Multiple-Substituent Parameter Analysis of the Effects of Substituents at Nitrogen on the Barriers to Rotation in Amides

Claude H. Yoder* and Roblyn D. Gardner

Department of Chemistry, Franklin and Marshall College, Lancaster, Pennsylvania 17604

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The free energies of activation for rotation about the carbonyl–nitrogen bond in a series of 14 tertiary formamides and 12 tertiary acetamides were correlated with steric (E_s,υ), inductive (σ_I, σ^*), and resonance (σ_R) parameters. In all cases the steric parameter was the most significant variable, i.e., accounted for more of the variability in $\Delta G^{\ddagger}$. The best correlation was obtained for the *N*-methylacetamides where $R = 0.987$ and the standard error was 0.24. The correlation for the combined set of formamides and acetamides was improved by accounting for the carbonyl methyl group of the acetamides by adding the steric parameter for the methyl group but substracting the inductive and resonance parameters for the methyl group from the parameters for the substituents of the nitrogen. The $\Delta G^{\ddagger}$'s for *N*-methylformamide and -acetamide calculated from the regression equation were higher than the experimental values, suggesting that hydrogen bonding lowers the free energies of activation.

Although substituents are generally believed to affect the rotational barriers in amides by some combination of steric and electronic effects,[1,2] the interplay of these effects has been quantitatively explored only for substitution at the carbonyl carbon.[3,4] The results of these studies revealed that $\Delta G^{\ddagger}$ for the rotational process could be correlated with the steric parameter, υ, and σ_I and σ_R^-, and that the steric effect was of considerably greater importance in explaining the barrier than the inductive effect.

A qualitative examination of the available barriers for amides with simple substituents at nitrogen indicates the following: (a) an increase in size of the substituent on nitrogen lowers the barrier ($\Delta G^{\ddagger}$) to rotation in acetamides,[1,2] but in formamides this trend is barely discernible;[5,6] (b) an increase in electron-withdrawing ability of the substituent appears to increase the barrier[1,5] although this generalization is drawn from comparisons of only a few cases such as $HCON(CH_3)_2$ (for which $\Delta G^{\ddagger}$ = 20.6 kcal/mol[7]) and $HCON(CH_3)CH_2CH_2Cl$ (for which $\Delta G^{\ddagger}$ = 21.6 kcal/mol[8]); (c) an increase in resonance delocalization of electron density from the nitrogen to the substituent probably decreases the barrier, although this generalization is also based on only a few comparisons such as $CH_3CON(CH_3)_2$ ($\Delta G^{\ddagger}$ = 18.1 kcal/mol[9]) and $CH_3CON(CH_3)CH{=}CH_2$ ($\Delta G^{\ddagger}$ = 16.6 kcal/mol[8]), where steric, inductive, and resonance effects cannot easily be disentangled.

The present study was designed to determine whether the barriers to rotation in a variety of nitrogen-substituted amides could be correlated with substituent steric and electronic parameters by multiple regression analysis and, if so, to determine which effects are more significant in explaining the variation in barriers. Finally, these results can be contrasted to those obtained previously for substitution at the carbonyl carbon.

