York, N.Y., 1973, for several cogent discussions). The mere fact that the thermodynamic properties of solvation for an homologous series of organic ions are correlated with their reciprocal volumes or reciprocal radii cannot by itself justify the invocation of a simple electrostatic interpretation.

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Novel Activation Parameters and Catalytic Constants in the Aminolysis and Methanolysis of *p*-Nitrophenyl Trifluoroacetate[1]

Sir:

We wish to report here that the third-order reaction of *n*-butylamine with *p*-nitrophenyl trifluoroacetate is accompanied by substantial *negative* activation energies when carried out in both chlorobenzene and 1,2-dichloroethane solvents. Although small negative activation energies are known, we are not aware of any previous report of one of the present magnitude[2,3] (ca. −10 kcal). Table I records the third-order rate constants and activation parameters. Conventional stopped-flow kinetic methods have been used to obtain the kinetic results.

In contrast, a normal (but small) positive activation energy is observed for the methanolysis of *p*-nitrophenyl trifluoroacetate in aprotic solvent containing methanol. Rate constants obtained from 13.5 to 37.8° in 1,2-dichloroethane containing 4.92 *M* methanol give: $E_a = 5.0$ kcal; $\Delta G^{\ddagger} = 18.3$ (298 °K); $\Delta H^{\ddagger} = 4.4$ kcal; $\Delta S^{\ddagger} = -46.7$ eu.

The aminolysis of *p*-nitrophenyl acetate in polar aprotic solvents has been studied recently by the groups of Watson and of Menger. Watson[4] reports the reaction to be catalyzed by general bases, but, rather than Brönsted law catalysis, the third-order catalytic constants are closely correlated by the hydrogen-bonding parameters, pK_{HB}.[5] Menger[6] has observed very large meta- and para substituent effects in the aminolysis of phenyl acetate esters in aprotic solvents. This and other observations have led Menger to conclude that the reaction proceeds through a zwitterionic tetrahedral intermediate.[6,7]

We have also found general base catalysis of the *n*-butyl aminolysis of *p*-nitrophenyl trifluoroacetate in aprotic solvents. First-order kinetics with respect to each ester, *n*-butylamine, and catalyst are observed. The third-order catalytic constants, however, do not follow the Brönsted catalysis law, as may be seen from the data of Table II. The only satisfactory correlation of the third-order catalytic constants which we have been able to find is shown in Figure 1, which illustrates application of eq 1 to the *n*-butyl aminolysis of *p*-nitrophenyl trifluoroacetate in 1,2-dichloroethane at 24.9°.

Table I. Rate Constants and Activation Parameters[a] for the Third-Order[b] *n*-Butyl Aminolysis of *p*-Nitrophenyl Trifluoroacetate

1,2-Dichlorethane[c]		Chlorobenzene[c]	
Temp, °C	$10^5 k_3$, M^{-2} sec^{-1}	Temp, °C	$10^5 k_3$, M^{-2} sec^{-1}
4.3	22.1	5.6	8.92
16.5	10.3	16.7	5.16
24.9	5.83	24.9	3.01
31.2	4.20		
E_a, kcal	−10.9	E_a, kcal	−9.9
$\Delta H^{\ddagger}$, kcal	−11.5	$\Delta H^{\ddagger}$, kcal	−10.5
$\Delta G^{\ddagger}$, kcal	9.62	$\Delta G^{\ddagger}$, kcal	10.02
$\Delta S^{\ddagger}$, eu	−70.9	$\Delta S^{\ddagger}$, eu	−68.9

[a] The standard temperature is 25°. [b] First order in ester and second order in amine. [c] Solvent.

