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METAL ION EFFECTS ON THE RATE OF INTRAMOLECULAR O-ALKYLATION OF THE ANION OF ETHYL(3-CHLOROPROPYL)ACETOACETATE

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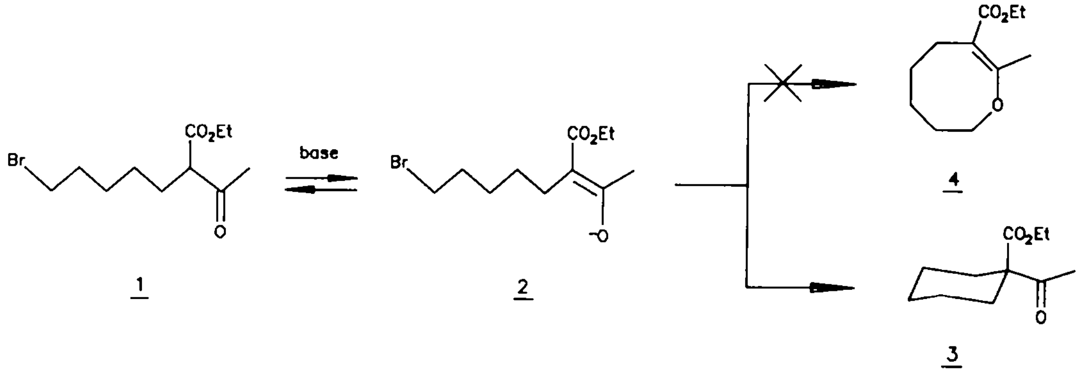
Abstract - The retarding effect of alkali metal and alkaline-earth metal ions on the rate of intramolecular O-alkylation of the title compound has been thoroughly investigated in 99% aqueous Me_2SO at 25°C. Rate data have been dissected into contributions of free ions (k_i) and ion pairs (k_{ip}). Comparison of the present results with available data for intramolecular C-alkylation of a strictly related system, reveals that rate-depressing effects due to cation pairing turn out to be remarkably similar in the two processes, which is at variance with the expectation of a more pronounced cation dependence of the k_{ip}/k_i ratios for O-alkylation than for C-alkylation.

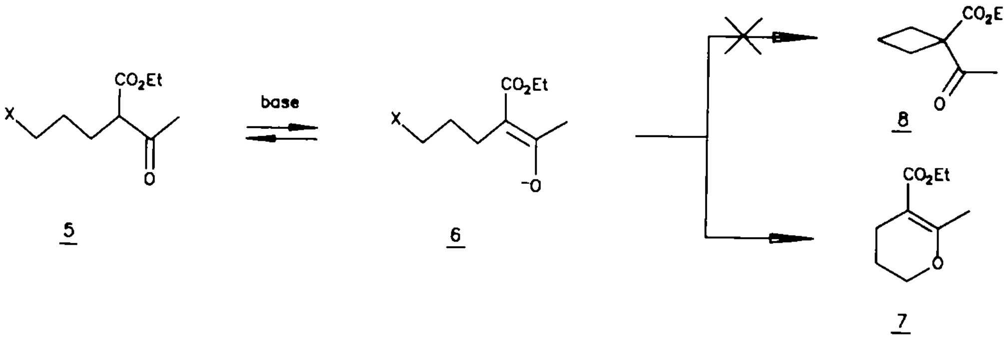
The reactivity of anionic nucleophiles is greatly affected by alkali and alkaline-earth metal ions under conditions where ion pairing and higher-order associations are important.[1]

Our previous kinetic work on metal ion effects on the reactivity of aryloxide,[2,3] β-ketoenolate,[4,5] and carboxylate[6] nucleophiles in alkylation reactions of the S_N2-type has shown that under a suitable set of conditions a meaningful dissection of the overall rate into contributions of free ions, ion pairs, and higher aggregates is possible. One of the above studies[5] dealt with ion pairing effects on the rate of intramolecular C-alkylation in 99% aqueous Me_2SO of the anion **2** derived from ethyl(5-bromopropyl)-acetoacetate **1**, which leads to the cyclohexane derivative **3** as the sole reaction product, with no trace of the O-alkylation product which would involve a highly disfavoured 8-membered ring **4** (Scheme I).

