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AN AB INITIO TREATMENT OF THE DEPENDENCE ON AMINE BASICITY OF THE RELATIVE ENERGIES OF NEUTRAL ORTHOAMIDE INTERMEDIATES IN AMIDE HYDROLYSIS.

C.-H. Lam*, R.H. Kluger and I.G. Csizmadia

Department of Chemistry, University of Toronto, Toronto, Ontario, Canada.

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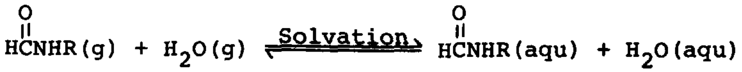
The rates of hydrolysis of amides derived from amines of varying basicities should be affected by these basicities. One important factor that is difficult to measure experimentally is the dependence of the free energy of addition of water to the amide on the basicity of its amine moiety. We have used an ab initio molecular orbital calculation to arrive at a linear free energy relationship between hydration energy and basicity. We have been able to use this information to analyze some cases in which this relationship leads to observable rate constant dependencies[1].

Consider the following thermochemical cycle:

$$\mathrm{H\overset{O}{\overset{\|}{C}}NHR(aqu) + H_2O(aqu) \xrightleftharpoons{Addition} HC(OH)_2NHR(aqu)}\quad \text{(orthoamide)} \qquad (1)$$



$$\mathrm{H\overset{O}{\overset{\|}{C}}NHR(g) + H_2O(g) \xrightleftharpoons{Solvation} H\overset{O}{\overset{\|}{C}}NHR(aqu) + H_2O(aqu)} \qquad (2)$$

$$\mathrm{HC(OH)_2NHR(aqu) \xrightleftharpoons{Desolvation} HC(OH)_2NHR(g)} \qquad (3)$$

$$\mathrm{H\overset{O}{\overset{\|}{C}}NHR(g) + H_2O(g) \xrightleftharpoons{Addition} HC(OH)_2NHR(g)} \qquad (4)$$

Then for any substituent R:

$$\Delta G^\circ(1) = \Delta G^\circ(4) - \Delta G^\circ(3) - \Delta G^\circ(2) \qquad (5)$$

and the change in the free energy upon change of substituent R:

$$\Delta\Delta G^\circ(1) = \Delta\Delta G^\circ(4) - \Delta\Delta G^\circ(3) - \Delta\Delta G^\circ(2). \qquad (6)$$

If the effect of substituent group on the changes of solvation and desolvation energies of amide and orthoamide are similar, i.e. $-\Delta\Delta G^\circ(3) \simeq \Delta\Delta G^\circ(2)$, we have

$$\Delta\Delta G^\circ(1) \simeq \Delta\Delta G^\circ(4). \qquad (7)$$

Furthermore, the difference of the change of entropy for equation (4) should be independent of substituent groups[2]. (Changes of degrees of freedom for translation, rotation, vibration and symmetries due to substitution are the same for the reactants and the products.) Thus, equation (8) should be a good approximation for the addition reaction.

$$\Delta\Delta G^\circ(\text{Addition}) \simeq \Delta\Delta E_T(\text{Addition}) \qquad (8)$$

With the total energies of all the molecules calculated by ab initio MO methods, we can relate the change in energy due to addition of water to a formamide molecule to the basicity of its substituent group. Since $\Delta G^\circ = -RT\ln K$, the plot of ΔG° of addition vs ΔG° of protonation should give the same slope as a plot for corresponding logarithmic values of equilibrium constants.

All calculations were performed by using a minimal basis set Gaussian 70 STO-3G approximation[3,4]. Our calculations give the following values for E_{Total} (a.u.): H_2O, -74.9590; $H\overset{O}{C}NH_2$, -166.68461; $HC(OH)_2NH_2$, -241.70246; $H\overset{O}{C}NHF$, -264.09105; $HC(OH)_2NHF$, -339.11605; $H\overset{O}{C}NHCH_3$, -205.26247; $HC(OH)_2NH_3CH_3$, -280.27904; $H\overset{O}{C}NHOH$, -240.48014; $HC(OH)_2NHOH$, -315.50177. A plot[5] of $\Delta\Delta E$ vs $\Delta G^\circ(PA)$[6] is shown in Fig. 1.

