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Proximity Effect Induced by Hydrogen-Bonding Association. A Detailed Kinetic Study

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Abstract: The proximity effect induced on a carboxylate by an urea binding site positioned near an electrophilic centre, as exemplified by the reaction of butanoate ion with the compound **1**, has been investigated in DMF at 25 °C. The maximum catalytic effect observed at low butanoate concentrations is *ca.* 11. The proximity effect as measured by the effective molarity of the intramolecular process is *ca.* 3 mol dm^{-1}. The effect of added *N,N'*-dimethylurea on the reaction of butanoate ion with *p*-nitrophenyl acetate, serving as intermolecular model reaction, has been also investigated.

It has recently been demonstrated that even simple mono ureas can bind carboxylates in polar aprotic solvents by hydrogen bond.[1] Owing to our interest in catalysis in supramolecular systems,[2] we decided to exploit this type of interaction to investigate the proximity effect induced on a nucleophile (Nu) by a binding site (BS) positioned near an electrophilic centre (El), as schematically depicted in Fig. 1. Accordingly we chose a carboxylate as nucleophile, urea group as binding site, and *p*-nitrophenyl ester as electrophilic centre, in that the reaction between a carboxylate and a *p*-nitrophenyl ester in DMF had proven to be a clean second-order reaction occurring as shown in Eq. 1.[3]

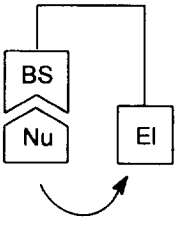


Fig. 1

$$RCO_2^- + R'CO_2C_6H_5\text{-}p\text{-}NO_2 \xrightarrow{DMF} RCO_2COR' + p\text{-}NO_2C_6H_5O^- \qquad (1)$$

Before tackling the system sketched in Fig. 1, it was firstly necessary to evaluate the effect of the hydrogen-bonding coordination on the nucleophilicity of the carboxylate ion. To this end it was studied the effect of added *N,N'*-dimethylurea (DMU) on the intermolecular reaction shown in Eq 1 with R = Pr and R' = Me. Rate measurements were carried out in DMF at 25.0 °C on very dilute *p*-nitrophenyl acetate (PNPA) solutions (*ca.* $4x10^{-5}$ mol dm^{-3}) in the presence of excess ($2.00x10^{-2}$ mol dm^{-3}) tetramethylammonium butanoate (TMAB) and of varying amounts of DMU. Reactions were followed spectrophotometrically by monitoring the appearance of *p*-nitrophenoxide ion at λ 420 nm.

Preliminary rate measurements in the absence of DMU and with varying amounts of TMAB in the range *ca.* $1x10^{-3}$ to $5x10^{-2}$ mol dm^{-3} allowed the evaluation of the second-order rate constant (k_0 1.93 dm^3 s^{-1} mol^{-1}).

Second-order rate constants k_{obs} for reactions carried out in the presence of DMU were calculated from the observed pseudo-first-order rate constants and the known concentration of TMAB. The ratios k_{obs}/k_0, plotted in Fig. 2 against the analytical concentration of DMU, were taken as a measure of the reactivity inhibition of

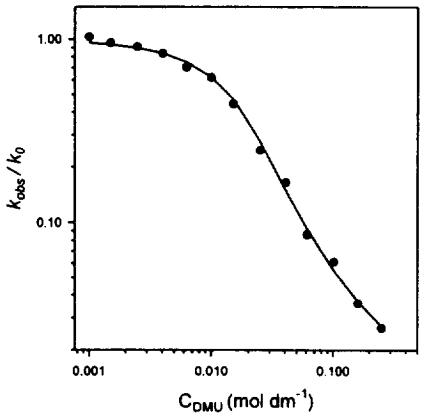


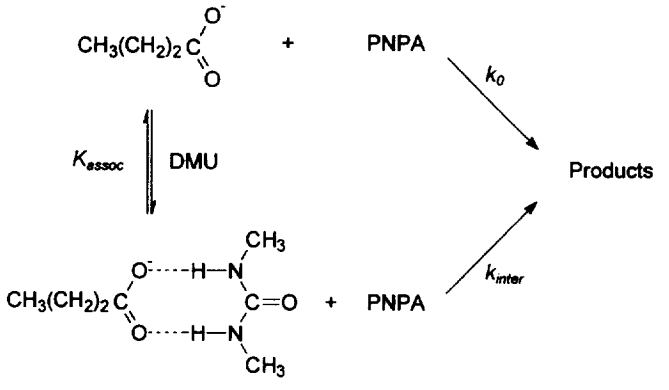
Fig. 2. Effect of DMU on the rate of acetyl transfer from PNPA to butanoate ion in DMF at 25°C

butanoate ion because of hydrogen bond with DMU. At the maximum concentration of DMU (*ca.* 0.25 mol dm^{-3}) the reaction is slowed down by *ca.* 40 times.

