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THE BARRIER TO INTERNAL ROTATION IN AMIDES. VI. ACETAMIDE. SOLVENT DEPENDENT ENTROPY OF ACTIVATION.*

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In our series of pmr studies of the torsional barrier in the peptide bond we have previously considered the parent primary amide, formamide[1a], and several secondary[1b] and tertiary amides[1c]. The rotational barriers in primary and secondary amides are difficult to determine accurately by means of pmr line shape methods. For the primary amides the evaluation of the intramolecular rate process is aggravated by the very broad amino proton signals, the result of ^{14}N quadrupolar relaxation, while for secondary amides, the population ratio is, in most solvents, far from unity, thus rendering the observation of the smaller signal very difficult. The difficulty due to the broad amino signal can be circumvented in two ways: either by the use of ^{14}N heteronuclear double resonance[2,3] or the use of ^{15}N enriched amides[1a,4-6].

In the present paper we wish to report the results of a study of the barrier to internal rotation in acetamide dissolved in acetone (0.5M) and DMF (1.5M). The ^{14}N resonance has been irradiated with a strong radiofrequency field in order to simplify the proton resonance spectrum. The signals of the high field portion of this AB spectrum are broader than those of the low field portion, due to a differential coupling between the methyl protons and the amino protons of 0.6 Hz. The coupling constant, J_{AB}, is found to be 2.8 Hz in good agreement with the value for formamide[1a,2,4,6], the shift, $\Delta\nu_{AB}$, is

*Part V in this series is ref. 1b.

however, much larger for acetamide than for formamide, 0.54 ppm vs. 0.24 ppm in ketonic solutions.

The rotational rate constants were evaluated by comparison of experimental and calculated line shapes of the amino proton spectrum. To obtain the calculated spectra, the equation for an AB spectrum given by Alexander[7] was used; in order to account for the coupling between the methyl group protons and the amino protons, the final spectrum was taken to be the sum of four AB spectra with intensities as 1:3:3:1.

The activation parameters were calculated in the usual manner[1c] from the Eyring equation[8], and are given in the Table.

Table.

Activation parameters for hindered internal rotation in acetamide.

Solvent	Amide conc. M	T_c °C	$\Delta\nu_{T_c}$ Hz	$\Delta G^{\neq}_{298}$ kcal/mol	$\Delta H^{\neq}$ kcal/mol	$\Delta S^{\neq}$ cal/mol.K
DMF	1.5	73	66	17.3	20.1	9
Acetone	0.5	60	56	16.7	18.2	5

As long as the intermolecular proton exchange rate is slow (less than 1 sec^{-1}), fine structure on the methyl signal due to coupling with the amino protons can be observed; at low temperature a doublet (J = 0.6 Hz) and at higher temperatures, i.e. above 30°C, a triplet (J = 0.3 Hz). The triplet was observable for all temperatures used in this investigation, thus insuring that intermolecular proton exchange does not contribute to the broadening of the amino proton signals.

The barrier ($\Delta G^{\neq}_{298}$) to internal rotation in acetamide (acetone solvent) is ca. 1 kcal/mol lower than in formamide (methylpropylketone solvent). The steric effects are presumably very small and therefore the change in barrier height may be interpreted as being caused by the "electronic effect" of the methyl group, which can be looked upon as a preferential stabilization of the transition state over the ground state, that is a decrease in the double bond

character of the peptide linkage due to electron donation from the methyl group.

When reliable methods have been used to determine the torsional barrier in tertiary amides, the entropy of activation is always found to be close to zero, even when protic solvents are used[1c,9-11]. For acetamide in DMF, however, $\Delta S^{\neq}$ is found to be ca. 9 cal/mol.K; similar values may be calculated from the data of Newman et al.[12] for neat NMF and NMF in formamide. This large positive entropy of activation may be attributed to the breaking of the hydrogen bond between the NH proton(s) of the amide bond and the solvent carbonyl group in the rotational process. The observed zero entropy of activation for the torsional barrier in tertiary amides dissolved in protic solvents indicates that the hydrogen bonding between the carbonyl group of the amide bond and the solvent protons is not broken in the internal rotation. Siddall et al.[11] have, however, argued that a large positive entropy of activation is not expected in such hydrogen bonded systems, since the interaction is extended over large domains and the rupture of one hydrogen bond, in the rotational process, should not appreciably change the total order of the domain. With this model there is no reason to expect a large positive entropy of activation when the amino proton(s) of the peptide bond take part in hydrogen bonding to the solvent. Since the interaction domains are very similar for DMF in formamide (zero entropy of activation)[10] and acetamide in DMF ($\Delta S^{\neq}$ = 9 cal/mol.K), we believe that this divergence is caused by a breaking of the NH to solvent hydrogen bond in the former, while the C=O to solvent hydrogen bond is maintained in the latter during the internal rotation.

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