Ion Pairing and Reactivity of the Alkali-metal Derivatives of Diethyl 5-Bromopentylmalonate[1]

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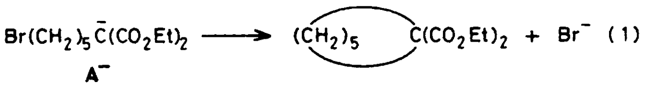
The effect of added tetraethylammonium and alkali-metal (Li, Na, K) bromides on the rate of cyclisation of the anion derived from diethyl 5-bromopentylmalonate has been studied over a wide concentration range in 99% aqueous Me_2SO at 25.0 °C. Whereas the rate of cyclisation is unaffected by the tetraethylammonium salt, it is significantly retarded by the alkali-metal salts. These rate-depressing effects are quantitatively accounted for on the basis of a reaction scheme involving independent kinetic contributions from the free reactant anion and from the cation-paired reactant anion. A self-consistent kinetic analysis has allowed determination of both the reactivities of the associated species and the ion-pairing equilibrium constants. The results show that the latter vary in the order $Li^+ > Na^+ > K^+$, showing that the ion-pairing tendency is dominated by coulombic interactions. Consistently, the opposite trend is observed with the ion-pair reactivities, indicating a greater reduction of the nucleophilicity of the nucleophilic carbon by the stronger interaction with the smaller cations in the cation-associated species.

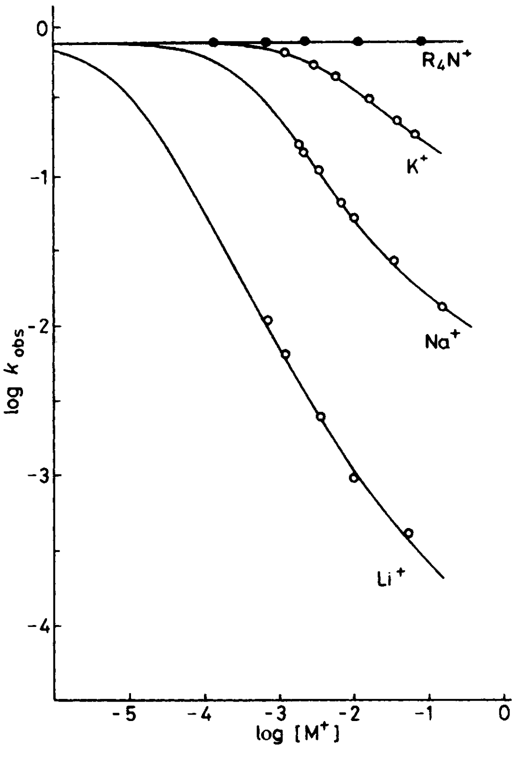
There is substantial evidence that dissociated anionic nucleophiles are more reactive than the corresponding ion pairs in S_N2 reactions.[2] A physico-organic approach to the study of structure effects on reactivity calls for correlations of the relative reactivity of free ions and ion pairs with the stability and structure of ion pairs. In addition to the paucity of ion-pairing constants, severe limitations to such studies derive from the general difficulty of a meaningful separation of ion pair from free ion contributions to the overall reaction rate, mostly due to the markedly non-ideal behaviour of electrolyte solutions, which is especially so in many solvents of interest to organic chemists.

In connection with previous studies on ion-pairing effects on the reactivity of phenoxide ions,[3] a self-consistent kinetic approach has been presented, which under favourable circumstances provides a measure of ion-pair reactivity even when it is significantly lower than free ion reactivity, as well as a determination of ion-pairing association constants.

In view of the mechanistic and synthetic importance of the alkali derivatives of malonic ester, and of our current interest in cyclisation reactions of diethyl ω-bromoalkylmalonates,[4] we have undertaken a systematic investigation of the effect of added alkali-metal ions on the rate of cyclisation of the anion derived from diethyl 5-bromopentylmalonate in 99% aqueous Me_2SO at 25.0 °C [equation (1)] which affords 1,1-bisethoxycarbonylcyclohexane in quantitative yield.[4b] Beyond the mechanistic value of ion-pairing effects on reactivity, we are currently interested in checking the validity and applicability of the self-consistent kinetic approach.



$$\underset{A^-}{Br(CH_2)_5\bar{C}(CO_2Et)_2} \longrightarrow (CH_2)_5C(CO_2Et)_2 + Br^- \quad (1)$$



Cation concentration *versus* rate profiles for the cyclisation of $Br(CH_2)_5C^-(CO_2Et)_2$ in the presence of added cations, at 25.0 °C in 99% aqueous Me_2SO. The points are experimental (k_{obs}/s^{-1}) and the solid lines are calculated from equation (3).