Because of the general interest in the regiochemical course of enolate alkylations, and of the question of ion pairing effects on the O/C ratio, we decided to carry out a complementary investigation of an analogous system where exclusive O-alkylation takes place. To this end, we turned our attention to the anions **6** derived from 3-halopropyl derivatives of ethyl acetoacetate **5** where the formation of the six membered dihydropyran derivative **7** is highly favoured[7] compared to the four member cyclobutane derivative **8** (Scheme II). Whereas the 3-bromopropyl derivative (**5**, X = Br)



Scheme I



Scheme II

turned out to be unsuitable for rate measurements, a complete study of the effect of alkali and alkaline-earth metal ions on the rate of the ring-closure step **6** → **7** could be carried out for the 3-chloropropyl derivative (**5**, X = Cl), in 99% aqueous Me_2SO at 25.0°C. The results of such an investigation are reported herein.

RESULTS

The remarkable ease of formation of the ring product 7 was already apparent in the first attempts at preparing the 3-halopropyl derivatives 5. Treatment of an equimolar mixture of ethylacetoacetate and 1,3-dibromopropane with 1 equiv. of sodium ethoxide in refluxing ethanol gave 7 as the sole detectable product, with no trace of its open chain precursor (5, X = Br). With the aim at minimizing the intramolecular O-alkylation step,[10,11] the reaction was carried out on lithio ethylacetoacetate in THF. With 1,3-dibromopropane as the alkylating agent, 7 was still the main reaction product, the (6, X = Br)/7 ratio being about 1:8. With 1-bromo-3-chloropropane the (6, X = Br)/7 ratio increased up to about 2:1. In no case evidence was obtained for the formation of even minute amounts of the cyclobutane derivative 8. A few experiments were deliberately devoted to test the possibility of diverting at least some of intramolecular alkylation toward carbon. The lithium salt of (5, X = Cl) was reacted both in MeOH and in THF, and the resulting mixtures were carefully analyzed by GLC-MS. In both cases 7 was far the main reaction product (> 93%), accompanied by tiny amounts of unknown by-products, the more abundant of which showed mass spectra inconsistent with structure 8. Similar results were obtained with the magnesio derivative in THF. It appears therefore that intramolecular O-alkylation is the sole available pathway to anion 6, even under conditions that are known to greatly disfavour O-alkylation with respect to C-alkylation.[10,11]

Rate Measurements and Treatment of Kinetic Data . The kinetics of the ring closure step (6, X = Cl) ⟶ 7 were followed by monitoring in the neighborhood of 300 nm the absorption decrease due to the disappearance of the enolate ion, whose concentration was typically 1.5×10^{-4} M. Generation of the anion was carried out *in situ* by neutralization of the parent acetoacetic ester derivative with a calculated amount of Me_4NOH either in the absence or in the presence of salts. With the exception of Mg^{2+}, for which the source was the perchlorate, the metal ions and Et_4N^+ ion were added as bromides.

Preliminary experiments carried out on the bromo derivative (5, X = Br) showed that the rate of proton abstraction was comparable with that of the subsequent cyclisation step. In the absence of added salts, the former reaction was faster than the latter ($t_{\frac{1}{2}}$ = 25 ms). In the presence of added salts, both reactions were slowed down, but the former was more markedly so, with the result that with LiBr, for example, proton transfer to the base became rate limiting. Slow production of the enolate ion upon reaction with OH^- had been already observed[5] with compound **1**, but this did not interfere with the rate measurements, because the cyclisation step was significantly slower in all cases.

