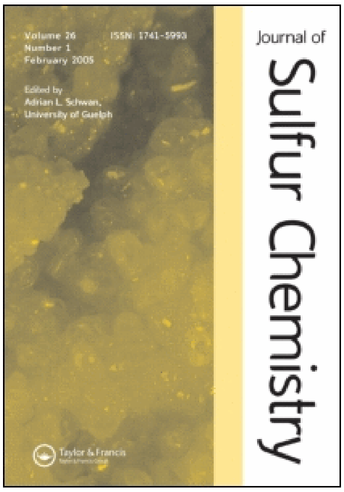

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Solvation models in the reaction between phenacyl bromide and 2-mercaptobenzimidazole

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The reaction between phenacyl bromide and 2-mercaptobenzimidazole has been studied in 12 different protic and aprotic solvents. The kinetic study shows that the reaction is second-order with first-order dependence each on (phenacyl bromide) and (2-mercaptobenzimidazole). Analysis of rate data shows that there is no direct correlation between the rate constant and dielectric constant of the solvent. Correlation of rate data with different solvent parameters like hydrogen bond acceptor basicity, polarizability and solvent electrophilicity, using linear multiple regression analysis shows that the reaction is influenced by these properties of the solvent. From the regression coefficients, information on the mode of solvation of the reactants and the transition state is obtained. The reaction has also been studied at different temperatures and the thermodynamic parameters $\Delta H^{\#}$, $\Delta S^{\#}$ and $\Delta G^{\#}$ are evaluated.

Keywords: solvent effects; linear solvation energy relationship (LSER); phenacyl bromide; 2-mercaptobenzimidazole; solvation parameters

1. Introduction

A solvent influences the rate of a reaction by solvating the reactants and the transition state. A substance is solvated due to two types of interactions with the solvent, namely specific and non-specific interactions (*1*). All solvents interact with the substances non-specifically. The intensity of these non-specific interactions is measured in terms of polarity of the solvent (Y) and polarizability (P) of the solvent. Specific solvation of the substance primarily occurs when the solvent interacts with a charged atom or group in a molecule. The intensity of these interactions is measured in terms of electrophilicity (E), nucleophilicity (B), hydrogen bond donor (HBD) ability (α), hydrogen bond acceptor ability (β), etc. So, the general term 'polarity' means the solvating ability of the solvent due to either all or some of the above properties of the solvent. Therefore, the effect of solvent on reaction rate is to be expressed not by a single parameter equation, but by a multiparameter equation (*2*), *i.e.*

$$\log k = \log k_o + aA + bB + cC + \cdots \tag{1}$$

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where k is the rate constant of the reaction in any solvent and k_o is the rate constant in a reference solvent which is inert. The coefficients a, b, c are the susceptibilities of k to the respective solvent parameters A, B, C, etc. These coefficients indicate the relative solvation of the reactants over the transition state and the mode of solvation. With this end in view, the reaction between phenacyl bromide and 2-mercaptobenzimidazole has been studied in 12 protic and aprotic solvents and the results are presented. The role of solvent effects in the rates of reactions has been studied extensively (*3–12*) for nucleophilic substitution at sp^3 and sp^2 carbon using a variety of nucleophiles. Similar studies using phenacyl halide are few (*13*, *14*). However, the substituent effect and nucleophile effect involving phenacyl bromide as substrate, and the oxidation of phenacyl bromide by V^{5+}, Mn^{3+} and Ce^{4+} are reported in the literature (*15–17*).