Results

The choice of the anion derived from diethyl 5-bromopentylmalonate as the substrate for the present kinetic investigation is motivated by the fact that its cyclisation rate, lying conveniently in the stopped-flow range, is sufficiently fast to be unaffected by the already noted 'spontaneous' decay of diethyl alkylmalonate anions.[4] This condition was fulfilled even in the presence of the rate-retarding effect of added salts, with the exception of the runs where the LiBr concentration was $\geqslant 3.7 \times 10^{-3}$M. A correction was required in these cases because of the non-quantitative yield of ring product (see Experimental section). The alkali-metal ions (Li^+, Na^+, and K^+) and the Et_4N^+ ion were added as bromides, which behave as strong electrolytes in Me_2SO solution.[3] Kinetic runs were started by fast addition of Me_4NOH to the solution of reactant AH and salt. As shown by control experiments carried out with diethyl butylmalonate as model compound, excess of base was required to promote full ionization of the malonic ester

Table 1. Effect of ion pairing on the cyclisation of $Br(CH_2)_5C^-(CO_2Et)_2$ in 99% Me_2SO at 25.0 C[a]

[Salt] M	k_{obs}/s^{1}	k_{obs}/k_i	f[b]	$f \times \frac{k_{ip}}{k_{obs}}$[c]
		Et_4NBr		
1.50×10^{4}	0.765			
7.50×10^{4}	0.767			
2.50×10^{3}	0.773			
1.25×10^{2}	0.762			
8.91×10^{2}	0.769			
	av. $k_{obs} = k_i = 0.767 \pm 0.003$			
		LiBr		
7.69×10^{4}[d]	1.06×10^{-2}	1.38×10^{2}	0.9876	0.010
1.28×10^{3}[d]	6.25×10^{3}	8.15×10^{3}	0.9922	0.017
3.73×10^{3}[d]	2.40×10^{3}[e]	3.13×10^{3}	0.9970	0.046
1.02×10^{2}	9.27×10^{4}[e]	1.21×10^{-3}	0.9987	0.12
5.54×10^{2}	3.95×10^{4}[e]	5.15×10^{4}	0.9997	0.28
		NaBr		
1.98×10^{-3}	0.158	0.206	0.799	0.04
2.28×10^{3}	0.140	0.183	0.818	0.05
3.69×10^{3}	0.108	0.141	0.873	0.07
7.41×10^{3}	6.32×10^{2}	8.24×10^{2}	0.926	0.13
1.09×10^{2}	5.12×10^{2}	6.68×10^{2}	0.945	0.16
3.66×10^{2}	2.63×10^{2}	3.43×10^{2}	0.978	0.32
1.56×10^{1}	1.29×10^{2}	1.68×10^{2}	0.994	0.66
		KBr		
1.33×10^{3}	0.641	0.836	0.188	0.03
3.17×10^{3}	0.538	0.701	0.336	0.06
6.38×10^{3}	0.439	0.572	0.480	0.10
1.76×10^{2}	0.314	0.409	0.678	0.20
4.17×10^{2}	0.229	0.299	0.806	0.33
7.21×10^{2}	0.182	0.237	0.866	0.45

[a] The initial substrate concentration was *ca.* 1.1×10^{4}M. [b] Fraction of ion pairing calculated as $K\gamma_\pm^2[M^+]/1 + K\gamma_\pm^2[M^+]$. [c] Fractional contribution of the ion-pair pathway to the overall rate. [d] Corrected value (see text). [e] Corrected for non-quantitative yield of ring product, as determined by g.l.c. (see Experimental section).

derivative, because of the acidity content of the solvent. Typically the reactant concentration was 1×10^{-4}M and the formal concentration of added base was 2×10^{-4}M. The kinetics were monitored by following the disappearance of the malonate ion absorption at 285 nm. In all cases good first-order plots were obtained up to at least 80% conversion. The observed first-order rate constants k_{obs} are given in detail in Table 1 and are plotted as a function of the salt concentration in the Figure. In contrast to the marked rate-depressing effect exerted by the alkali-metal bromides in the order $Li^+ > Na^+ > K^+$, the lack of any significant influence of Et_4NBr was taken as evidence of a negligible association between A^- and the tetra-alkylammonium ion. This led to the conclusion that the k_{obs} value of 0.767 s^{-1} obtained when the Me_4N^+ ion accompanying the added base is the sole cation present may be taken with confidence as the specific rate k_i for the reaction of the unassociated anion A^-. On the other hand, the observed retarding effects exerted by the alkali-metal ions were accounted for in terms of classical kinetics by a reaction scheme[5] involving independent contributions to the overall rate from the free ion A^- and from the ion pair A^-M^+, namely equation (2).