To overcome the above difficulty, we have slowed down the cyclisation step by replacing a chloro for the bromo leaving group. With the 3-chloropropyl derivative (**5**, X = Cl) a virtually quantitative generation of the enolate absorption took place upon addition of Me_4NOH, both in the absence and in the presence of added salts. The subsequent decay of the enolate absorption followed strict first-order kinetics in all cases. Product analyses, carried out on scaled-up kinetic runs after at least 10 half-lives, showed the yield of **7** to be 92% in the absence of added salt, 98% both in the presence of 0.1 M LiBr and 0.1 M $CaBr_2$, and 99% in the presence of 0.1 M $Mg(ClO_4)_2$. In a control experiment, octyl chloride was exposed to the action of 0.1 M $CaBr_2$ in 99% Me_2SO at 25°C for 200 min, which corresponds to about 2.5 half-lives for cyclisation of (**6**, X = Cl) under the same conditions. It was found that a quantity as low as 0.3% of octyl chloride had been converted into octyl bromide, showing that any disturbance from Finkelstein substitution of bromo for chloro was negligible even under the most severe conditions used in the kinetic runs.

The observed rate constants k_{obs} are listed in the Experimental and are shown as log plots *vs.* the concentration of added salt in Fig. 1. Inspection of Fig. 1 reveals an extremely varied reactivity picture, ranging from the very strong rate retardations exterded by Li^+ ion and by the divalent metal ions, to the remarkable insensitivity to Et_4N^+ and K^+ ions, that is clearly diagnostic for the occurrence of significant associations of the enolate reactant with the rate-depressing metal ions, but not with Et_4N^+ and K^+ ions. When only 1:1 associations are involved [eq. (1) and (2)], analysis of rate data is carried out in terms of eq. (3),[2] which is consistent with the well known Acree's concept[12] of independent kinetic contributions form the free ion (k_i) and from the ion

$$\text{enolate} + M^+ \overset{K_{ip}}{\rightleftharpoons} \text{enolate}\cdot M^+ \qquad (1)$$

