

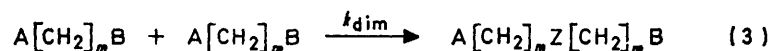
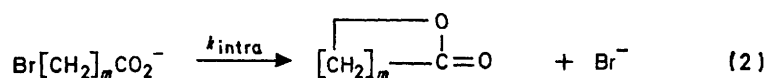
Ring Closure Reactions. Part 6.¹ Intermolecular Models for Intramolecular Reactions. Reactions between Long-chain Alkanoate Ions and Alkyl Bromides as Intermolecular Analogues of the Lactonization of ω -Bromoalkanoate Ions

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The search for a general intermolecular model for lactonization of the anions of straight-chain ω -bromoalkanoic acids led to the determination of the rate constants of the S_N2 reaction between some alkanoate ions and alkyl bromides, involving straight-chains of varying lengths up to C_{18} in both reactants. The experimental results show the appearance of a slight rate-enhancing effect on increasing chain length which may be attributed, at least in part, to lyophobic interactions of alkyl chains. Since on going from the C_4 to the C_{18} reactants the observed rate varies by a factor of two, it is concluded that any of the reactant pairs in the set of compounds examined provide a reasonably good model for the intermolecular analogue of the lactonization reaction.

In view of our continuing interest in the energetics of intramolecular reactions and of the basic principles underlying intra- and inter-molecular reactivity,¹ we have considered reaction (1) as a model for the intermolecular analogue of the lactonization (2) of ω -bromoalkanoate ions, one of the reactions currently being considered in our investigations on ring closure reactivity.² In principle, for any cyclization reaction of a bifunctional

to arise from special effects associated with the chain length and the mutual interactions of the reactive groups in the bifunctional compounds involved as substrates in the cyclizations. Even a qualitative prediction of the factors involved seems unlikely, since little information and conflicting evidence only are available on the factors affecting the reactivity of long-chain compounds, *viz.* the interplay of steric and conformational



monomer, the intermolecular counterpart is the related dimerization (3). However, since the experimental determination of k_{dim} is not generally practicable, even though it has been measured in special cases,^{2,3} it seemed worthwhile to search for a simple model close enough to the system for which a comparison is required and to investigate its limits of application for use in intramolecular problems. For example, the model would require only one k_{inter} value to be used in the calculation of the effective molarity⁴ for all terms of a given cyclization series. Difficulties in finding such a model are expected

effects,⁵ the role of remote substituents capable of inductive and/or field effects,⁶ and the rate enhancement attributable to lyophobic interactions of carbon chains.⁷⁻⁹

We have carried out a systematic investigation on the effect of chain length and of some ω -substituents on reaction (1), involving straight-chain alkanoate anions

¹ Part 5, G. Illuminati, L. Mandolini, and B. Masci, *J. Amer. Chem. Soc.*, 1975, **97**, 4960, and previous papers of the series.

² C. Galli, G. Illuminati, and L. Mandolini, *J. Amer. Chem. Soc.*, 1973, **95**, 8374, and unpublished work.

³ C. Galli and L. Mandolini, *Gazzetta*, 1975, **105**, 367.

⁴ (a) W. P. Jencks, 'Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969, p. 10; (b) M. I. Page, *Chem. Soc. Rev.*, 1973, **2**, 295.

⁵ These could be held responsible for the alternation effects sometimes observed in homologous series. This has been reviewed by E. Eliel, in 'Steric Effects in Organic Chemistry,' ed. M. S. Newman, Wiley, New York, 1956, p. 138. For additional examples see D. T. Mowry, *Chem. Rev.*, 1948, **42**, 197; R. Foster, 'Organic Charge Transfer Complexes,' Academic Press, London, 1969, p. 199.

⁶ See, for example, N. Bodor, *Rev. Roumanie Chim.*, 1968, **13**, 555.

⁷ J. R. Knowles and C. A. Parsons, *J.C.S. Chem. Comm.*, 1975, 755; C. A. Blyth and J. R. Knowles, *J. Amer. Chem. Soc.*, 1971, **93**, 3017, 3021.

⁸ D. Oakenfull, *J.C.S. Perkin II*, 1973, 1006.

⁹ J. P. Guthrie and Y. Ueda, *J.C.S. Chem. Comm.*, 1974, 991.

and alkyl bromides in 99% dimethyl sulphoxide (DMSO) at 50 °C.

EXPERIMENTAL

Materials.—The mixed solvent was prepared as previously described.² 8-Bromo-octanoic acid was available from a previous investigation.² All the other materials were readily available reagent-grade chemicals, purified for kinetic purposes by fractional distillation and/or crystallization. All b. and/or m.p.s. agreed well with those reported in the literature. When desirable, the purity of the compounds was checked by g.l.c.