The experimental data were accomodated to a good precision by the binding isotherm in Eq. 2, which is easily derived from Scheme 1.

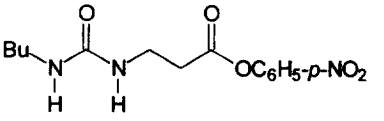
$$\frac{k_{obs}}{k_0} = \frac{1 + \frac{k_{inter.}}{k_0} K_{assoc}[DMU]}{1 + K_{assoc}[DMU]} \qquad (2)$$

The curve shown in Fig. 2 was calculated according to Eq. 2[4] with K_{assoc} = 270 ± 20 dm^3 mol^{-1} and k_{inter} = (2.2 ± 0.4)x10^{-2} dm^3 s^{-1} mol^{-1}. The latter figure indicates that butanoate associated with DMU is less nucleophilic than the free ion by *ca.* 88 times.



Scheme 1

In order to study the process illustrated in Fig. 1, we prepared the compound **1**.[5] The methylene chain between the urea group and the ester function was kept as shorter as possible[6] in order to minimize the entropic loss upon the intramolecular process.[7]



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Rate mesurements were carried out in DMF at 25.0 °C on very dilute solutions of the compound **1** (*ca.* 5x10^{-5} mol dm^{-3}) in the presence of varying amounts of TMAB in the range *ca.* 6x10^{-4} to 6x10^{-2} mol dm^{-3}. The observed pseudo-first-order rate constants k'_{obs} are plotted against the concentration of TMAB in Fig. 3. The experimental points show an undeniable tendency to saturation well described by Eq. 3, which is obtained on the basis of Scheme 2.

$$k_{obs} = \frac{\left(1 + \frac{k_{intra}}{k_0} K_{assoc}\right) k_0 [TMAB]}{1 + K_{assoc}[TMAB]} \qquad (3)$$

Non-linear least squares of the experimental data according to Eq. 3, by assuming for k_0 the value obtained in the reaction with PNPA, yielded K_{assoc} = 280 ± 60 dm^3 mol^{-1} and k_{intra} = (6.9 ± 0.4)x10^{-2} dm^3 s^{-1} mol^{-1}. These values inserted in Eq. 3 allowed the calculation of the curve shown in Fig. 3. The fact that the

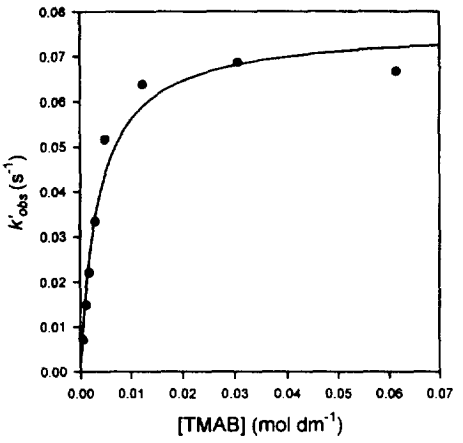


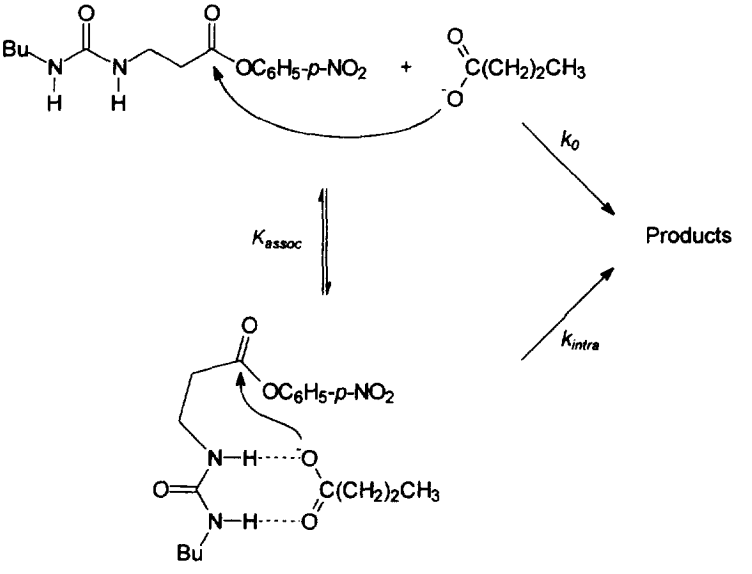
Fig 3. Plot of pseudo-first-order rate constants of the reaction shown in Scheme 2 in DMF at 25°C against the butanoate ion concentration

association constant of butanoate ion with **1** is, within the experimental errors, equal to that with DMU lends support to the reliability of the data analysis.

