

Effect of solvent on the free energy of activation of S_N2 reaction between phenacyl bromide and amines

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The kinetics of S_N2 reaction between phenacyl bromide and various amines in 12 different solvents were studied. Solvent effects on the rate of this reaction and free energy of activation, ΔG^\ddagger , were interpreted by applying the Abraham-Kamlet-Taft (AKT) equation. The solvent polarity (π_1^*), solvent hydrogen-bond basicity (β_1) and Hildebrand cohesive density energy (δ_H^2) are those parameters which increase the rate constant and decrease ΔG^\ddagger , while solvent hydrogen-bond acidity (α_1) will have the compensatory effect. A comparison among obtained values of second rate constants, k_2 , for different amines in a given solvent indicates that the amine reactivities are highly dependent on their structures. The consequent decrease of the rate constant for different amines in any given solvent was found to be: primary > secondary > tertiary. This order results from steric effects of amines.

Keywords Solvent effect, phenacyl bromide, *n*-butylamine, diethylamine, triethylamine

Introduction

Most organic reactions are carried out in solution, therefore it is important to recognize some of the general ways in which solvent can affect the course and rate of reactions.¹

For many years most studies of solvent effect on reaction rates were limited to a simple regression of rate constants (as $\log k$ or ΔG^\ddagger) against some particular solvent parameters, such as dielectric constant, ϵ , dipole

moment, μ , viscosity, η , solubility parameter, δ , and spectroscopically determined parameters, Z and E_T (parameters considered to reflect solvent acidity, basicity, etc.). Steiner *et al.*² showed that for a restricted range of solvents, usually aliphatic non-halogenated, non-hydroxylic solvent, there is often a quite good correlation between rate constant (as $\log k$ or ΔG^\ddagger) and function, such as $1/\epsilon$ or $(\epsilon - 1)/(2\epsilon + 1)$. Such a correlation, by itself, leads to no information whatsoever of a microscopic nature.

Kirkwood³ derived an equation for the electrostatic part of the Gibbs energy, ΔG_E , of a species that could be regarded as a dipole of moment μ in a sphere of radius r . Laidler and Eyring⁴ then combined ΔG_E with the transition state theory, to yield an equation for the effect of solvent dielectric constant on rate constant, as ΔG^\ddagger .

It is now quite clear that there is no single solvent parameter that will satisfactorily correlate $\log k$ values for a variety of different reactions.⁵ Hence, there has been developed considerable interest into correlation by the method of multiple linear regression analysis. More sophisticated methods of analysis are now available, and we consider such one particular method that was advocated by Abraham, Kamlet and Taft.⁶⁻⁸ AKT equation has been applied not only to the kinetics phenomena but also to non-kinetics phenomena.⁹⁻¹⁸ When AKT equation is applied to a given reaction in a number of solvents, the full equation takes the following form:

$$XXZ = XYZ_0 + s(\pi_1^* + d\delta) + a\delta + b\beta_1 + h(\delta_H^2/100) \quad (1)$$

where, π_1^* a measure of solvent dipolarity, δ a polariz-

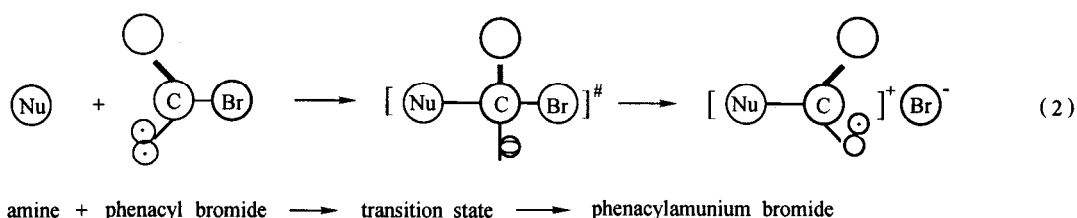
ability correction term, δ_1 the solvent hydrogen-bond

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acidity, β_1 the solvent hydrogen-bond basicity, and δ_H the Hildebrand solubility parameter of the solvent. The variable XYZ may be a $\log k$ or ΔG^\ddagger value, and can also be a Gibbs free energy of transfer, ΔG_t^0 , for non-kinetic processes.¹⁹

Piskunova *et al.*^{20,21} studied the reaction between phenacyl bromide and different amines in benzene, acetonitrile, dioxane and methanol at 25°C in order to investigate the nucleophilic reactivity of amines. Since the work of Piskunova was only limited to study nucleophilic reactivity of amines in four different solvents and there was no single solvent parameter that will satisfactorily

interpret the kinetics of the reaction, our interest was centered around the method of multiple linear regression analysis (MLRA) to investigate the solvent effects on the course and rate of reaction. On the other hand, application of AKT Eq. to chemical kinetics was clearly limited only by the number of reactions studied in a wide variety of solvents. Therefore, in this work the reactions between phenacyl bromide and three different amines, *n*-butylamine, diethylamine, and triethylamine (Eq. (2)) were studied in a variety of polar and nonpolar solvents at 298 K, and the reaction rate constants were determined.



