

Nucleophilic substitution reactions in solution – A molecular orbital approach

B H BHIDE*, M B BHIDE and ARABINDA RAY

Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar 388 120, India

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Abstract. The bimolecular nucleophilic substitution reaction of phenacyl bromides with anilines has been studied in pure solvents and also in mixed media. The kinetics of the system has been analysed by a molecular orbital approach and by linear free energy relations.

Keywords. CNDO/2 approach; Hammett and mY correlation.

1. Introduction

The kinetics of the reaction of phenacyl bromides with substituted anilines have been investigated (Mohanty *et al* 1967; Rath *et al* 1968; Mishra *et al* 1969; Soni *et al* 1972). However no molecular orbital study appears to have been made to explain the results of the kinetics of this system. We, therefore, undertook the study of the kinetics of *p*-bromo-(electron-withdrawing group), *p*-methyl-(electron-donating group) and unsubstituted phenacyl bromide with different anilines in pure alcohols and mixed media. All these molecules are subjected to CNDO/2 MO calculations (Pople and Segal 1966). Following the generalized perturbation treatment (Klopman 1968), attempts are made to determine whether these are charge-controlled reactions or not. The necessary molecular orbital energies and coefficients required for the perturbation calculation are obtained from the CNDO/2 treatment. The usual Hammett and mY correlations with rate constants have also been examined.

2. Materials and methods

Anilines were purified by either double distillation over zinc dust or by crystallization. *p*-Bromo, *p*-methyl- and unsubstituted phenacylbromides were prepared by standard methods. Freshly purified solvents were used for each kinetic run. The reaction kinetics were followed by the conductometric method reported in the literature (Soni *et al* 1972). The uncertainty in the value of rate constant k is of the order of $\pm 2\%$. The method of least squares was used for calculating the rate constant and other parameters.

* For correspondence

3. Results and discussion

3.1 CNDO/2 calculations

Nucleophilic substitution may be viewed as a donor-acceptor interaction in which the nucleophile transfers its electrons from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO) of the electrophilic acceptor (Klopman 1974). Hence we thought it appropriate to look into the HOMO energy of nucleophiles and the 'LUMO energy' of electrophilic acceptors to understand the trend in the rate constant values of these second order nucleophilic substitution reactions.

The simple Pariser Parr Pople (PPP) method has been found to be inadequate for molecules containing polar groups (Hammond 1970; Kulkarni *et al* 1978). Accordingly the semiempirical all-valence method, CNDO/2, was employed. The semiempirical parameters required for the CNDO/2 method are taken from literature (Pople and Segal 1966) without modification. Since the calculations were carried out without optimization of the geometry of the molecules it was essential to keep the lengths of similar bonds and the magnitudes of comparable angles constant in all the molecules, so that the main influence on the orbital energies is the change of electronic environment due to the variation of functional groups.

The energies of HOMO and LUMO of the nucleophiles and electrophilic acceptors are shown in table 1. It is interesting to note that the HOMO of the anilines are the π -type, while those for the phenacyl bromides are σ -type. The LUMO for all these molecules however are π -type. In so far as the HOMO energy gives a measure of the electron-donor ability of a molecule, *p*-phenetidine appears to be the best and *m*-nitroaniline the worst donor amongst the anilines investigated. The nature of the HOMO of the anilines and the phenacyl bromides being different, it is not

Table 1. HOMO and LUMO energies of nucleophiles and substrates*, second-order rate constants for the reaction of phenacyl bromides with anilines in methanol[†] at 40°C.

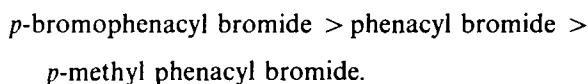
Anilines (σ)	Energy (eV) of		$k \times 10^4 (\text{l mol}^{-1} \text{s}^{-1})$		
	HOMO	LUMO	<i>p</i> -bromo phen	phen	<i>p</i> -methyl phen
<i>p</i> -phenetidine (-0.25)	-10.156	3.991	93.9	66.1	57.4
<i>p</i> -toluidine (-0.17)	-10.605	4.144	44.0	32.6	27.1
<i>m</i> -toluidine (0.07)	-10.922	4.046	35.0	23.5	19.9
Aniline (0.0)	-11.044	4.176	21.0	15.0	14.4
<i>m</i> -chloroaniline (0.37)	-11.252	3.929	4.6	3.7	3.6
<i>m</i> -nitroaniline (0.71)	-11.816	1.739	1.09	0.93	—
<i>Substrate*</i>					
<i>p</i> -Methyl phen	-5.712	0.234			
Phen	-5.810	0.121			
<i>p</i> -Bromophen	-5.914	0.025			

* Phenacyl bromides have been abbreviated as phen and the HOMOs for these are the σ type.

[†] In other solvents also the same is followed.

appropriate to compare them for their donor abilities. The comparison of the energy of the LUMO, however, indicates the superior ability of phenacyl bromides as electron acceptors.