Product Analysis.—A solution of butyl bromide (2.64 g, 193 mmol) and butyric acid (1.70 g, 193 mmol) in DMSO (140 ml) was rapidly added with stirring to 85% KOH (1.28 g, 193 mmol) dissolved in water (2 ml). The mixture was stirred at 50 °C for 30 min. After cooling, it was diluted with a concentrated aqueous solution of sodium chloride and extracted with ether. The organic layer was washed with water and dried (Na₂SO₄). Removal of solvent left practically pure (t.l.c.) butyl butyrate (2.65 g, 95%), b.p. 162–164 °C at 760 mmHg, *n*_D²⁰ 1.409 6 (lit.,¹⁰ b.p. 166 °C at 760 mmHg, *n*_D²⁰ 1.407 5).

Rate Determinations.—Solutions were prepared by placing in a 50 ml volumetric flask *ca.* 40 ml of solvent containing the required amount of acid which was exactly neutralized by addition of the stoichiometric amount of 1.94×10^{-2} M CO₂-free KOH stock solution in a mixed solvent containing 7% water to allow for the low solubility of KOH in DMSO. In most experiments the initial concentration of acid was in the range $2-5 \times 10^{-4}$ M. Small volumes (0.4–1.0 ml) of the KOH standard solution were required. The small variations in water content for runs with different initial concentrations had a negligible effect on the rate constants. After thermal equilibration at 50 ± 0.1 °C, the reaction was started by rapidly adding the calculated volume of a standard solution of alkyl bromide in the same solvent. The reaction was monitored at given intervals by taking samples of the solution which were quenched in 1N-H₂SO₄, and potentiometrically titrated with silver nitrate as previously described.² 'Infinity' titres were generally calculated on the basis of the initial concentration of the less concentrated reactant present in the reaction mixture. Whenever tested, the experimental values were found to be in good agreement with the calculated ones. In the reactions of 8-bromo-octanoate ion, a large excess of the second reactant (see experiments 12 and 13 in the Table) was required in order to make the bimolecular process compete significantly with intramolecular lactonization.² Under the given conditions first-order behaviour is predicted, according to equation (4), where *k*_{intra} (1.24×10^{-4} s⁻¹) is the first-order lactonization rate coefficient and R represents the second reactant.

$$k_{\text{obs}} = k_{\text{intra}} + k_{\text{inter}}[\text{R}] \quad (4)$$

The dimerization rate constant of 8-bromo-octanoate ion (as the sodium salt) has been already determined² by the use of a mixed first- and second-order equation in the concentration range 1×10^{-4} – 1×10^{-3} M. There results were *k*_{intra} 1.06×10^{-4} s⁻¹, *k*_{inter} 0.038 l mol⁻¹ s⁻¹.^{*} The intrinsic

* Data reported in ref. 2 as *k*_B and *k*_P values, respectively.

¹⁰ J. C. Munch, *J. Amer. Chem. Soc.*, 1926, **48**, 997.

¹¹ C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' Cornell University Press, Ithaca, 2nd edn., 1969, p. 432.

difficulty in estimating with any precision the parameters in a two parameter equation is well known. Moreover, the determination of *k*_{inter} was rendered more erratic by the fact that under the reported conditions² the overall process is essentially first order, with only minor disturbance from the incursion of the second-order dimerization. Thus, the kinetic parameters for the self-reaction of 8-bromo-octanoate ion have been redetermined, great care being devoted to experimental accuracy. The trial and error calculation method² gave *k*_{intra} 1.24×10^{-4} s⁻¹, *k*_{inter} 0.14 l mol⁻¹ s⁻¹, as 'best' values. Whilst the *k*_{intra} values from the two independent determinations are in fair agreement with each other, if allowance is made for the difficulty in obtaining the mixed solvent with exactly the same features, the *k*_{inter} values differ markedly. Since the present estimation is probably more accurate than the previous one, the two results have been weighted (on the log scale), a weight twice as great being given to the present value.

RESULTS AND DISCUSSION

The nucleophilic substitution reactions of a series of potassium alkanoates with primary alkyl bromides have been studied in 99% aqueous DMSO at 50.0 °C. The reactions of such nucleophiles as EtO⁻, PhO⁻, and Et₃N with homologous series of alkyl halides are known¹¹

Rate data for the ester-forming reaction of the potassium salts of alkanoate ions with primary alkyl bromides in 99% aqueous DMSO (v/v) at 50.0 °C