Results and Discussion

It is now firmly established that free energies of activation for rotation are much less sensitive to experimental and calculational errors than other activation parameters such as $\Delta H^{\ddagger}$ and E_a.[1,2] The free energy of activation is also usually not strongly dependent upon temperature and therefore $\Delta G^{\ddagger}$ at the coalescence temperature was chosen as the activation parameter to be used as the dependent variable in the analyses. Actually a more pragmatic consideration also dictated its use—many of the earlier barrier studies employed approximate methods which can produce only $\Delta G^{\ddagger}$ at the coalescence temperature. All but a few studies of unsymmetrical N,N-disubstituted amides also used an approximate equation suitable only for the equal population case.[10] Because the populations of the two rotamers were in most cases not very disparate, this probably does not produce large errors in $\Delta G^{\ddagger}$. In the few cases where the free energies of activation of unsymmetrical amides were calculated either by total line shape analysis or approximate methods (such as that of Shanan-Atidi and Bar-Eli[11]) which incorporate rotamer populations, the free energies of activation at coalescence were recalculated by using the equation $k = (\pi/2^{1/2})(\Delta\nu)$ and the Eyring equation. The following free energies of activation (kcal/mol) were judged to be the most reliable of those reported in the literature (recalculated values are designated by an asterisk) for $HCONR^1R^2$: ($R^1 = R^2 = CH_3$, 20.6;[7] $R^1 = R^2 = CH_3CH_2$, 20.9;[6] $R^1 = R^2 = (CH_3)_2CH$, 20.6;[6] $R^1 = R^2 = (CH_3)_2CHCH_2$, 21.0;[6] $R^1 = R^2 = Si(CH_3)_3$, 11.6;[12] $R^1 = CH_3$, $R^2 = CH_2{=}CH$, 20.1;*[8] $R^1 = CH_3$, $R^2 = C_6H_5CH_2$, 21.6;[13] $R^1 = (CH_3)_2CH$, $R^2 = C_6H_5CH_2$, 21.7;[14] $R^1 = C_6H_5$, $R^2 = (CH_3)_2CH$, 18.2;[15] $R^1 = C_6H_5$, $R^2 = (CH_3)_3C$, 18.1;*[5] $R^1 = C_6H_5$, $R^2 = CH_3CH_2$, 18.0;*[5] $R^1 = (C_6H_5)_2CH$, $R^2 = CH_3$, 20.0;[15] $R^1 = ClCH_2CH_2$, $R^2 = CH_3$, 21.6;*[8] $R^1 = (CH_3)_3Si$, $R^2 = CH_3$, 19.15.*[16] For $CH_3CONR^1R^2$: $R^1 = R^2 = CH_3$, 18.1;[9] $R^1 = R^2 = CH_3CH_2$, 17.75;[6] $R^1 = R^2 = (CH_3)_2CH$, 16.2;[6] $R^1 = CH_3$, R^2 =

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Table I. Multiple Regression of $\Delta G^{\ddagger}$ with Steric, Inductive, and Resonance Parameters

		variables in equation[b]			F values[c]			coefficients[d]						
	n[a]	1	2	3	1	2	3	1	2	3	const[d]	F[e]	S[f]	R[g]
formamides	14	E_s	σ_I	σ_R	32	5.8	0.08	1.48	10.63	−0.99	26.02	17.0	1.21	0.914
N-methyl	6	υ	σ^*	σ_R	8.9	4.7	1.9	−2.14	2.11	2.94	23.84	4.1	0.57	0.927
excluding isobutyl and phenyl derivatives	10	E_s	σ_I	σ_R	21	6.1	0.02	1.66	11.87	0.42	26.85	21.7	1.06	0.957
acetamides	12	υ	σ^*	σ_R	57	14	0.0	−3.18	1.38	0.06	21.63	20.6	0.38	0.941
N-methyl	8	υ	σ^*	σ_R	139	37	4.5	−3.35	2.02	1.75	22.22	48.8	0.24	0.987
formamides and acetamides	26	E_s	σ_I	σ_R	5.2	3.9	0.07	0.79	9.86	−0.95	21.68	3.6	2.0	0.573
h	26	E_s	σ^*	σ_R	36	3.4	3.7	1.52	1.51	−4.20	24.49	18.0	1.31	0.843

[a] Number of compounds in series. [b] Variables in regression equation $\Delta G^{\ddagger} = aV_1 + bV_2 + cV_3 +$ constants. [c] F values for variables when entered simultaneously. [d] Coefficients and constant in regression equation. [e] F value for overall correlation. [f] Standard error. [g] Multiple correlation coefficients. [h] Addition of steric parameters, subtraction of electronic parameters for methyl group with acetamides (see text).

CH_3CH_2, 18.0;[9] $R^1 = CH_3$, $R^2 = CH_3CH_2CH_2CH_2$, 17.9;[9] $R^1 = CH_3$, $R^2 = (CH_3)_2CH$, 17.0;[9] $R^1 = R^2 = C_6H_5CH_2$, 17.14;[17] $R^1 = CH_3$, $R^2 = CH_2{=}CH$, 16.6;*[8] $R^1 = CH_3$, $R^2 = ClCH_2CH_2$, 18.1;*[8] $R^1 = CH_3$, $R^2 = C_6H_5CH_2$, 18.3;[14] $R^1 = C_6H_5CH_2$, $R^2 = (CH_3)_2CH$, 17.45;[14] $R^1 = CH_3$, $R^2 = (CH_3)_3Si$, 15.1.[16]