It is heartening to note that the values of rate constant for the reaction between anilines (nucleophiles) and any electrophile more or less follow the same trend as that of the electron-donor ability of the anilines, the k being highest for *p*-phenetidine (most unstable HOMO) and lowest for *m*-nitro aniline (most stable HOMO) (table 1). Also, amongst the different electrophiles, the rate with a particular nucleophile increases with electron-accepting ability of the electrophile i.e.



The small difference in energy of the LUMO of various phenacyl bromides may be traced to the fact that the geometries were not optimized.

The perturbation energy (ΔE) for the electrophile-nucleophile interaction is calculated to ascertain whether these are charge-controlled reactions or not (Klopman 1968). Accordingly ΔE for charge-controlled reactions is calculated by the following expression.

$$\Delta E = \sum_m \sum_n \frac{2(C_r^m)^2 (C_s^n)^2 \cdot \beta^2}{E_m - E_n}$$

In the present study, ΔE for the reaction between different nucleophiles and electrophiles is found to be $\Delta E \approx |0.1 \text{ eV}|$, which is indicative of charge-controlled reactions. This is in conformity with the fact that when $|E_m - E_n|$ is large, the reaction is charge-controlled.

Since the reactions are all charge-controlled very little electron transfer occurs. This is further supported by the fact that the C^* of the $-\text{COC}^*\text{H}_2\text{Br}$ moiety in phenacyl bromides makes a negligibly small contribution to the LUMO of these electrophiles.

3.2 Effect of nucleophile

The Hammett plot was found to be linear. The relation at 40°C was worked out as:

$$\log k = -2.61 - 1.94\sigma \quad (\text{for } p\text{-bromophenacyl bromide})$$

$$\log k = -2.72 - 1.87\sigma \quad (\text{for phenacyl bromide})$$

$$\log k = -2.80 - 1.80\sigma \quad (\text{for } p\text{-methyl phenacyl bromide})$$

where σ is the substituent constant. The correlation coefficient was around 0.99 for all the reactions. The values of the reaction constant ρ at 40°C from above equation are -1.94 , -1.87 , and -1.80 for *p*-bromophenacyl bromide, phenacyl bromide and *p*-methyl phenacyl bromide respectively. The negative sign of the reaction constant (ρ) suggests that the reaction is favoured by the presence of electron-donating groups in aniline.

The second-order rate constants and kinetic parameters for the reaction of phenacyl bromides with aniline in different solvents are listed in table 2. The competing solvolysis rates were found to be very negligible when compared to S_N^2

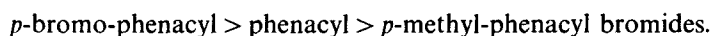
Table 2. Second-order rate constants for the reaction of phenacyl bromide + aniline in pure solvents.

Solvent (ϵ)	Substrate	$k \times 10^4$ ($l \text{ mol}^{-1} \text{ s}^{-1}$) at				E_s (kcal mol^{-1})	$\log A$	ΔG^\ddagger (± 0.14 kcal mol^{-1})	ΔH^\ddagger (± 0.38 kcal mol^{-1})	ΔS^\ddagger (± 0.78 cal degree mol^{-1})
		30°	35°	40°	45°					
Methanol (32.6)	<i>p</i> -bromophen	10.1	14.4	21.0	28.8	14.52	7.46	22.18	13.89	-26.49
	phen	7.6	10.3	15.0	22.4	14.86	7.57	22.39	14.24	-26.00
	<i>p</i> -methyl phen	6.9	10.2	14.4	19.6	14.15	7.04	22.42	13.53	-28.41
Ethanol (24.3)	<i>p</i> -bromophen	11.6	15.9	23.3	31.8	14.02	7.15	22.12	13.4	-27.88
	phen	9.6	13.1	17.9	25.1	12.93	6.30	22.28	12.31	-31.81
	<i>p</i> -methyl phen	7.2	10.9	14.7	22.3	15.12	7.75	22.40	14.50	-25.15
Isopropanol (18.3)	<i>p</i> -bromophen	26.4	34.8	50.7	66.6	12.94	6.73	21.63	12.32	-29.80
	phen	16.7	24.1	32.2	48.2	14.25	7.48	21.92	13.63	-26.37
	<i>p</i> -methyl phen	13.1	18.4	25.3	34.2	13.10	6.55	22.07	12.48	-30.63
<i>t</i> -Butanol (12.2)	<i>p</i> -bromophen	—	83.3	—	—	—	—	—	—	—
	phen	—	47.8	—	—	—	—	—	—	—
	<i>p</i> -methyl phen	—	35.7	—	—	—	—	—	—	—

* Rate of solvolysis in pure solvents was very slow, of the order of $k \times 10^6 \text{ s}^{-1}$ for all the substrates
Abbreviations as in table 1

rates (see foot note of table 2). Hence the effect of solvolysis on bimolecular reaction^{IV} rates was ignored. The rate constants of the reactions are higher in ethanol than in methanol, while in isopropanol the values are unusually high. It could be due to steric effects as the reaction rates were found even higher in *t*-butanol. Such unusual behaviour, that of increase in reaction rate with decrease in dielectric constant and the effect of steric bulk of the solvents on S_N^2 reactions, has been reported earlier (Soni *et al* 1982; Bhide and Patel 1985).