As Eq. (1) is based on the assumption that individual effects act independently and can be summarized to yield an overall effect, it has then been applied to correlate the rate constants. It must also be kept in mind, however, that just as kinetic data relate only to differences between the transition state and the initial states, all the regressions are based on $\log k$ or ΔG^\ddagger values.

Experimental

All chemicals used in this work were of the best available commercial (Merck) grades and prior to any experiment they were purified and dried by standard methods. Pure phenacyl bromide is a light yellow crystalline with melting point of 50°C, but the commercial one has a dark brown color due to the impurities such as acetophenone and bromine which must be removed by standard purification. Into a separatory funnel containing a mixture of 10 mL of distilled water and 10 mL of petroleum ether (40–60°C) was added 80 g of commercial phenacyl bromide (Merck, purity > 98.5%, mp. 45–50°C), and was shaken for 15 minutes prior to filtration. This procedure was repeated 10 times. Pure phenacyl bromide (mp. 50–51°C and $\lambda_{\text{max}} = 251$ nm) was then obtained by recrystallization from methanol (20–30 mL) and stored under vacuum in a

vacuum desiccator in the dark.

To monitor the reaction, a single beam UV-VIS Unicam-8620 spectrophotometer including 1 cm fused silica cell and a double layer constant temperature cell container device was used. The half-life of the reaction between phenacyl bromide and amines (especially in polar solvents) was very short. Therefore, a fast and a new method of homogenous addition of the reagents had to be devised. Two third of the fused silica cell was filled up by the solution of the amine (excess amine) and placed into the cell container at a constant temperature (25 ± 0.01°C). A special device denoted as BD (Fig. 1) was then used to transfer 8 μL of phenacyl bromide solution (10⁻³ mol/L) into the cell. BD (PVC, devised by Dr. Buist, J.J. Department of Chemistry, University of Surry, Guildford, Surrey, England) has four open end holes (2 μL each) and its size is nearly identical to the internal size of the fused silica cell. Since BD transfers and also stirs the reaction solution simultaneously, the transfer process can be carried out homogeneously.

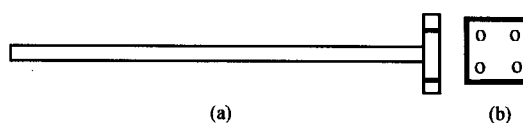


Fig. 1 PVC BD device, (a): Side view, (b): Head view with 4 open end holes.

The kinetic measurements were carried out spectrophotometrically ($\lambda_{\max} = 251 \text{ nm}$) based on the consumption of phenacyl bromide. The reaction was followed by a computer connected to the spectrophotometer through an interface. The computer was programmed to sample four points of the process in each second, and calculate the rate constant of the reaction by both Infinity and Guggenheim methods using Eqs. (3) and (4). It should be noted that the use of excess amine had very important practical consequences, and the result was that mathematically the reactions became equivalent to pseudo-first-order.

$$\log(A_{\infty} - A_t) = -\frac{k}{2.303}t + \log(A_{\infty} - A_0) \quad (3)$$

where A_0 , A_t , A_{∞} , and k are the absorbances at $t = 0$, at time t , at $t = \infty$ and rate constant, respectively. Clearly the accurate measurement of the final (infinity time) instrument reading, A_{∞} , is necessary for the application of the infinity method. It sometimes happened, however, that this final value could not be accurately measured. Guggenheim's method²² as a more reliable method has been devised to allow the rate constant to be evaluated without a known value of A_{∞} .

$$\ln(A_{t+\Delta t} - A_t) = -kt + \ln(A_{\infty} - A_0)(1 - e^{-K\Delta t}) \quad (4)$$

where Δt is a constant time increment. Eqs. (3) and (4) are both the equations of straight lines, whose slopes yield the rate constant, k . All experiments were repeated three times and the average values of second-order rate constants, $k_2 = k/[\text{amine}]$, were calculated. Free energy of activation was then calculated by Eq. (5).

$$\Delta G^{\ddagger} = RT \ln \frac{kT}{h} - RT \ln k_2 \quad (5)$$

where $R = 8.314 \text{ J/(K}\cdot\text{mol)}$, $h = 6.626 \times 10^{-34} \text{ J}\cdot\text{s}$, $k = 1.3807 \times 10^{-23} \text{ J/K}$ and k_2 are universal gas constant, Planck constant, Boltzmann constant and second rate constant respectively.