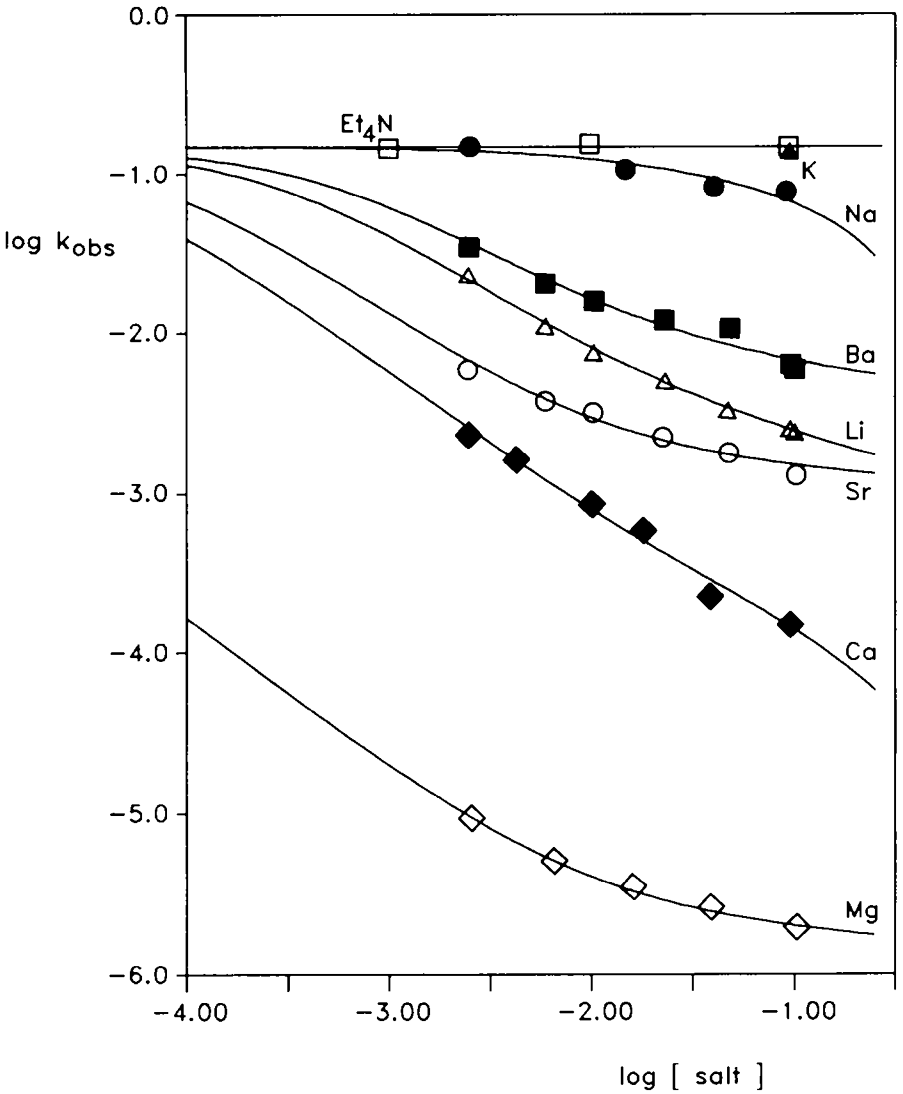


Figure 1. Effect of tetraethylammonium and metal salts on the rate of intramolecular alkylation of β-ketoenolate (6, X = Cl) in 99% Me_2SO. The horizontal line represents the specific rate k_i for reaction of the free ion. The points are experimental (k_{obs} in s^{-1}) and the lines are calculated by using eq.(3).

$$K_{ip} = \frac{[\text{enolate}\cdot M^+]}{[\text{enolate}]\ [M^+]\ \gamma_\pm^2} \qquad (2)$$

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

pair (k_{ip}). According to transition state theory,[13] eq. (3) can be written in the operationally equivalent form of eq. (4), where the quantity $K_T\#$ has

$$k_{obs} = \frac{k_i + k_i\ K_T\#\ \gamma_\pm^2\ [M^+]}{1 + K_{ip}\ \gamma_\pm^2\ [M^+]} \qquad (4)$$

the formal meaning of the ion pairing association constant of the transition state $T^\#$, eq. (5).

$$T^\# + M^+ \overset{K_T\#}{\rightleftharpoons} T^\#\cdot M^+ \qquad (5)$$

Application of eq. (3) requires the quantity $[M^+]$ to be precisely known for any added salt concentration. With the alkali metal bromides the problem is easily solved, since they behave as strong electrolytes in Me_2SO solution.[2] Furthermore, since the salt was added in all cases in large excess, its analytical concentration was taken as a reasonable approximation for $[M^+]$. The situation was more complicated with the divalent metal salts. Here we resorted to the usual assumption,[5] possibly a very rough one, of treating them as 1:1 electrolytes of the $(MX)^+X^-$ type, and took as before the quantity $[M^+]$ of eq. (3) as equal to the total salt concentration. We further note that non-ideal behavior of charged species has to be accounted for with high precision. The mean activity coefficient $\gamma_\pm$ was calculated from the extended Debye-Hückel equation (6), which was found[2] to apply well to salts of organic anions in 99% Me_2SO. Finally, in

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

view of the negligible tendency of tetraalkylammonium ions to bind anions in Me_2SO solution,[2,4] the k_{obs} value measured when the Me_4N^+ ion accompanying the added base was the sole counterion was taken as a reliable measure of the free ion reactivity k_i. This has the obvious advantage of reducing an equation with the three unknown quantities to one containing only two adjustable parameters. Operationally, a non-linear least-squares procedure was used for curve-fitting of the kinetic data to an equation of the form (7), where $y = (k_{obs}/k_i)$ and $x = \gamma_{\pm}^2[M^+]$. The numerical values of

$$y = \frac{1 + Ax}{1 + Bx} \qquad (7)$$

the A and B parameters were translated into the rate and equilibrium constants reported in Table I.