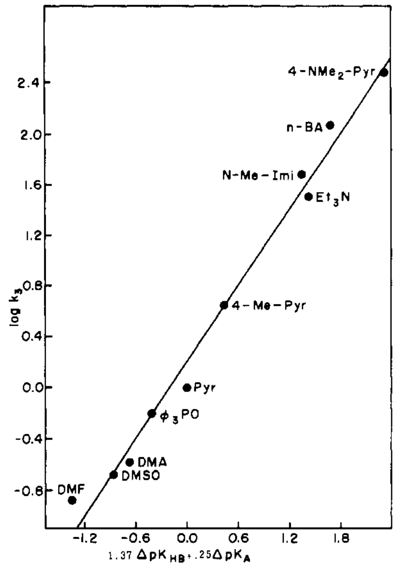


Figure 1. Correlation of the catalytic constants for the *n*-butyl aminolysis of *p*-nitrophenyl trifluoracetate by eq 1: ordinate, log k_3, in $Cl(CH_2)_2Cl$, 24.9°; abscissa, 1.37 ΔpK_{HB} + 0.25 ΔpK_A.

Table II. Catalytic Constants for the *n*-Butyl Aminolysis of *p*-Nitrophenyl Trifluoroacetate in 1,2-Dichloroethane, 24.9°

Catalyst	Log (k/k_0)	ΔpK_A	ΔpK_{HB}	Log $(k/k_0)_{calcd}$[a]
DMF[c]	−0.98	−6.51	0.18	−1.17
DMSO[d]	−0.68	−7.01	0.65	−0.66
DMA[e]	−0.59	−5.41	0.50	−0.46
$(C_6H_5)_3PO$	−0.20	−8.6	1.28	−0.19
C_5H_5N	(0.00)[b]	(0.00)[b]	(0.00)[b]	0.20
$4\text{-}MeC_5H_4N$	0.64	0.72	0.15	0.59
Et_3N	1.51	5.54	0.05	1.65
N-MeIA[f]	1.69	1.99	0.62	1.55
n-$BuNH_2$	2.07	5.43	0.23	1.87
$4\text{-}NMe_2C_5H_4N$	2.48	4.34	0.93	2.56

[a] Calculated from eq 1 with $a = 1.37$, $b = 0.25$, $c = 0.20$; SD = 0.14, SD/RMS = 0.101. If *a* is constrained to zero: $b = 0.21$, $c = 0.79$, SD = 0.51, SD/RMS = 0.386. If *b* is constrained to zero: $a = 0.064$, $c = 0.56$, SD = 1.19, SD/RMS = 0.900. [b] $k_0 = 4.96 \times 10^3$ $l.^2$ mol^{-2} sec^{-1}; $pK_A = 5.21$, H_2O, 25°; $pK_{HB} = 1.88$, CCl_4, 25°. [c] *N,N*-Dimethylformamide. [d] Dimethyl sulfoxide. [e] *N,N*-Dimethylacetamide. [f] *N*-Methylimidazole.

$$\log (k/k_0) = a\Delta pK_{HB} + b\Delta pK_A + c \qquad (1)$$

Pyridine has been taken arbitrarily as the reference catalyst with catalytic constant, k_0. ΔpK_A is the aqueous pK_A of the catalyst relative to that of pyridine. ΔpK_{HB} is the value of the hydrogen-bonding complex formation parameter of the catalyst relative to that for pyridine. The pK_{HB} scale has been generated[5] from the formation constants for hydrogen-bonded complex formation between *p*-fluorophenol and bases in CCl_4, 25°.

Table III summarizes the fitting parameters for eq 1 obtained from results such as those of Table II in the solvents chlorobenzene and 1,2-dichloroethane for both the *n*-butyl aminolysis and the methanolysis (a fixed methanol concentration of 0.495 *M* was used) of *p*-nitrophenyl trifluoroacetate.