Results and discussion

Since the half-life of the reaction (especially in polar solvents) was very short we devised a new method of

homogenous addition of the reagents to obtain highly accurate data. Rate constants and free energies of activation were given in Tables 1—3, which show that both Guggenheim and Infinity methods in terms of ΔG^{\ddagger} values (kJ/mol) give nearly the same results in most cases. The small expected differences are due to the nature of the Guggenheim and Infinity methods that use different sets of data and it is obvious that two different methods do not give exactly the same results. Since there is not a single solvent parameter that correlates $\log k$ values satisfactorily for a variety of widely different reactions, the AKT Eq. of multiple linear regression analysis was applied using solvatochromic parameters from Ref. 18. The correlation factors (s , a , b , and h of Eq. (1)) obtained by applying this equation were listed in Table 4, where the superscripts I and G indicate the Infinity and Guggenheim methods, respectively. Table 4 indicates the factors that influence the reaction, *i. e.*, solvent dipolarity, π_1^* , Hildebrand cohesive density energy, δ_H^2 , and solvent nucleophilicity, or hydrogen-bond basicity, β_1 , which greatly increase the rate constant and decrease ΔG^{\ddagger} .

In order to see clearly what is happening during reaction it is necessary to separate the effect of solvent on ΔG^{\ddagger} into transition-state and initial-state contributions. In terms of the transition state, the values of ΔG^{\ddagger} in alcohols are more positive than in dipolar solvents, such as dimethylsulphoxide, and dimethylformide. Therefore, results for the hydroxylic solvents show that the rather anomalous effect of these solvents is to increase the free energy of the transition state, and to lower the initial-state free energy. Since the free energy of activation of a reaction is the difference between the free energies of the transition state and of the reactants, it follows that if no other factors are considered, then increased solvation of the reactants with respect to the transition state, which would happen if the reactants were more polar than transition state, will increase the free energy of activation. A more polar solvent will therefore, reduce the reaction rate. Conversely, preferential solvation of the transition state in the reaction where the transition state is more polar than the initial state, will produce a smaller free energy of activation, and so greater solvent polarity will result in a faster rate of reaction. It can also be said that there is some interaction between the transition state and polar hydroxylic molecules.

Table 1 Second rate constants and free energies of activation of the reaction between phenacyl bromide and *n*-butylamine in different solvents at 25°C.

Solvent	[Amine] (mol/L)	$k \times 10^3$ ^I (L/(mol·s))	$k \times 10^3$ ^G (L/(mol·s))	$\Delta G^\#$ ^I (J/mol)	$\Delta G^\#$ ^G (J/mol)
Dimethyl sulfoxide	0.0016	6169.40	6015.63	68509	68572
Dimethylformamide	0.0221	1557.92	1626.24	71920	71814
Formamide	0.1016	436.61	444.88	75074	75027
Acetonitrile	0.5075	313.10	324.93	75897	75806
Ethyl acetate	0.3755	34.94	38.88	81334	81069
Cyclohexane	0.2072	1.97	2.18	88462	88211
<i>n</i> -Hexane	0.6744	1.52	1.70	89105	88827
Methanol	0.2524	11.88	10.43	84009	84331
Ethanol	0.4650	12.95	15.73	83794	83312
2-Propanol	0.2503	12.01	12.03	83981	83977
<i>t</i> -Butanol	0.7174	17.44	17.52	83056	83045
Benzene	0.5047	12.36	11.98	83911	83988

^I Infinity method; ^G Guggenheim method.**Table 2** Second rate constants and free energies of activation of the reaction between phenacyl bromide and diethylamine in different solvents at 25°C.

Solvent	[Amine] (mol/L)	$k \times 10^3$ ^I (L/(mol·s))	$k \times 10^3$ ^G (L/(mol·s))	$\Delta G^\#$ ^I (J/mol)	$\Delta G^\#$ ^G (J/mol)
Dimethyl sulfoxide	0.0179	1831.29	2060.89	71520	71227
Dimethylformamide	0.1023	508.41	501.47	74896	74731
Formamide	0.1015	233.50	226.31	78825	76703
Acetonitrile	0.5001	236.35	230.95	76595	76652
Ethyl acetate	0.3065	12.73	12.67	83837	83848
Cyclohexane	1.0970	0.4947	0.3678	91883	92622
<i>n</i> -Hexane	1.0980	1.4200	0.8360	89274	90587
Methanol	0.5004	4.5711	3.8805	86376	86782
Ethanol	0.6040	4.1810	3.9570	86597	86733
2-Propanol	1.0004	6.7480	6.2500	85410	85600
<i>t</i> -Butanol	1.0003	8.8200	5.8080	84751	85782
Benzene	0.5002	6.5310	5.8540	85491	85762

^I Infinity method; ^G Guggenheim method.**Table 3** Second rate constants and free energies of activation of the reaction between phenacylbromide and triethylamine in different solvents at 25°C.