DISCUSSION

The rate-retarding effects due to increasing amounts of metal salts on the rate of cyclisation of (**6**, X = Cl) via intramolecular O-alkylation of the S_N2-type, have been quantitatively accounted for by means of a self-consistent approach, as based on the classical Acree's hypothesis[12] of independent contributions from free and cation paired reactant anions to the overall rate, eq. (3). The full lines drawn in Fig. 1, which were calculated from the least-squares parameters listed in Table I, show how closely the experimental data fit to eq. (3).

The log K_{ip} data listed in Table I show that ion-pairing is strongly cation-dependent, ranging from the negligible association with K^+ ion, to the more than a million-fold stronger association with Mg^{2+}. With the

Table I. Ion Pairing and Reactivity of β-Ketoenolates in 99% Me_2SO at 25°C

Metal ion	O-Alkylation of (6, X = Cl)[a]				C-Alkylation of 2[b]			
	$\log K_{ip}$	$\log K_{T\neq}$	$k_{ip}(s^{-1})$	$(k_{ip}/k_i)^c$	$\log K_{ip}$	$\log K_{T\neq}$	$k_{ip}(s^{-1})$	$(k_{ip}/k_i)^d$
K^+	< 1				< 1			
Na^+	1.48 ± 0.08	< 1		<< 1	1.40 ± 0.04	< 1		<< 1
Li^+	3.50 ± 0.02	1.47 ± 0.04	1.4×10^{-3}	9.3×10^{-3}	3.72 ± 0.02	1.35 ± 0.06	4.4×10^{-4}	4.3×10^{-3}
Ba^{2+}	3.25 ± 0.07	1.77 ± 0.13	4.9×10^{-3}	3.3×10^{-2}	3.71 ± 0.08	1.98 ± 0.15	1.9×10^{-3}	1.9×10^{-2}
Sr^{2+}	4.12 ± 0.05	2.04 ± 0.09	1.2×10^{-3}	8.3×10^{-3}	4.33 ± 0.03	1.82 ± 0.07	3.2×10^{-4}	3.1×10^{-3}
Ca^{2+}	4.47 ± 0.04	< 1		$< 3 \times 10^{-4}$	5.09 ± 0.04	1.16 ± 0.19	1.2×10^{-5}	1.2×10^{-4}
Mg^{2+}	7.00 ± 0.02	2.02 ± 0.04	1.5×10^{-6}	1.0×10^{-5}	7.33 ± 0.06	2.57 ± 0.08	1.7×10^{-6}	1.7×10^{-5}

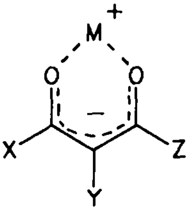
(a) Data from the present work.

(b) Data from ref. 5. Since error estimates were not given in ref. 5, and since the curve-fitting procedure was less refined than that used in the present work, the original rate data have now been worked out again in the same manner as those from the present work. The new set of least squares parameters listed above differs slightly from that reported in the original reference.

(c) $k_i = 0.148\ s^{-1}$.

(d) $k_i = 0.102\ s^{-1}$.

alkali metal ions, widely spaced association constants grading in the order Li>Na>K are observed, in agreement with the general behaviour exhibited by β-ketoenolates for which the U-type conformation **9** is available for chelate interaction with the metal ion.[14-16] This finding clearly suggests that the stability of ion pairs is dominated by the stronger electrostatic interaction with the smaller metal ions. Fully consistent with this view is the stability order among the divalent metal ions, namely, Mg>Ca>Sr>Ba. It is of interest to compare the set of log K_{ip} values from the present work with the corresponding data available for enolate **2** (Table I).[5] That the two sets of data are much the same is not really surprising, in view of the close structural similarity of the anions involved. But there seems to be a definite tendency for the ion pairing constants related to (**6**, X = Cl) to be lower by some 0.2-0.5 log units, which might well be a consequence of the shorter distance between the electron withdrawing group and the region where the negative charge is concentrated.