The steric parameters employed in the multiple regression analyses included Charton's υ values[18] and E_s values.[19] σ_I[20] and σ^*[21] were selected as inductive parameters, while σ_R ($\sigma_R = \sigma_P$[22] $-\sigma_I$) was used to represent the resonance effect. Use of σ_R° or σ_R^- values[23] in place of σ_R did not significantly improve correlation. The use of molar refractivities[19] in place of any one of the other parameters (steric, inductive, or resonance) also did not significantly improve the correlation. A variety of constants could not be found and were consequently estimated: E_s $CH_2{=}CH$ (−2.99) and υ $(CH_3)_2CHCH_2$ (0.93), both obtained from a least-squares relation between E_s and υ; σ_R $C_6H_5CH_2$ (0.006) calculated from the correlation of the acidities of naphthoic acids[24] with σ_I and σ_R; σ_R $(C_6H_5)_2CH$ (0.012) estimated as $2 \times \sigma_R(C_6H_5CH_2)$; σ_P $CH_2{=}CH$ (−0.243) obtained from the least-squares relation between σ_G[25] and σ_P; σ_P $ClCH_2CH_2$ (0.067) obtained from $\sigma_P(ClCH_2) \times [\sigma^*(ClCH_2CH_2)]/[\sigma^*(ClCH_2)]$.

Table I presents the results of correlations of $\Delta G^{\ddagger}$ with these parameters. For each series of compounds at least four different sets of three independent variables (E_s, σ_I, σ_R; E_s, σ^*, σ_R, υ, σ_I, σ_R; υ, σ^*, σ_R) were used in separate correlations. Only the results of the best correlation, as measured by its F value, are reported in the table. The F values for each variable provide a means of assessing the significance of each variable in the equation (that is the relative extent to which it accounts for the variability in the dependent variable, $\Delta G^{\ddagger}$). The coefficients of the variables are those in the regression equation $\Delta G^{\ddagger} = aV_1 + bV_2 + cV_3 +$ constant.

Correlations involving unsymmetrical tertiary amides are complicated by the fact that the effects of two different substituents on nitrogen must be taken into account. Although these effects are probably not strictly additive, the assumption of additivity is certainly the simplest solution to the problem. Hence the values of the steric, inductive, and resonance parameters used in the correlations are actually sums of the values for each nitrogen substituent.

As indicated in Table I, the best correlation of $\Delta G^{\ddagger}$ for all 14 formamides was obtained with the variables E_s, σ_I, and σ_R. The F value for each variable reveals that the steric parameter accounts for more of the variability in $\Delta G^{\ddagger}$ than the other parameters. The second most significant variable is the inductive parameter. With few exceptions, the same trend was observed in all the series, regardless of the steric (E_s or υ) and inductive (σ_I or σ^*) constants employed.

When the correlations were performed for only the *N*-methylformamides, the correlation coefficient increased and the standard error decreased, but the set consists of only six members. When the phenyl and isobutyl derivatives were excluded, the correlation also improved. The reason for this is not clear. The steric and electronic constants for these groups were adjusted through a fairly broad range, but no marked improvement in the correlation resulted. It is possible that some other interaction is important in these derivatives. Indeed these groups are among the largest and most polarizable in all the series. However, as indicated above, the inclusion of a "polarizability" constant (the molar refractivity) did not improve the correlations significantly.

With the acetamides, the correlations were significantly better with a standard error of only 0.4, approximately the same as the experimental error involved in the measurement of $\Delta G^{\ddagger}$. The significance of the correlations was maximized by using υ as the steric parameter and σ^* as the inductive parameter. The correlation of just the *N*-methyl derivatives was again significantly better, perhaps an indication that the additivity of constants is not completely justified. (In the *N*-methyl series, the methyl group is present in all members of the series and therefore additivity is of no consequence.)

The final entries in Table I report the correlations obtained for the set ($n = 26$) containing *both* the formamides and acetamides. As expected, the correlation of $\Delta G^{\ddagger}$ with the steric, inductive, and resonance parameters used in the previous correlations is poor. The formamides and acetamides differ by a methyl group attached to the carbonyl, a difference that affects $\Delta G^{\ddagger}$ by the greater size and electron-releasing effect of the methyl group. In an attempt to compensate for the carbonyl methyl group in the acetamides another correlation was performed with steric

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parameters to which the E_s or v value of a methyl group was added and with electronic parameters (σ_I, σ^*, and σ_R) from which the σ_I, σ^*, or σ_R value of a methyl group had been subtracted. For example, the E_s value used for dimethylacetamide was $E_s = 3E_s(CH_3)$, whereas σ_I was taken as $\sigma_I = 2\sigma_I(CH_3) - \sigma_I(CH_3)$. Subtraction of the CH_3 electronic parameter was dictated by the opposite effects of substituents at the carbonyl as opposed to the nitrogen. Electron-releasing substituents at the carbonyl lower the barrier, whereas at nitrogen they increase the barrier. The correlation obtained with this procedure was definitely superior and produced a standard error only slightly worse than that obtained with the formamide series.