The large *a*/*b* ratios for *n*-butyl aminolysis of *p*-nitrophenyl trifluoroacetate indicate that the energetics of hydrogen-bonded complex formation are dominant in the transition states for this reaction. The importance of proton

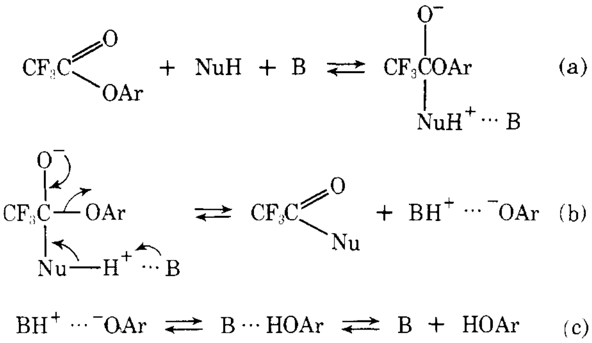
Table III. Summary of Fitting Results for Catalytic Constants of *p*-Nitrophenyl Trifluoroacetate from Equation 1

Solvent	*a*	*b*	*a*/*b*	*c*	SD
1. *n*-Butyl Aminolysis					
Chlorobenzene, 24.9°	2.08	0.22	8.86	0.41	0.22
1,2-Dichloroethane, 24.9°	1.37	0.25	5.49	0.20	0.14
2. Methanolysis (MeOH = 0.495 *M*)					
Chlorobenzene, 25.0°	0.61	0.48	1.28	−0.17	0.21
1,2-Dichloroethane, 25.0°	0.14	0.48	0.29	0.03	0.41

transfer energetics[8] is increased somewhat (*a*/*b* decreases) in the more polar solvent 1,2-dichloroethane. The appreciably weaker Lewis acid strength of *p*-nitrophenylacetate leads to a substantial decrease in the contribution of proton transfer energetics (*a*/*b* increases). The *n*-butyl aminolysis catalytic constants of Watson for this ester in chlorobenzene,[4a] 25°, are fitted by eq 1 with the following results: $a = 1.17$, $b = 0.01$, $a/b > 120$, SD = 0.14. Clearly, only the first term of eq 1 is significant in this case.

The relatively small *a*/*b* ratios for methanolysis (Table III) indicate that proton transfer energetics are dominant for the transition states of this reaction. In 1,2-dichloroethane, only the second term of eq 1 is significant for the methanolysis reaction, i.e., Brönsted catalysis is observed.

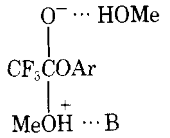
Mechanisms for ester aminolysis and methanolysis in hydroxylic solvents have been detailed by Jencks and others.[7] We believe an additional distinction[6a] to be made between these reactions under the former conditions as compared with the aprotic solvents employed in this work derives from the inaccessibly high energies required for the formation of free ions in the latter solvents. The fact that catalysis for both reactions (Table III) follows eq 1 suggests common mechanistic features. The fact that tertiary amines as well as the other catalysts follow this relationship further rules out bifunctional cyclic mechanisms.[7] The following reactions sequences are consistent with all of our results.



Reaction a may either be termolecular or consist of two sequential bimolecular reactions giving the hydrogen-bonded zwitterionic tetrahedral intermediate. The unimolecular collapse of this intermediate must involve essentially simultaneous breaking of the Nu–H and C–O bonds in order that completely free ion formation is avoided.[9] This is, reaction b, pictured as the conversion of a zwitterionic-like intermediate to an ion-pair intermediate, a process we believe to be energetically accessible under the aprotic solvent conditions.

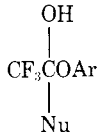
The substantial negative activation for aminolysis (Nu = n-BuNH$_2$) we believe results from the strong Lewis acidity of the trifluoroacetate ester and the strong base strength of the amine. The weaker base strength of CH_3OH (Nu in methanolysis) leads to an appreciably higher activation energy (actually the normal positive kind) as well as transition states with increased contributions from proton transfer energetics relative to hydrogen-bonded complex energetics.