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At variance with the strong and strongly cation dependent associations with the enolate reactant, the corresponding cation interactions with the transition state are much weaker and affected by cation nature but to a modest extent, the observed $K_T\#$ values spanning a range of a power of ten, or slightly more. This is consistent with the idea that during the activation process the negative charge of the anionic reactant is shifted towards the region of the bond being formed and, consequently, is much less available for interaction with the metal ion. If one remembers that $k_{ip}/k_i = K_T\#/K_{ip}$, the approximately inverted relationship between reactivity and stability of the enolate-cation pairs is easily understood, since metal ion effects on the ratio $K_T\#/K_{ip}$ are dominated by metal ion effects on the quantity in the denominator.

We finally note that the close similarity of the K_{ip} values in the two sets of measurements reported in Table I, is paralleled by a close similarity of the $K_T\#$ values as well, which is equivalent to noting that the k_{ip}/k_i values are much the same for the two given reactions. This is an entirely unexpected result, that is in marked contrast with a widely held generalization on the regiochemical course of alkylations of ambident anions,[10,11] namely, that "the freer the anion, the greater the tendency for alkylation at the most electronegative site".[10] On the basis of this generalization one would predict a more pronounced cation dependence of the k_{ip}/k_i ratios for O-alkylation than for C-alkylation. A possible objection is that, because of the assumptions and approximations involved and of the well-known adaptability of equations containing two adjustable parameters, caution is needed in the interpretation of the results of the curve-fitting procedure. We stress, however, that the two sets of data refer to kinetic measurements which were obtained under virtually identical conditions and elaborated in the same way. We further note that for the Mg^{2+} reactions the measured quantities y are very close to the limiting value $A/B = k_{ip}/k_i$ approached at high concentration (saturation kinetics). As a consequence, the k_{ip}/k_i values for the Mg^{2+} reaction, as well as for the Sr^{2+} and Ba^{2+} reactions that are not too far from saturation, are determined with an inherently high precision. Therefore, we are rather inclined to believe the close similarity of the k_{ip}/k_i values to reflect a real phenomenon, and not an experimental artifact.

The general meaning of these findings is unclear. The results of our kinetic investigations, as carried out on intramolecular model reactions, might be affected in an unpredicted manner by the very intramolecular nature of the models themselves, as well as by the presence of different leaving groups in the reactants. Furthermore, they refer to carefully controlled conditions where only free ions and ion pairs are involved, whereas enolate alkylations are often carried out in highly concentrated solutions and/or in aggregating solvents, such as THF, where higher aggregates most likely predominate.

Clearly, a careful investigation of metal ion effects on the rate of reaction of β-ketoenolates with external alkylating agents, matched with a dissection of rate data into contributions of C- and O-alkylation, would provide a useful insight into the question of ion-pairing effects on the regiochemistry of enolate alkylations. This question deserves careful attention in future work.

EXPERIMENTAL

Materials. The alkali metal and alkaline-earth metal bromides, $Mg(ClO_4)_2$, and Et_4NBr were available from a previous investigation.[5] The mixed solvent (99% aqueous Me_2SO) and the Me_4NOH stock solution were prepared and handled as previously described.[5] Ethyl acetoacetate, 1,3-dibromopropane, 1-bromo-3-chloropropane, octyl chloride and octyl bromide were AR grade materials.