$$v = k_i[A^-] + k_{ip}[A^-M^+] \tag{2}$$

If the concentration of the cation is large compared with that of the substrate, then equation (2) predicts first-order kinetics, with the observed specific rate k_{obs} given by equation (3) where equation (4) applies. K is the equilibrium constant for ion

Table 2. Rate and equilibrium parameters

Cation	k_{ip}/k_i[a]	k_{ip}/s^{1}	log K	log $K_{T\neq}$
Li^+	1.4×10^{4}	$(1.1 \pm 0.4) \times 10^{4}$	5.08 ± 0.03	1.25 ± 0.13
Na^+	1.1×10^{2}	$(8.6 \pm 1.1) \times 10^{3}$	3.39 ± 0.02	1.44 ± 0.05
K^+	1.2×10^{1}	$(9.4 \pm 1.8) \times 10^{2}$	2.32 ± 0.04	1.40 ± 0.10

[a] Calculated as A/B.

$$k_{obs} = k_i \frac{1 + (k_{ip}/k_i)K\gamma_\pm^2[M^+]}{1 + K\gamma_\pm^2[M^+]} \tag{3}$$

$$K = \frac{[A^-M^+]}{[A^-][M^+]\gamma_\pm^2} \tag{4}$$

pairing. In terms of transition-state theory equation (3) may be written in the form (5) where $K_{T\neq} = (k_{ip}/k_i)K$ and the equilibrium constant for association of M^+ with the transition state $T^{\neq}$.[6,7]

$$k_{obs} = k_i \frac{1 + K_{T\neq}\gamma_\pm^2[M^+]}{1 + K\gamma_\pm^2[M^+]} \tag{5}$$

Since the alkali-metal bromides behave as strong electrolytes in Me_2SO, the formal concentration of salt was taken as a reasonable approximation for $[M^+]$, with the exception of the runs where the LiBr concentration was $\leqslant 3.7 \times 10^{-3}$M. Since there are indications[3] of a strong interaction between Li^+ and OH^-, the added salt concentration was corrected in these cases for the excess of base, to account for the amount of Li^+ possibly sequestered by OH^-. In the least favourable case, the magnitude of this correction was *ca.* 15% of the total concentration, and significantly less in the other cases. Activity coefficients for charged species were calculated from equation (6) which was found[3] to account well for the non-ideal behaviour of the alkali-metal salts of organic anions in 99% Me_2SO up to ionic strength in the neighbourhood of 0.1M.

$$\log \gamma_\pm = -1.12\,\mu^{\frac{1}{2}} + 1.65\,\mu \tag{6}$$

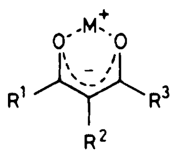
A non-linear least-squares procedure[8] was used to fit the experimental data to an equation of the type (7) where $y = (k_{obs}/k_i)$ and $x = \gamma_\pm^2[M^+]$. The least-squares procedure gave

$$y = \frac{1 + Ax}{1 + Bx} \tag{7}$$

the following results for the numerical values of the A and B parameters, which are reported in the given order for the various alkali-metal ions together with the standard deviations: Li^+, 17.7 ± 5.5, $1.19 \pm 0.06 \times 10^5$; Na^+, 27.8 ± 3.5, $2.49 \pm 0.11 \times 10^3$; K^+, 25.5 ± 6.1, $2.08 \pm 0.20 \times 10^2$. The Figure shows that the experimental points are well fitted by the full lines calculated by means of the least-squares parameters. According to equations (3) and (5) the A and B values were translated into the rate and equilibrium constants collected in Table 2, from which the fractions of ion pairing and the fractional contributions of the ion-pair pathway to the overall rate (Table 1) were calculated.