Solvent	[Amine] (mol/L)	$k \times 10^3$ ^I (L/(mol·s))	$k \times 10^3$ ^G (L/(mol·s))	$\Delta G^\#$ ^I (J/mol)	$\Delta G^\#$ ^G (J/mol)
Dimethyl sulfoxide	0.0136	480.220	444.42	74838	75030
Dimethylformamide	0.0505	129.500	138.16	78087	77926
Formamide	0.2014	107.950	121.10	78536	78253
Acetonitrile	0.5004	46.530	57.77	80624	80087
Ethyl acetate	0.2132	2.600	2.970	87774	87444
Cyclohexane	1.0078	0.280	0.072	93298	96665
<i>n</i> -Hexane	1.0104	0.112	0.160	95569	94685
Methanol	1.2900	1.720	1.830	89521	88806
Ethanol	0.6001	0.880	0.210	90460	94011
2-Propanol	1.0970	1.940	1.440	88500	89239
<i>t</i> -Butanol	1.0008	1.530	1.050	89089	90022
Benzene	0.5002	2.070	2.050	88339	83363

^I Infinity method; ^G Guggenheim method.

Table 4 Correlation factors of the AKT equation

Amine	XYZ	XYZ ₀	s	a	b	h
<i>n</i> -Butylamine ^c	log <i>k</i> ^I	-3.115	1.644	-2.138	1.539	0.538
	log <i>k</i> ^G	-3.096	1.481	-2.337	1.687	0.584
	Δ <i>G</i> ^{# I}	90802	-9385	12205	-8787	-3072
	Δ <i>G</i> ^{# G}	90597	-8941	12487	-8995	-3155
Diethylamine ^d	log <i>k</i> ^I	-3.398	1.637	-2.006	1.363	0.527
	log <i>k</i> ^G	-3.550	1.919	-1.975	1.313	0.493
	Δ <i>G</i> ^{# I}	92414	-9342	11451	-7780	-3007
	Δ <i>G</i> ^{# G}	93280	-10952	11272	-7493	-5106
Diethylmethyamine ^e	log <i>k</i> ^I	-4.182	1.471	-2.088	1.472	0.696
	log <i>k</i> ^G	-4.349	1.817	-2.294	1.399	0.694
	Δ <i>G</i> ^{# I}	96625	-10021	11305	-6849	-3576
	Δ <i>G</i> ^{# G}	97590	-12038	11630	-5804	-3583

The correlation coefficient, *R*, standard error, *SE* and degree of freedom of multiple regression analysis, *F*, for each amine were found to be: ^c *R* = 0.98, *SE* = 0.30, *F* = 37, ^d *R* = 0.97, *SE* = 0.37, *F* = 26, ^e *R* = 0.96, *SE* = 0.41, *F* = 24. It should be noted that regression analysis of each data set (log *k*'s or Δ*G*[#]'s) for each amine gave the same *R*, *SE* and *F*. ^I Infinity method, ^G Guggenheim method.

The coefficients of solvent polarity (π_1^*) and solvent nucleophilicity (β_1) for these reactions are all large and negative, reflecting stabilization of the dipolar transition states, a lowering of Δ*G*[#], and hence an increase in log *k*. This could be chemically quite reasonable, because the transition-state seems to behave as a dipolar species, and there is no doubt that the influence of solvent dipolarity (π_1^*) and solvent hydrogen-bond basicity (β_1) is almost exclusively transition-state effect and proves that transition state is rather stable in solvents of more dipolarity and *vice versa*. The transition state should, therefore, form compounds of the multipolar type with solvents which also contain strong localized dipoles. Therefore, it can be concluded that there should be a charge distribution in the transition state, so that an increase in solvent polarity will produce a large rate increase. The coefficients of solvent electrophilicity, or solvent hydrogen-bond acidity (α_1) for these reactions are all large and positive, reflecting a large increase in Δ*G*[#], and hence a decrease in log *k*. Solvent electrophilicity, or solvent hydrogen-bond acidity, α_1 , would therefore stabilize the initial state of the amine and the hydrogen bond basicity term might derive from lone pair interactions between the solvent and the amine in the initial state. These results indicate that there is some interaction between amine and the solvent molecules which results in the formation of some type of complex. Clearly the formation of multipolar complexes²³ between polar solvent and reactant is important factor in

the effect of solvent on reactivity. Of course the formation of the complex is due to charge separation on both the solvent and solute molecules. The formation of this complex in hydroxylic solvents is obviously due to hydrogen bonding between amine and acidic hydrogen in the solvent molecules and the solvation of amine molecule will result in lowering its free energy.

A comparison among obtained values of the second rate constants, *k*₂, or free energy of activation in a given solvent indicates that the amine reactivity is highly dependent on the structure of the amine molecule. The consequent decrease of rate constant for different amines in any given solvent was found to be: primary > secondary > tertiary. This order results from steric effects of the amines.

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