Ethyl(3-bromopropyl)acetoacetate (**5**, X = Br). Lithio ethyl acetoacetate, prepared from ethyl acetoacetate (2 g, 0.015 mol) and EtOLi (0.015 mol) in dry EtOH followed by removal of the solvent, was suspended in sodium-dried THF (40 mL), and brought to boil. 1,3-Dibromopropane (5.4 g 0.027 mol) was then added under stirring, and the resulting mixture was reacted under reflux for 70 h (92% reaction by titration with acid). After cooling to room temperature and standard work-up, any unreacted ethyl acetoacetate and dibromopropane were distilled under vacuum. The residue was column chromatographed on acid-washed silica gel with light petroleum (b.p. 40-70°C)/EtOAc 7:1, to afford an impure sample of (**5**, X = Br) (440 mg) after a forerun of **7** (^1H NMR, 60 MHz, $CDCl_3$: δ 4.15 (q, 2H, $-CO_2CH_2-$), 4.0 (t, 2H, $-OCH_2CH_2-$), 2.2 (s, 3H, $-CH_3$), 2.5-1.6 (m, 4H, $-OCH_2CH_2CH_2-$), 1.25 (t, 3H, $-CO_2CH_2CH_3$); Mass: m/e 170, M^+). Further elution on acid-washed silica gel with $CHCl_3$/hexane 2:1 gave 60 mg of a sample of (**5**, X = Br) which was 98% pure (GLC on a 10 m x 530 µm fused silica column coated with 2.6 µm methylsilicone HP-1, operated at 100-200°C ^1H NMR, 60 MHz, $CDCl_3$: δ 4.15 (q, 2H, $-CO_2CH_2-$), 3.5-3.2 (two superimposed triplets, 3H, $-CH_2Br$ and methyne), 2.2 (s, 3H, $-COCH_3$), 2.0-1.7 (m, 4H, "central" methylene protons), 1.25 (t, 3H, $-CO_2CH_2CH_3$).

Ethyl(3-chloropropyl)acetoacetate (**5**, X = Cl). Lithio ethyl acetoacetate was reacted as above with 1-bromo-3-chloropropane (13 g, 0.083 mol) for 80 h (60% reaction). The crude product was refluxed overnight in 80% aqueous acetone containing excess LiCl in order to convert any (**5**, X = Br) possibly formed into (**5**, X = Cl). Purification by flash chromatography on acid-washed silica gel with AcOEt/hexane 1:8 gave 3.44 g of the title compound in a low purity state. A pure sample for kinetic and analytical purposes was obtained by prepative GLC on a SE 30 column operated at 190°C.

Anal. Calcd for $C_9H_{15}O_3Cl$: C, 52.30; H, 7.32. Found: C, 52.16; H, 7.34 ^1H NMR, 80 MHz, $CDCl_3$: δ 4.2 (q, 2H, $-CO_2CH_2-$), 3.65-3.25 (two superimposed triplets, 3H: $-CH_2Cl$ and methyne), 2.2 (s, 3H, $-COCH_3$), 2.1-1.5 (m, 4H, "central" methylene protons), 1.2 (t, 3H, $-CO_2CH_2CH_3$).

Rate Measurements. These were carried out as previously reported[5] by using either conventional or stopped-flow spectrophotometry.

Rate constants (s^{-1}) are listed below at the various added salt concentrations given in parentheses in mol L^{-1}.

$$k_i = (0.148 \pm 0.003)\ s^{-1}\ \text{(no added salt)}$$

Et_4NBr: 0.148 (1.00×10^{-3}); 0.155 (1.00×10^{-2}); 0.154 (1.00×10^{-1}).

KBr: 0.148 (1.00×10^{-1}).

NaBr: 0.150 (2.50×10^{-3}); 0.104 (1.50×10^{-2}); 8.34×10^{-2} (4.00×10^{-2}); 7.66×10^{-2} (9.15×10^{-2}).