More specifically, the substantial negative activation energy for aminolysis we believe tends to exclude any single elementary step mechanism for this reaction. Step a is strongly exothermic for aminolysis and thermoneutral or endothermic for methanolysis. Step b has small postive activation energies for both reactions. For aminolysis, $\Delta H^\ddagger_{\text{obsd}} = \Delta H^\circ_{(a)} + \Delta H^\ddagger_{(b)} = -$, since $-\Delta H^\circ_{(a)} > \Delta H^\ddagger_{(b)}$; further, aprotic solvation and translational (and other) entropy loss leads to $\Delta G^\circ_{(a)} = \Delta H^\circ_{(a)} - T\Delta S^\circ_{(a)} = +$, in accord with our inability to detect the intermediate spectroscopically. The same qualitative relationships (and interpretation) between standard free energy and enthalpy have been obtained by Baba[10] for the reaction of *p*-nitrophenol with triethylamine to form a hydrogen-bonded ion-pair in 1,2-dichloroethane. Small activation parameters, $\Delta H^\ddagger_{(b)}$, are rational on the grounds of the partial proton transfer involved and the loss of the excellent leaving group *p*-nitrophenolate ion from an electron-rich center. Methanolic solvation of the hydrogen-bonded zwitterionic intermediate for methanolysis



$$\begin{array}{l} O^- \cdots HOMe \\ | \\ CF_3COAr \\ |_{+} \\ MeOH \cdots B \end{array}$$

is expected to reduce the endothermicity of step a, but to increase $\Delta H_{(b)}$ through dispersal of the negative charge. A neutral tetrahedral intermediate, e.g.



$$\begin{array}{c} OH \\ | \\ CF_3COAr \\ | \\ Nu \end{array}$$

is apparently kinetically ineffective for similar reasons. Evidence for these assertions comes from the fact that the negative activation energy for the aminolysis reaction disappears when the reaction is carried out in the presence of 0.487 *M* methanol in 1,2-dichloroethane solvent. Activation parameters obtained for these conditions are: $\Delta G^\ddagger = 17.10$ kcal mol^{-1}, $\Delta H^\ddagger \simeq 0$, $\Delta S^\ddagger = -57.4$ eu.

It is possible that step a is the rate determining step for the methanolysis reaction. However, step b as rate determining step seems to accommodate better the low *a*/*b* ratios of Table III, and the isotope effect, $k_H/k_D = 2.16$, obtained in 0.495 *M* CH_3OH or CH_3OD.[11]

It will be noted that the marked change in activation parameters between "hydrophobic" and "hydrophilic" environments may provide a model for temperature regulatory action in certain enzymatic processes. Effective catalytic activity of carbonyl and other dipolar groups at the active site of enzymes is also suggested by the catalysis observed for aminolysis in aprotic solvents.[4b]

Acknowledgments. We are pleased to acknowledge the important and useful comments of Professors W. P. Jencks, F. M. Menger, and R. L. Schowen.

References and Notes

(1) (a) Taken in part from the Ph.D. Thesis of T. D. Singh, University of California, Irvine, 1974; (b) this work was supported in part by a grant from the Public Health Service.

(2) Some termolecular gas phase reactions, e.g., 2NO + O_2, have small apparent negative activation energies; cf. A. A. Frost and R. G. Pearson, "Kinetics and Mechanism", Wiley, New York, N.Y., 1961, p 109.

(3) J. E. Crooks and B. H. Robinson, *Trans. Faraday Soc.*, **66**, 1436 (1970), have reported a small negative enthalpy of activation ($\Delta H^\ddagger = -1.4$ kcal mol^{-1}) for the reaction of Bromophenol Blue with 2,6-lutidene in chlorobenzene solvent to form the hydrogen-bonded ion pair. Their interpretation is similar to that proposed herein: a two-step mechanism in which the first step (hydrogen-bonded complex formation) has an exothermicity which is greater than the activation energy for the second rate-determining step.

(4) (a) P. W. Arana, C. Su, and J. W. Watson, *Chem. Commun.*, 363 (1970); (b) C. W. Su and J. W. Watson, *J. Am. Chem. Soc.*, **96**, 1854 (1974).