2. Results and discussion

The second-order rate constants are determined in 12 different protic and aprotic solvents in the 303–318 K temperature range. These are presented in Table 1. Correlation of these $\log k_{\mathrm{II}}$ values with different solvent parameters, namely polarity (Y) (*18*), polarizability (P) (*18*), solvent electrophilicity (E) (*18*), solvent nucleophilicity (B) (*18*), HBD acidity (α) (*19*), hydrogen bond acceptor basicity (β) (*19*) and specific polarizability (π^*) (*19*), did not give satisfactory results, indicating that the rate of reaction is not influenced by any single property of a solvent. Out of these, a better correlation is observed with polarity – polarizability parameter with the following relation:

$$\begin{aligned} \log k_{\mathrm{II}} &= -1.50 + 0.76\pi^* \quad r = 0.81 \\ \mathrm{SE} &= (0.14)(0.18) \quad (0.14) \end{aligned} \tag{2}$$

The values in the parentheses are standard errors of the coefficients. A glance at these values indicates that these values are highly dependent on the nature of the solvent. However, there appears to be no correlation between log k_{II} and the dielectric constant of the solvent. Addition of the second parameter to the single parametric equation improved the strength of the correlation

Table 1. Second-order rate constants at different temperatures and thermodynamic parameters at 303 K. [Phenacyl bromide] = [2-mercaptobenzimidazole] = 2.00×10^{-2} mol dm^{-3}.

	$k_{\mathrm{II}} \times 10^2$ dm^3 mol^{-1} s^{-1} at T/K				Ea	$\Delta H^{\#}$	$\Delta S^{\#}$	$\Delta G^{\#}$	$\delta\Delta G^{\neq}$
Solvent	303	308	313	318	(kJ mol^{-1})	(kJ mol^{-1})	(Jk^{-1} mol^{-1})	(kJ mol^{-1})	(kJ mol^{-1})
Methanol	10.96	23.99	36.31	53.71	81.88	79.36	−1.55	79.83	0
Ethanol	7.94	15.85	22.92	34.66	95.67	93.15	41.29	80.64	0.81
n-Propanol	7.58	29.08	46.77	67.61	111.49	108.97	93.13	80.75	0.92
i-Propanol	7.08	13.80	19.06	27.54	69.41	66.89	−46.35	80.93	1.10
n-Butanol	6.61	31.62	60.23	93.33	110.05	107.53	87.22	81.10	1.27
2-Butanol	11.22	33.88	53.70	83.18	102.36	99.84	66.24	79.77	−0.06
i-Butanol	8.91	20.28	42.62	63.43	104.92	102.40	72.78	80.35	0.52
Benzyl alcohol	26.92	41.69	53.70	67.61	47.69	45.17	−106.93	77.57	−2.26
N,N-dimethyl formamide	22.39	36.31	47.86	61.66	52.42	49.90	−92.85	78.04	−1.79
Formamide	20.89	33.88	45.71	64.57	38.13	35.61	−140.60	78.21	−1.62
Dimethyl sulfoxide	17.38	20.62	28.48	51.29	55.97	53.45	−83.24	78.67	−1.16
2-Ethoxy ethanol[a]	38.91	41.69	50.12	61.65	24.7	22.18	−179.76	76.65	−3.19

Note: [a] Eliminated from statistical analysis as complete set of solvent parameters data is not available.

slightly, and some of these biparametric relationships are

$$\begin{aligned} \log k_{\mathrm{II}} &= -1.28 + 0.62\,\pi^* - 0.19\,\alpha \quad R = 0.84 \\ \mathrm{SE} &= (0.24)(0.22)(0.17) \quad (0.13) \end{aligned} \tag{3}$$

$$\begin{aligned} \log k_{\mathrm{II}} &= -0.80 + 0.64\,\pi^* - 0.77\beta \quad R = 0.96 \\ \mathrm{SE} &= (0.16)(0.099)(0.16) \quad (0.071) \end{aligned} \tag{4}$$

Although there is an increase in the value of the multiple regression coefficient R, it is not a satisfactory correlation. So the analysis is extended using three parameters:

$$\begin{aligned} \log k_{\mathrm{II}} &= -0.66 - 0.14\,\alpha - 0.74\,\beta + 0.53\,\pi^* \quad R = 0.97 \\ \mathrm{SE} &= (0.16)(0.079)(0.14)(0.11) \quad (0.063) \\ t\text{-stat} &= (-4.07)(-1.79)(-5.32)(4.99) \quad F = 37.95 \end{aligned} \tag{5}$$