The catalytic effect is given by the ratio of the second-order rate constants k_{obs}/k_0 where $k_{obs} = k'_{obs}/[TMAB]$ (Eq. 4).

$$\frac{k_{obs}}{k_0} = \frac{1 + \frac{k_{intra}}{k_0} K_{assoc}}{1 + K_{assoc}[TMAB]} \qquad (4)$$

Eq. 4 shows that catalysis is observed only when [TMAB] < k_{intra}/k_0 (*ca.* 3.6×10^{-2} mol dm^{-3}), whereas when [TMAB] > k_{intra}/k_0 the reaction of butanoate ion with **1** is slower than that with PNPA. The maximum catalytic effect (*ca.* 11) is observed in the region where $1 >> K_{assoc}$[TMAB], *i.e.* when [TMAB] < *ca.* 3.6×10^{-4} mol dm^{-3}. This behaviour is due to the fact that the catalytic contribution of the intramolecular process ($k_{intra}K_{assoc}/k_0$) is constant whereas the inhibitory contribution due to the association of the substrate **1** increases on increasing [TMAB].



Scheme 2

The effectiveness of an intramolecular process with respect to the corresponding intermolecular counterpart, or in other word, the proximity effect, is measured by the effective molarity (EM)[7] which is defined as the ratio k_{intra}/k_{inter} (*ca.* 3 mol dm^{-3}). The EM should be viewed as a reduced intramolecular reactivity, i.e. a

reactivity that is corrected for the inherent reactivity of the associated butanoate ion. In the present case the intramolecular process involves the formation of a six-membered cyclic transition state. The entropic component of the EM for ring closure of a bifunctional chain leading to a six-membered ring has been estimated to be *ca.* 150 mol dm^{-3}.[8] The effective value of the EM, however, can be considerably lower if some strain is present in the cyclic transition state. Although saturated six-membered rings are normally devoid of strain, in the present case the necessary co-linearity of N-H-O atoms imposed by hydrogen bonding coordination might be the cause of severe strain in the transition state, thus explaining the low EM value that has been obtained.

Work is in progress to establish the effect of the length of the methylene chain, and of the nature of the binding site.

REFERENCES AND NOTES

1. (a) Fan, E.; Van Arman, S. A.; Kincaid, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 369-370.
   (b) Albert, J. S.; Hamilton, A. D. *Tetrahedron Lett.* **1993**, *34*, 7363-7366.
   (c) Hamann, B. C.; Branda, N. R.; Rebek Jr., J. *Tetrahedron Lett.* **1993**, *34*, 6837-6840.
   (d) Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072-7080.
2. (a) Doddi, G.; Ercolani, G.; La Pegna, P.; Mencarelli, P. *J. Chem. Soc., Chem. Commun.* **1994**, 1239-1240.
   (b) Ercolani, G.; Mandolini, L. *J. Am. Chem. Soc.* **1990**, *112*, 423-427.
   (c) Ercolani, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1983**, *105*, 6146-6149.
3. Cacciapaglia, R.; Mandolini, L.; Tomei, A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 367-372.
4. In the quantitative analysis of rate data, allowance was made for the fraction of DMU sequestered by butanoate ion. The free DMU appearing in Eq. 2 is related to the analytical concentration of DMU (C_{DMU}) by the folloving equation: $[DMU] = [- J + (J^2 + 4K_{assoc}C_{DMU})^{1/2}]/2K_{assoc}$. In this equation $J = 1 + K_{assoc}(C_{TMAB} - C_{DMU})$, where C_{TMAB} is the analytical concentration of butanoate ion.
5. The ester **1** was prepared by condensation of the corresponding acid with *p*-nitrophenol in dioxane by using dicyclohexylcarbodiimide as condensing agent. Yield 35 %. The acidic precursor was prepared by reaction of β-alanine and butyl isocyanate in acetonitrile. Yield 75 %.
6. There are indications that the compound with only one methylene between the urea group and the ester function would tend to spontaneously cyclise yielding a hydantoin derivative. Cohen, S.; Oppenheimer, E. Biological Formation and Reactions of Cyanates. In *The Chemistry of Functional Groups: The Chemistry of Cyanates and their Thio Derivatives*; Patai, S. Ed; John Wiley and Sons, Inc.: Chichester, 1977; pp. 929-931.
7. (a) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183-278.
   (b) Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 1-111.
8. Ref. 7b; p. 84.

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