LiBr: 2.35×10^{-2} (2.46×10^{-3}); 1.13×10^{-2} (5.88×10^{-3}); 7.57×10^{-3} (1.02×10^{-2}); 5.01×10^{-3} (2.27×10^{-2}); 3.35×10^{-3}; (4.74×10^{-2}); 2.52×10^{-3} (9.45×10^{-2}); 2.49×10^{-3} (1.00×10^{-1}).

$BaBr_2 \cdot 2H_2O$: 3.44×10^{-2} (2.46×10^{-3}); 2.08×10^{-2} (5.88×10^{-3}); 1.62×10^{-2} (1.02×10^{-2}); 1.23×10^{-2} (2.27×10^{-2}); 1.09×10^{-2} (4.74×10^{-2}); 6.24×10^{-3} (9.48×10^{-2}); 5.88×10^{-3} (1.00×10^{-1}).

$SrBr_2 \cdot H_2O$: 6.11×10^{-3} (2.45×10^{-3}); 3.86×10^{-3} (5.85×10^{-3}); 3.24×10^{-3} (1.02×10^{-2}); 2.35×10^{-3} (2.26×10^{-2}); 1.81×10^{-3} (4.71×10^{-2}); 1.32×10^{-3} (1.00×10^{-1}).

$CaBr_2 \cdot 2H_2O$: 2.32×10^{-3} (2.47×10^{-3}); 1.65×10^{-3} (4.18×10^{-3}); 8.93×10^{-4} (1.01×10^{-2}); 5.85×10^{-4} (1.79×10^{-2}); 2.33×10^{-4} (3.81×10^{-2}); 1.54×10^{-4} (9.51×10^{-2}).

$Mg(ClO_4)_2$: 9.41×10^{-6} (2.50×10^{-3}); 5.02×10^{-6} (6.44×10^{-3}); 3.49×10^{-6} (1.59×10^{-2}); 2.57×10^{-6} (3.79×10^{-2}); 1.92×10^{-6} (1.00×10^{-1}).

Computational Details. Non-linear least-squares calculations were carried out by a computer programme based on Marquardt method. The best fit to log (k_{obs}/k_o) *vs.* [salt] was sought, which was believed to give a sounder weight to the data. Standard deviations from the regressions ($S_{y,x}$) are as follows:

(**6**, X = Cl): Na^+, 0.052; Li^+, 0.021; Ba^{2+}, 0.066; Sr^{2+}, 0.048; Ca^{2+}, 0.067; Mg^{2+}, 0.021.

2: Na^+, 0.031; Li^+, 0.028; Ba^{2+}, 0.077; Sr^{2+} 0.034; Ca^{2+}, 0.055; Mg^{2+}, 0.032.

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7) Cyclisation of (**5**, X = Br) is a milestone in the history of closed carbon chains with less than six ring atoms, whose capability of existence was still out of question at the beginning of the 1880's. Contrary to the convinctions of such authoritative chemists as Victor Meyer, Baeyer, and Emil Fischer, it occurred to Perkin, a very young student in those times, that reaction of the sodium derivative of (**5**, X = Br) might yield the 4-carbon ring compound **8**. That was the first time in which the intramolecular counterpart of a known intermolecular reaction was deliberately chosen for the synthesis of a ring compound. Since no synthetic procedure was available for the preparation of (**5**, X = Br), Perkin carried out the condensation of trimethylene bromide with the sodium derivative of acetoacetic ester and obtained an ester, which was believed to be "acetyltetramethylene--carboxylic ester"[8], i.e., **4**. This new method gave rise to a vigorous development of the chemistry of closed carbon chains. But three years later Perkin discovered that the reaction had taken a different course, since "the bromopropylacetoacetic ester produced in the first stage yields, on treatment with sodium ethylate, the sodium derivative of the tautomeric modification, and this decomposes on heating with the formation methyldehydrohexonecarboxylic ester", i.e. **7**. A full account of these pioneering investigations was given by Perkin himself nearly fifty years later in the first Pedler lecture.[9]
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