Discussion

The rate-retarding effect exerted by alkali-metal ions on the rate of intramolecular alkylation of the anion derived from diethyl



(1)

5-bromopentylmalonate has been quantitatively accounted for in terms of a kinetic model based on Acree's concept of associated and dissociated ions as kinetically distinguishable species.[5] The basic feature of our method is that the mass-law effect exerted by varying amounts of an external strong electrolyte changes the relative proportions of free and ion-paired enolate ion over a relatively wide range. As a result, large effects on the reaction rate can be observed, provided that k_{ip} is sufficiently different from k_i. Another important feature is that in a given run the essential constancy of $[M^+]$ ensures a constant ratio of free over ion-paired anion, thus avoiding the complications arising from the lack of constancy of the dissociation degree in the course of the reaction.[9] Finally, the reactivity of the free ion (k_i) can be directly measured, with the obvious advantage that a three-parameter equation reduces to an equation with only two adjustable parameters. When applied to the present reaction, the method reveals a situation in which there is a strong and markedly cation-dependent ion pairing with the reactant anion A^-, but only a weak and little cation-dependent interaction with the transition state $T^{\neq}$. Experimental uncertainties in the K values are much smaller than those in the $K_{T^{\neq}}$ values because the investigated range of added salt concentrations was not extended to cover the 0.1—1M range, due to the obvious difficulties to account with any precision for the non-ideal behaviour of charged species in this region of high ionic strengths. The log K values (Table 2) compare well with the log K for ion-pair association of the diethylmalonate anion with alkali-metal ions obtained by Olmstead and Bordwell[10] in Me_2SO at 25 °C with an indicator method. These authors report a log K value of 4.56 ± 0.07 for Li^+, one of 3.30 ± 0.06 for Na^+, and one of 2.31 ± 0.02 for K^+. It is not clear whether the difference of some 0.5 in log K in the Li^+ case is due to experimental errors or to the different structures of the two substrate anions, but the agreement for the larger cations is remarkably good.

The situation presented by the log K values is one where the stability order is dominated by cation interaction, namely, one where the stronger cation–anion interaction with the smaller cations more than offsets the greater loss of solvation suffered by the smaller cations upon contact pairing.[3,10] Large and widely spaced association constants decreasing in the order $Li^+ > Na^+ > K^+$ have been reported in Me_2SO[10,11] for many β-ketoenolate ions which can adopt the U-type conformation **(1)** suitable for chelate interaction with the cation. Similar trends have been reported in the same solvent for anions presenting a localized charge on an electronegative atom such as oxygen[3,12] (*i.e.*, alkoxides and phenoxides).

However, as Olmstead and Bordwell[10] have shown, when the charge on the anion is more spread, the intensity of cation–anion interactions decreases, and the importance of cation solvation increases. This causes flattening in the differences among cations, with possible inversions in the trend of ion-pairing tendency, or even anomalous orders. On this basis the weak and nearly cation-independent associations with the transition state of reaction (1) (log $K_{T^{\neq}}$ in Table 2) are easily understood, in accord with the widely accepted picture of the transition state for an S_N2 reaction between an anionic nucleophile and a neutral molecule as a species with a diffuse negative charge. Given the substantial cation insensitiveness of the ion-pair transition states, the ion-pair reactivity order is substantially determined by the stability order of the ion-pair reactants. The lithium reaction represents a spectacular case of low ion-pair reactivity. It is noteworthy that in the presence of 5.54×10^{-2}M-LiBr a quantity as low as 0.03% of A^- is present as a free ion, yet *ca.* 70% of the reaction still proceeds *via* a transition state which does not contain Li^+.

Experimental

Diethyl 5-bromopentylmalonate[4] was available from a previous investigation. The mixed solvent (99% aqueous Me_2SO, v/v) and the Me_4NOH stock solution in 93% aqueous Me_2SO were prepared and handled as before.[3] Rate measurements were carried out at 25 °C as previously described[4b] either on a Durrum model 110 stopped-flow or on a Varian DMS 90 spectrophotometer.

Product Analyses.—These were carried out in the experiments with [LiBr] ⩾ 3.7×10^{-3}M on scaled-up kinetic runs. After at least ten half-lives a known amount of octadecane (internal standard) was added. The mixture was diluted with brine and extracted several times with $CHCl_3$. The organic extracts were washed with water, dried (Na_2SO_4), and carefully concentrated to a small volume by distillation at atmospheric pressure. G.l.c. analysis of the residue was performed in the interval 140—180 °C on a Hewlett–Packard 5830a flame ionization gas chromatograph fitted with a 250 cm × 3.2 mm 2% OV 17 on 80—100 Chromosorb GAW DMCS column.

The yields of 1,1-bisethoxycarbonylcyclohexane were 80, 65, and 53% in the runs with [LiBr] equal to 3.73×10^{-3}, 1.02×10^{-2}, and 5.54×10^{-2}M, respectively. The corresponding rate constants were corrected accordingly.

Acknowledgements

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