Expt. no.	Alkanoate ion	Alkyl bromide	<i>k</i> _{inter} /l mol ⁻¹ s ⁻¹ ^a	<i>k</i> _{rel}
1	CH ₃ [CH ₂] ₇ CO ₂ ⁻	CH ₃ [CH ₂] ₈ Br	0.196 ± 0.006	1.00
2	CH ₃ [CH ₂] ₆ CO ₂ ⁻	CH ₃ [CH ₂] ₇ Br	0.279 ± 0.002	1.42
3	CH ₃ [CH ₂] ₁₀ CO ₂ ⁻	CH ₃ [CH ₂] ₁₁ Br	0.290 ± 0.004	1.48
4	CH ₃ [CH ₂] ₁₄ CO ₂ ⁻	CH ₃ [CH ₂] ₁₅ Br	0.346 ± 0.002	1.77
5	CH ₃ [CH ₂] ₁₆ CO ₂ ⁻	CH ₃ [CH ₂] ₁₇ Br	0.368 ± 0.003	1.88
6	CH ₃ [CH ₂] ₂ CO ₂ ⁻	CH ₃ [CH ₂] ₁₁ Br	0.247 ± 0.003	1.26
7	CH ₃ [CH ₂] ₃ CO ₂ ⁻	CH ₃ [CH ₂] ₁₅ Br	0.285 ± 0.004	1.45
8	CH ₃ [CH ₂] ₄ CO ₂ ⁻	CH ₃ [CH ₂] ₁₇ Br	0.273 ± 0.010	1.39
9	CH ₃ CO ₂ ⁻	CH ₃ [CH ₂] ₅ Br	0.189 ± 0.004	0.96
10	CH ₃ [CH ₂] ₁₀ CO ₂ ⁻	CH ₃ [CH ₂] ₅ Br	0.217 ± 0.003	1.11
11	Br[CH ₂] ₁ CO ₂ ⁻	-O ₂ C[CH ₂] ₇ Br	<i>ca.</i> 0.09 ^b	0.46
12	Br[CH ₂] ₇ CO ₂ ⁻	CH ₃ [CH ₂] ₇ Br	0.217 ± 0.012	1.11
13	CH ₃ [CH ₂] ₆ CO ₂ ⁻	-O ₂ C[CH ₂] ₇ Br	0.080 ± 0.006	0.41

^a Runs in duplicate or triplicate. ^b See text.

to follow the reactivity order Me ≫ Et > Pr ≳ Bu ~ higher primary. Hence, no alkyl bromides with less than four carbon atoms were considered in the present investigation, which was aimed at searching for a general model.

Product analysis was performed in the reaction of potassium butyrate with butyl bromide. Butyl butyrate was actually isolated in nearly quantitative yield as the sole product. The synthetic usefulness of the above procedure for the preparation of esters of the type R¹CO₂-CH₂R² lies in simplicity, mild conditions, short reaction times, and good yields.¹²

The reactions were found to follow clean second-order kinetics up to 2–3 half-lives for all compounds examined. Second-order rate coefficients were independent of a two-

¹² Similar methods have appeared recently in the literature. See (a) J. H. Wagenknecht, M. M. Baizer, and J. L. Chroma, *Synth. Comm.*, 1972, **2**, 215; (b) J. E. Shaw, D. K. Kunerth, and J. J. Sherry, *Tetrahedron Letters*, 1973, 689; P. E. Pfeffer, T. A. Foglia, P. A. Barr, J. Schmeltz, and L. S. Silbert, *ibid.*, 1972, 4063.

to three-fold change in initial concentration of either reactant. Change in counter ion (from K^+ to Na^+) in selected cases produced no change in rate. The above observations clearly indicate that under the conditions of the kinetic runs ion-pairing and other association effects are unimportant. The kinetic results are collected in the Table. Inspection of the Table shows that the kinetic effects associated with chain-length variations (experiments 1—10) vary well within a factor of two, which is relatively unimportant when effective molarities are to be compared.^{4b} It follows that any of the reactant pairs in experiments 1—10 provide reasonably good intermolecular models for the lactonization reaction (2). However, such model systems provide only a rough approximation for the dimerization of 8-bromo-octanoate ion (experiment 11), where reduced reactivity is observed relative to monofunctional reacting systems (see, especially, experiment 2). Comparison with experiments 12 and 13 indicates that the above reactivity decrease could be mainly ascribed to the effect of the CO_2^- negative pole on the alkyl bromide reactant compared with that of the ω -bromo-substituent in the alkanoate reactant.

The observed chain-length effect on reactivity deserves a few additional comments. In experiments 1—5 the number of carbon atoms in either reactant was varied simultaneously from 4 to 18. It was found that the rate constants increased on increasing chain length, the C_{18} compounds showing a rate nearly twice as large as that of the C_4 reactants. The observed rate enhance-

ments are far smaller than those previously reported by Knowles and his co-workers⁷ and Oakenfull⁸ for the aminolysis of long-chain esters with long-chain amines, which involve several powers of ten and are attributed to hydrophobic interactions of alkyl chains of ten carbon atoms or so. The work by both groups has been recently criticized by Guthrie and Ueda,⁹ who claim that true rate enhancements due to hydrophobic interactions of alkyl groups as obtained with a steroidal enzyme model are actually much smaller. A log plot of the above rate enhancements *versus* the number of carbon atoms in the alkyl groups gave a reasonably straight line with slope 0.027. A similar plot of rate data from our experiments 1—5 (not shown here) gave a slope *ca.* 0.02. It appears that the rate enhancements observed by us are of the same order of magnitude as those reported by Guthrie. However, since lyophobic interactions of alkyl chains are likely to be much smaller in an aprotic solvent than in water, probably they are not the only factor responsible for the observed chain-length effect in reaction (1).

The existence of additional heretofore unknown factors involved in long-chain reactivity is possibly related to other phenomena. One of these is the alternation effect associated with some properties of homologous series, which has not yet received a sufficiently satisfactory interpretation.⁵

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