy of activation (ΔF^*) for the major isomer is greater than that for the minor isomer (ca. 1.4 kcal/mole) as expected. The differences between the free energies of activation ($\Delta\Delta F^*$) correspond closely to values of ΔF^o for isomer equilibrium calculated from the relative populations providing support for the kinetic data. The values of ΔF^* are slightly greater in the solvent formamide than in neat solution as observed in previous studies by us on N,N-dimethyl amides.[2a] In all cases the frequency factors are reasonably normal.[2]

The barriers for NMF are similar to those for N,N-dimethylformamide (DMF)[5] but somewhat larger than those recently reported for unsubstituted formamide (F)[3] (Table I). This difference could be due to a combination of steric, hydrogen bonding, and general solvent effects. However, the N-H protons served as the spectral probes in the study of formamide, and NH exchange could have led to errors in the C-N rotational barrier.[3] The similarity in the data for NMF and DMF suggest that good C-N rotational barrier data for N,N-dimethyl amides can be used as reasonable approximations to those for the corresponding monosubstituted systems. Thus, while C-N rotational barriers in proteins and peptides may be different than those for simple amides, monosubstituted amides will probably serve no better than their disubstituted derivatives as C-N barrier models.

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