The reactivity trend for phenacyl bromides followed the expected pattern



3.3 Study in mixed media

With a view to investigating the effect of solvent polarity on reaction rates the S_N^2 reactions of phenacylbromides with aniline in binary solvent mixtures of various compositions are studied at 40°C. The data are presented in table 3. In such a mixed media the solvent composition and nature of the solvent in the vicinity of the solute molecules are likely to be quite different from those in the bulk of the medium. No definite correlation was possible between rate constant and various dielectric constant functions like $1/\epsilon$, $\log \epsilon$, $\epsilon - \frac{1}{2}\epsilon + 1$. This then indicated that a bulk property like the dielectric constant of the medium cannot truly represent solvent property. Therefore an empirical approach (Grunwald and Winstein 1948) became necessary. It is a

Table 3. Second order rate constants for the reaction of phenacyl bromides + aniline at 40°C in mixed media.

Solvent composition (wt.%)	$k \times 10^4 (\text{l mol}^{-1} \text{s}^{-1})$			
	<i>p</i> -Bromo phen	Phen	<i>p</i> -Methyl phen	Y_s
<i>Methanol</i>				
60	69.3	53.9	48.9	0.27
70	51.4	37.2	36.1	0.11
80	39.1	28.7	26.1	0.00
90	28.3	20.9	17.9	-0.13
100	21.0	15.0	14.4	-0.28
<i>Ethanol</i>				
50	71.7	49.0	45.7	0.20
60	50.8	35.0	31.8	0.11
80	37.5	26.9	22.9	0.00
100	23.3	17.9	14.4	-0.17
<i>Dioxane*</i>				
35	142.5	128.1	106.0	0.82
45	112.4	79.6	69.4	0.61
60	64.4	44.8	37.2	0.37
70	42.3	27.8	24.7	0.16
80	28.3	19.1	18.4	0.00

* Problems with solubility prevented study in pure dioxane

Abbreviations as in table 1

relation which expresses the effect of the medium on the reactivity of S_N^1 solvolysis reactions in various water-organic solvent mixtures. The mY correlation has earlier been extended to the reactions following second-order kinetics and obeying the S_N^2 mechanism (Soni *et al* 1973; Shah *et al* 1981). In the present investigation Y_s is defined as

$$Y_s = \log k_0^s - \log k_0^0$$

where k_0^s and k_0^0 are the rate constants of standard reaction i.e. reaction of phenacyl bromide with aniline in medium 's' and reference solvent respectively (solvent + water mixture comprising 80% of solvent by weight was considered as reference solvent). The value of m for the standard reaction was considered as unity and the value of Y_s was assumed to be zero for the reference solvent. Linear plots were obtained for all the substrates in methanol + H₂O, ethanol + H₂O and dioxane + H₂O systems. The data are presented in tables 3 and 4. The correlation coefficient is of the order of 0.99 in all the cases. The calculated values of k_0 compare very well with the observed values. It is observed that the values of Y_s are negative for a system with solvent content higher than 80% by weight and are positive for the medium with solvent less than 80% by weight. It is indeed gratifying to note that the value of Y_s increases with increase in the water content of the medium i.e. the parameter Y_s reflects the relative order of solvent polarity.

It is clear from the data in table 2 that activation energy of the reaction has a value

Table 4. Parameters from the Grunwald–Winstein relation.

$$\log k = \log k_0 + m Y_s$$

Substrate	<i>m</i>	Correlation coefficient <i>r</i>	log <i>k</i> ₀	
			exp.	calcd.
<i>Methanol + H₂O</i>				
<i>p</i> -Bromo phen	0.95	0.99	-2.42	-2.40
<i>p</i> -Methyl phen	1.00	0.99	-2.63	-2.57
<i>Ethanol + H₂O</i>				
<i>p</i> -Bromo phen	1.1	0.99	-2.40	-2.42
<i>p</i> -Methyl phen	1.1	0.99	-2.58	-2.63
<i>Dioxane + H₂O</i>				
<i>p</i> -Bromo phen	0.86	0.99	-2.54	-2.52
<i>p</i> -Methyl phen	0.95	0.99	-2.73	-2.75

Abbreviations as in table 1

(13–15 kcal mol⁻¹) which is characteristic of polar bimolecular reaction taking place in solution. Free energy of activation in all the solvents is nearly the same i.e. about 22 kcal mol⁻¹.

Δ*S*[‡] is negative as expected for the bimolecular reaction taking place in solution. The frequency factor (log *A*) remains constant for a given set of reactants at different temperatures.

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