(5) (a) R. W. Taft, D. Gurka, L. Joris, P. v. R. Schleyer, and J. W. Rakshys, *J. Am. Chem. Soc.*, **91**, 4801 (1969); (b) L. Joris, J. Mitsky, and R. W. Taft, *ibid.*, **94**, 3438 (1972).

(6) (a) F. M. Menger and J. H. Smith, *J. Am. Chem. Soc.*, **94**, 3824 (1972); (b) F. M. Menger and A. C. Vitale, *ibid.*, **95**, 4931 (1973).

(7) J. P. Fox, M. I. Page, A. Satterthwait, and W. P. Jencks, *J. Am. Chem. Soc.*, **94**, 4729 (1972); W. P. Jencks, *ibid.*, **94**, 4731 (1972); J. P. Fox and W. P. Jencks, *ibid.*, **96**, 1436 (1974); A. Satterthwait and W. P. Jencks, *ibid.*, **96**, 7018 (1974).

(8) (a) H. B. Yang and R. W. Taft, *J. Am. Chem. Soc.*, **93**, 1310 (1971); (b) E. M. Arnett, E. J. Mitchell, and T. S. S. R. Murty, *ibid.*, **96**, 3875 (1974). This and related work by these authors indicate that aqueous pK_A values are approximate measures of proton transfer energetics in aprotic solvents.

(9) Professor Schowen has suggested the possibility that eq 1 could arise from both proton transfer and heavy-atom reorganization transition states contributing in series to determining the rate. In the heavy-atom reorganization transition state, the protonated catalyst may still be present as an elongated ion-pair "spectator"; cf. C. R. Hopper, R. L. Schowen, K. S. Venkatasubban, and H. Jayaraman, *J. Am. Chem. Soc.*, *95*, 3280 (1973).

(10) H. Baba, A. Matsuyama, and H. Kokubun, *Spectrochim. Acta, Part A*, **25**, 1709 (1969). Additional similar examples have been obtained by E. F. Caldi J. E. Crooks, and D. O'Donnell, *J. Chem. Soc., Faraday Trans. 1*, **69**, 993 (1972).

(11) This is the "normal" isotope effect for the uncatalyzed reaction. For pyridine catalysis, it is 2.97, for triethylamine catalysis, 2.23. The "inverse" solvent isotope effect has been observed for basic methanolysis in pure methanol for a number of esters in which formation of the intermediate is the rate determining step, cf. F. M. Menger, *J. Am. Chem. Soc.*, **88**, 5356 (1966), and C. G. Mitton, M. Gresser, and R. L. Schowen, *ibid.*, **91**, 2045 (1969).

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Equilibrium Studies by Electron Spin Resonance. XIII. Determination of Ion Association Constants for Diamagnetic Salts by the Use of Electron Spin Resonance

Sir:

Since the classic work of Brauman,[1] it is well understood that solvation energies are just as important in the determination of the thermodynamic stability of anions in solution as are the intramolecular considerations. One of the most important phenomena in the determination of solvation energy is ion pairing.

Although it has been shown that ESR is the most powerful tool in the investigation of the nature of ion pairing, this technique has been limited to the study of paramagnetic salts. For diamagnetic salts a variety of experimental techniques have been employed for the determination of ion pair association constants. These include NMR,[2] visible spectroscopy,[3] and conductivity.[4] Although conductivity is clearly the most versatile, even it is often useless for the determination of ion pair dissociation constants in strongly solvating solvents like hexamethylphosphoramide (HMPA).[5] Only with difficulty can conductivity be utilized in highly solvating aprotic solvents.[6] Consequently, for a series of potassium salts, on which conductivity measurements were carried out in HMPA, only KNO_3 yielded data allowing the calculation of the ion association constant (K_a). Here we wish to describe a new and more sensitive technique for the determination of K_a of diamagnetic salts.