All of the correlations discussed above involved only tertiary amides. When a secondary or primary amide such as *N*-methylformamide or acetamide was included in the correlations the correlations decreased dramatically. The value of $\Delta G^{\ddagger}$ for *N*-methylacetamide calculated from the regression equation for *N*-methylacetamide (for which $R = 0.987$, $S = 0.24$, $F = 49$) is 21 kcal/mol, a value that is 3 kcal/mol higher than the 18.0 kcal/mol value reported.[26] Similar results were obtained for formamide and *N*-methylformamide (8 and 3 kcal/mol, respectively, higher than literature values)[27,28] from the regression equation. Several explanations for these "high" barriers can be postulated: (a) that the steric, inductive, and resonance parameters for hydrogen lead to significant deviations from the regression "line" (it is well-known that the parent, unsubstituted derivative often exhibits the greatest deviation from the least-squares line in Hammett-type plots) and (b) that hydrogen bonding or other interactions not accounted for by the steric and electronic parameters lower the barrier to rotation. The second explanation requires that hydrogen bonding (or other interaction) lowers the energy of the transition state relative to the ground state or causes an increase in the entropy of activation. Although this is possible through hydrogen bonding to the sp^3 nitrogen of the transition state, most studies of the effect of hydrogen bonding on rotational barriers have suggested that hydrogen bonding of protic agents with tertiary amides lowers the energy of the ground state thereby increasing the barrier.[29,30] On the other hand, fairly large entropies of activation have been reported for acetamide and *N*-methylformamide and -acetamide in dimethylformamide where hydrogen bonding of the NH protons to the tertiary amide is presumably broken during the rotational process.[31] Intramolecular hydrogen bonding has also been found to lower $\Delta G^{\ddagger}$ in *o*-hydroxy- and *o*-amino-*N*,*N*-dialkylbenzamides.[32]

Finally, although it would be interesting to contrast the effect of substituents at nitrogen with their effect when attached to carbonyl, this is difficult because of (a) the small number of barriers reported for the same substituent at both sites and (b) the difference in significance of the correlations reported for both sites. It is probably true, however, that the steric effect is the most significant determinant of $\Delta G^{\ddagger}$ at both sites.

Registry No. *N*,*N*-Dimethylformamide, 68-12-2; *N*,*N*-diethylformamide, 617-84-5; *N*,*N*-bis(1-methylethyl)formamide, 2700-30-3; *N*,*N*-bis(2-methylpropl)formamide, 2591-76-6; *N*,*N*-bis(trimethylsilyl)formamide, 15500-60-4; *N*-ethenyl-*N*-methylformamide, 2867-48-3; *N*-methyl-*N*-(phenylmethyl)formamide, 17105-71-4; *N*-(1-methylethyl)-*N*-(phenylmethyl)formamide, 20278-21-1; *N*-(1-methyl)-*N*-phenylformamide, 52008-97-6; *N*-(1,1-dimethylethyl)-*N*-phenylformamide, 52008-98-7; *N*-ethyl-*N*-phenylformamide, 5461-49-4; *N*-(diphenylmethyl)-*N*-methylformamide, 75700-33-3; *N*-(2-chloroethyl)-*N*-methylformamide, 14578-77-9; *N*-methyl-*N*-(trimethylsilyl)formamide, 13889-02-6; *N*,*N*-dimethylacetamide, 127-19-5; *N*,*N*-diethylacetamide, 685-91-6; *N*,*N*-bis(1-methylethyl)acetamide, 759-22-8; *N*-ethyl-*N*-methylacetamide, 38806-26-7; *N*-butyl-*N*-methylacetamide, 10601-67-9; *N*-methyl-*N*-(1-methylethyl)acetamide, 41273-79-4; *N*,*N*-bis(phenylmethyl)acetamide, 10479-30-8; *N*-ethenyl-*N*-methylacetamide, 3195-78-6; *N*-(2-chloroethyl)-*N*-methylacetamide, 17225-69-3; *N*-methyl-*N*-(phenylmethyl)acetamide, 29823-47-0; -(1-methylethyl)-*N*-(phenylmethyl)acetamide, 55578-20-6; *N*-methyl-*N*-(trimethylsilyl)acetamide, 7449-74-3.

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