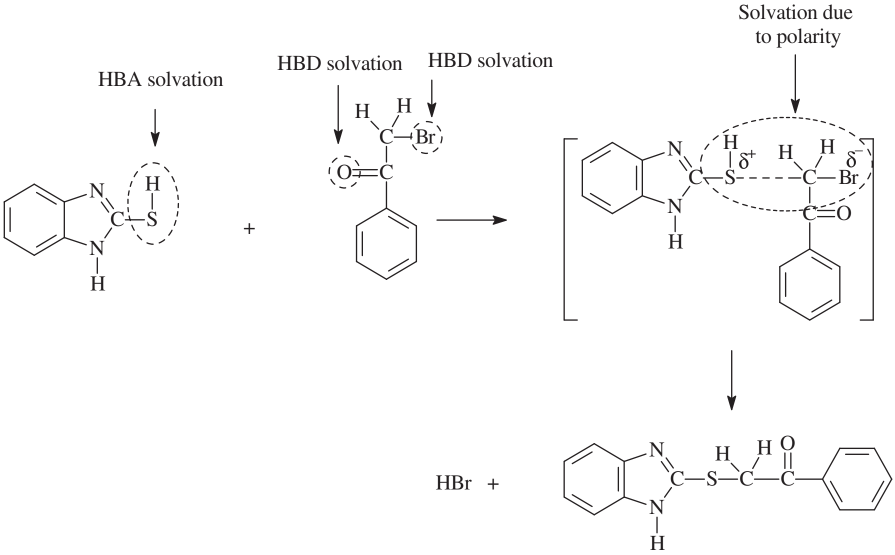
The statistical analysis is not extended further using four solvent parameters as there are no sufficient data points to use linear four parametric equations. The validity of this LSER obtained is tested by conducting the following tests:

1. F-test: The F_{cal} is very high (37.95) compared with the table value (F_{table}7.59) at 1% level of significance (*20*). This suggests that this LSER is not a chance correlation.
2. t-test: The significance of individual parameters is tested by comparing the t_{cal} with t_{table}. This comparison indicates that the parameters π^* and β are significant at 99% confidence level and α is significant at 90% confidence level (*20*).
3. Correlation of $\log k_{\mathrm{cal}}$ with $\log k_{\mathrm{obs}}$ (*21*): This correlation indicates that there is excellent correlation between these two values with a correlation coefficient (r) of 0.97 and a slope of 1.00.

From the above observations the following conclusions can be drawn:

1. The rate of the reaction is influenced by HBD acidity *i.e.*, α of the solvent. As there are polar centers in the reactants, the transition state solvent can easily form hydrogen bonds. The negative sign of this coefficient in the above equation suggests that the reactants are more solvated than the transition state due to hydrogen bond donation. The rate decreases due to decrease in the HBD ability of the solvent.
2. The reaction is facilitated in solvents having higher hydrogen bond acceptor ability measured by their β values. The negative sign and the magnitude of the coefficient of β in Equation (9) suggest that HBA solvents more strongly solvate the reactants than the transition state does and such solvents do not assist the formation of the transition state.
3. The rate of the reaction is influenced by π^*, which is a measure of the ability of the solvent to stabilize a charge or a dipole by virtue of its polarity – polarizability. The positive sign of this coefficient in the above equation suggests that the transition state is more extensively solvated by such solvents than the reactants. Hence, the rate of this reaction increases with the increase in the π^* value of the solvent.

Considering these points, the mode of solvation of the reactants and the transition state can be represented as follows.



The normalization of the coefficients used in the above LSER indicates that the contributions of the solvent parameters α, β and π^* towards overall solvation of the reactants and the transition state are 8, 55 and 37%, respectively. The solvation of the reactants by specific hydrogen bond acceptor interaction exceeds that of the transition state. The dipolar interactions between transition state and solvent is more than the reactant – solvent interactions. The second-order rate constants are evaluated in all the solvents at different temperatures ranging from 303 to 318 K.