The reduction of 2,6-di-*tert*-butylbenzoquinone in HMPA by potassium metal results in the formation of the free anion radical, which exhibits an ESR signal consisting of a triplet due to two equivalent protons with a coupling constant of 2.346 ± 0.005 G.[7] Successive additions of potassium nitrate to this solution result in a gradual decrease in the observed coupling constant. This decrease is due to the formation of the ion pair (β), which is in rapid equilibrium with the free ion (α), eq 1.[7]

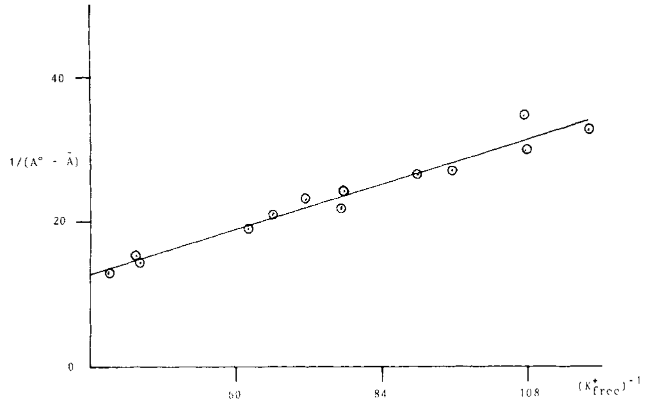

Figure 1. Plot of $1/(A^0 - \bar{A})$ vs. the reciprocal of (K^+_{free}) for the 2,6-di-*tert*-butylbenzoquinone anion radical with added potassium nitrate. The (K^+_{free}) was calculated from the total amount of dissolved potassium nitrate and the K_a of 59 ± 8 reported by Monica and coworkers.[5] This plot yields a value for the equilibrium constant controlling eq 1 of 0.076.

Table I. Observed Coupling Constant of the 2,6-Di-*tert*-butylbenzoquinone Anion Radical in HMPA at 25° with Added KNO_3[a]

$(KNO_3)_{total}$, *M*	$(K^+{}_{free})$, *M*	$\bar{A}$, G
0	0	2.346
0.0143	0.0093	2.323
0.0184	0.0111	2.319
0.0254	0.0139	2.299
0.0311	0.0160	2.294
0.0532	0.0227	2.276
0.0637	0.0255	2.270
	∞	2.05

[a] Only a representative set of data are shown.

$$\beta \rightleftharpoons \alpha + K^+ \qquad (1)$$

The observed coupling constant ($\bar{A}$) has been previously shown to be a weighted average between that for the free ion (A^0) and that for the ion pair (A').[7] This weighted average is given by

$$\bar{A} = \{(\alpha)A^0 + (\beta)A'\}/\{(\alpha) + (\beta)\} \qquad (2)$$

Combining this expression with that for the thermodynamic equilibrium constant for eq 1, $K_{diss} = (\alpha)(K^+{}_{free})/(\beta)$ leads to the following expression.

$$1/(\bar{A} - A^0) = K_{diss}/(K^+{}_{free})(A' - A^0) + 1/(A' - A^0) \qquad (3)$$

Knowing the ion association constant for KNO_3, $K_a = (K^+, NO_3^-)/(K^+{}_{free})(NO_3^-)$, the free potassium ion concentration can be calculated for any amount of KNO_3 that is added to the anion radical solution. A plot of the reciprocal of the potassium ion concentration free of ion pairing vs. $1/(\bar{A} - A^0)$ should be linear and have a slope of $K_{diss}/(A' - A^0)$ and an intercept of $1/(A^0 - A')$. Treated in this manner our data did yield a straight line, Table I, Figure 1.

Each time the experiment is performed, a sample is first taken without the addition of salt, then salt is dissolved and another sample is taken. Using the dual cavity technique, the sample containing added salt is placed in one cavity and the standard without added salt in the other. The coupling constant for the sample containing salt is then accurately determined by comparison with the standard sample, which is assigned a coupling constant of exactly 2.346 G.

KNO_3 is the only salt for which K_a is known in HMPA. However, a salt with an unknown K_a can now be added to the anion radical solution and the coupling constant deter-