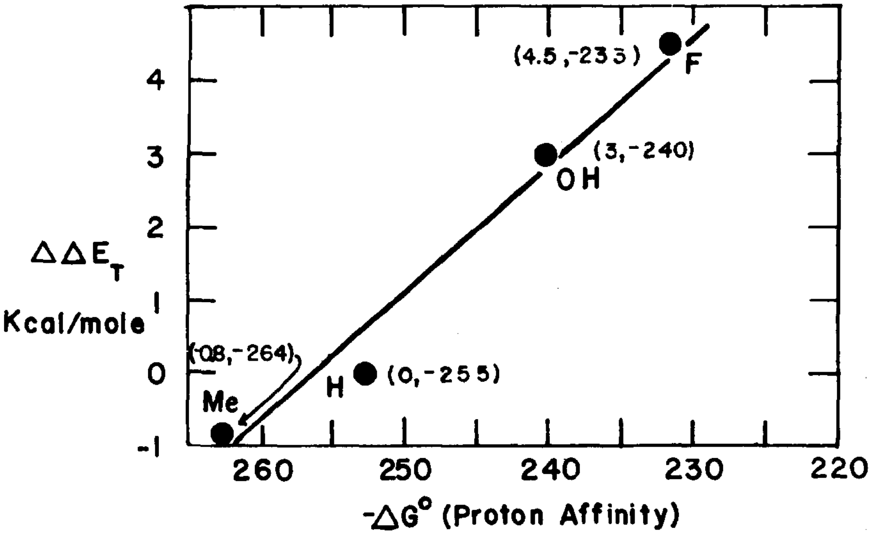


Figure 1. Energy of intermediate formation as a function of proton affinity, calculated for N-substituted formamides vs. N-substituted amines (gas phase). "Proton Affinity" refers to the amine from which the amide is derived and "E_T" refers to the tetrahedral addition product of water and amide.

There are several examples of calculations of other systems by simple MO treatments which gave successful accounts of the energy changes associated with simple reactions[7]. In the present study, the total energy of $H\overset{O}{\overset{\|}{C}}NH_2$ calculated is -166.68461 hartrees. A value of -168.872 hartrees was arrived at using a more sophisticated method for the same molecule[8]. When relative energies are used, systematic errors cancel. A plot of $\Delta\Delta E$(Addition) vs $\Delta G°$(protonation) of four differently substituted amines gives a linear correlation with a slope of 0.18 (correlation coefficient, 0.990).

By applying a thermochemical cycle, Guthrie[9] was able to estimate the free energies of addition of water to N,N-dimethyl formamide and acetamide. However, to our knowledge, no theoretical determination of free energies of water addition to formamide as a function of varying basicities of the substituent amines has been reported. Based on estimates from experimental data involving protonation of an amide followed by addition of hydroxide ion, we can estimate the value of the correlation slope to be 0.2 for addition of water to an amide.[10] Our calculated correlation slope of 0.18 for addition of water to formamides in the gas phase, however, is based on calculated gas phase amine basicities[6]. Solvation appears to deattenuate relative amine basicities, by stabilizing charged species[11]. We can expect a higher value for a correlation slope in solution, on the order of a factor of two[11], because the solvation of neutral amides and orthoamides will not be deattenuated. More refined calculations should resolve these discrepancies.

Acknowledgement

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References

1. R. Kluger and C.-H. Lam, J. Am. Chem. Soc., 98, 4154 (1976).
2. J. Hine "Structural Effects on Equilibria in Organic Chemistry", John Wiley & Sons, Inc., New York, New York, 1975; Sec. 1-2C.
3. W.J. Hehre, R.F. Stewart and J.A. Pople, J. Chem. Phys., 51, 2657 (1969).
4. The following molecular geometries are used: (a) All the bond angles were set to 120° or 109.5°. (b) For $H\overset{\overset{O}{\|}}{C}NH_2$, all bond lengths were subjected to bond length optimization by the program. (c) All C-H and N-H bond lengths for substituted formamides were taken from the formamide molecule without further optimization. (d) Geometry for $HC(OH)_2NH_2$ was taken from Ref. (5). The C-H, N-H, O-H bond lengths were kept constant without further optimization. (e) The C-H bond length in the methyl group was set to 1.10 Å (f) All molecules were subjected to C-O, C-N and N-X (X = F, OH, CH_3) bond length optimization.
5. A.C. Hopkinson, R.A. McClelland, K. Yates and I.G. Csizmadia, Theoret. Chim. Acta (Berl.) 13, 65 (1969).
6. A.C. Hopkinson and I.G. Csizmadia, Theoret. Chim. Acta (Berl.) 34, 93 (1974).
7. (a) W.J. Hehre, R. Ditchfield, L. Radom and J.A. Pople, J. Am. Chem. Soc., 92, 4796 (1970).
   (b) W.A. Lathan, W.J. Hehre and J.A. Pople, J. Am. Chem. Soc., 93, 808 (1971).
8. M.A. Robb and I.G. Csizmadia, J. Chem. Phys., 50, 1819 (1969).
9. J.P. Guthrie, J. Am. Chem. Soc., 96, 3608 (1974).
10. See reference 1, pp. 4156-4157 for our procedure.
11. D.H. Aue, M H. Webb, M.T. Bowers, C.L. Liotta, C.J. Alexander, and H.P. Hopkins, Jr., J. Am. Chem. Soc., 98, 854 (1976). D.H. Aue, H.M. Webb, and M.T. Bowers, J. Am. Chem. Soc., 98, 318 (1976).