The thermodynamic parameters $\Delta H^{\#}$, $\Delta S^{\#}$ and $\Delta G^{\#}$ computed are given in Table 1. A perusal of this data shows that $\Delta H^{\#}$ and $\Delta S^{\#}$ are also dependent on the nature of the solvent. The reaction is entropy-controlled, indicating that the extent of solvation of the reactants is strongly dependent on the nature of the solvent. The present reaction involves a neutral nucleophile and a negatively charged leaving group Br^-. Therefore, the charges on the two ends of the transition state, and hence their solvation energies, are different. A change from a protic to dipolar aprotic solvent results in a large difference in the relative solvation energies of the two ends of the transition state. This difference in solvation energies is large enough to cause a shift in the electron density in the area between −S and −Br atoms along Br−C−S bond axis in the transition state, resulting in a change in the structure of the transition state, as the solvent is changed.

The inherent limitation in the applicability of multiparameter correlation for any reaction is that the mechanism of the process under examination should not change with change in the solvent. The free energy of activation $\Delta G^{\#}$ is nearly constant ($79.38 \pm 2.25\,\mathrm{kJ\,mol^{-1}}$), suggesting the operation of a common mechanism in all the solvents. Thus it can be concluded that in the present system, the transition state and the reactants are solvated by specific solvent – solute interactions.

The differential free energy values computed by taking methanol as the reference solvent are presented in Table 1. These values suggest that the transition state is more stabilized in 2-butanol, benzyl alcohol, formamide, N,N-dimethyl formamide, dimethyl sulfoxide and 2-ethoxy ethanol when the reaction system is changed from methanol. This data also suggests that the differential solvation is maximum in the case of benzyl alcohol and 2-ethoxy ethanol. This suggests the role of intramolecular hydrogen bonding in stabilizing the transition state. In the rest of the solvents, it is less stabilized compared with methanol.

3. Experimental

The solvents methanol, ethanol, n-propanol, i-propanol, n-butanol, i-butanol, benzyl alcohol, dimethyl sulfoxide, formamide, N,N-dimethyl formamide and 2-ethoxy ethanol were all of analytical reagent (AR) grade and were used after purification by methods in the literature. Phenacyl bromide (Merck) and the nucleophile 2-mercaptobenzimidazole (Aldrich) were used as such.

The solutions of the reactants of required concentrations were prepared by dissolving a known volume/weight of phenacyl bromide/nucleophile in a known volume of the solvent. The reaction was initiated by mixing the thermally equilibrated solutions of the substrate and the nucleophile at the required temperature. The course of the reaction was followed by measuring the conductance of the reaction mixture at different time intervals using a conductivity bridge (CENTURY make). Measurement of rates at different concentrations of the substrate and the nucleophile showed that the reaction is overall second-order, with first-order dependence each on the (substrate) and the (nucleophile). The second-order rate constants were calculated using the relation (*22*)

$$k_{\mathrm{II}} = \frac{1}{at} \frac{C_t}{C_\infty - C_t} \tag{6}$$

where C_t and C_∞ are the conductances of the reaction mixture at t and infinite time intervals, and a is the initial concentration of the reactants. The rate constants thus determined were found to be reproducible within ±5% error. A PCL personal computer was used to carry out the multiple regression analysis. F-test (*23*) and student t-test (*23*) were used to know the validity of the bi-and tri-parameter equations obtained. The product separated from methanol had a melting point of 120 ± 2°C. The IR spectral data (KBr) of this compound shows absorption bands around 2690 cm^{-1} and 1400 cm^{-1} indicating the presence of an S–$\mathrm{CH_2}$ group and another band around 700 cm^{-1} indicating the thioether link, C–S–C. These values agree with the literature values (*24*) of 2700–2600, 1420 and 720 cm^{-1}. These data suggest the formation of S-phenacyl 2-mercaptobenzimidazole. One of the products formed in this reaction is HBr, and therefore the conductance of the reaction mixture increases. Thus by noting the conductance at different time intervals, the rate constant of the reaction is calculated.

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