most favorable cases.[6-15] This, however, is consistent with the results of the pressure studies. Since "normal" values of ΔV^* for homolytic bond scission are +4 to +5 ml/mol,[1b] the contributions from solvation are on the order of −2 to −3 ml/mol; in contrast, reactions leading to formation of ions (*e.g.*, solvolysis) not atypically show values of ΔV^* as "large" as −20 ml/mol.[1b,20]

While it could be argued that the differences in ΔV^* for these peresters reflect only differences in extent of bond stretching in the transition state *à la* the Hammond postulate,[7b] we consider this unlikely. Values of ΔV^* for decomposition of several symmetrical azo compounds not characterized by polar contributions, but of substantially different reactivity, are remarkably similar to each other (+4 to +5 ml/mol).[1b] Further, their rate–pressure plots do not show the curvature which we have associated with pressure dependence of solvent compressibility, a factor entering into reactions involving solvation.

Experimental Section[21]

Compounds. *tert*-**Butyl perpivalate** (K and K), obtained as a 75% solution in mineral spirits, was first purified by low temperature crystallization from pentane. It was subsequently recrystallized four times from pentane, taken up in pentane and dried over anhydrous magnesium sulfate, and recovered by evaporation of the solvent. The infrared spectrum showed a single carbonyl band at 1767 cm^{-1} and was free of any OH bands. The nmr spectrum in carbon tetrachloride solvent showed two equal intensity singlets at δ 1.21 and 1.27.

tert-**Butyl perisobutyrate** was synthesized from reaction of isobutyryl chloride with the sodium salt of *tert*-butyl hydroperoxide by conventional procedures.[8,21] The crude perester obtained by evaporation of the solvent pentane after filtration was purified by "bulb-to-bulb" distillation five times at low pressure (0.03 mm) and room temperature. The infrared spectrum of the purified material showed a single carbonyl band at 1775 cm^{-1}. The nmr spectrum in carbon tetrachloride solvent showed a doublet at δ 1.17, a singlet at 1.27, and a multiplet at 2.50; the combined area of the doublet and singlet was 15 times as great as the area of the multiplet.

Kinetic Studies. Thermal decomposition of 0.1 M solutions of the respective peresters in carefully purified cumene was monitored by infrared spectroscopy. The high pressure apparatus and procedures concerning its use in such kinetic studies have been described in detail.[16,17]

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(20) See W. J. le Noble, *Progr. Phys. Org. Chem.*, **5**, 207 (1967).

(21) For detailed experimental procedures, see R. P. Pankratz, Ph.D. Dissertation, University of California, Riverside, 1972.

Ring-Closure Reactions. I. Kinetics of Lactone Formation in the Range of Seven- to Twelve-Membered Rings

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Abstract: The kinetics of the formation of lactones from ω-bromoalkanoate ions in the range of 7- to 12-membered rings have been investigated in 99% aqueous DMSO solution at 50°. They were followed by a potentiometric technique allowing precise measurements at reactant concentrations as low as 1×10^{-4} M. Vpc product analyses were carried out in typical cases. The reaction proved to be first order in all cases at the lowest concentrations used. However, at higher concentrations, incursion of second-order kinetics which was attributed to a dimerization reaction was observed for the reaction of the 7-bromoheptanoate and 8-bromooctanoate ions. A kinetic analysis based on a mixed-order rate equation allowed the evaluation of the first- and second-order rate constants by a trial-and-error procedure. The reactivity pattern for ring closure shows a minimum at the eight- and nine-membered rings whose location is discussed in terms of conformational stability of the lactone as a function of ring size.

Bifunctional molecules can either undergo polymerization or ring formation, depending on their structure and reaction conditions. The scope of ring-formation reactions is not only broad in their own right but also includes neighboring group participation[1] and intramolecular catalysis,[2] as related topics in the general field of intramolecular reactions.

The factors affecting intramolecular reactivity[3] are several, but we cannot expect to make an even empirical assessment of their role, unless we obtain a substantial body of information of kinetic nature enabling us to understand the energetics of the processes. Most kinetic studies have concerned the formation of three- to six-membered rings[1,4] whereas little or no attention has been given to the seven-membered ring and to the so-called medium (8- to 11-membered) and large (12-membered and larger) rings.

Experimental difficulties of several kinds have contributed to limit some of the studies.[5] Since few and fragmentary data,[6-9a,10] whose reliability is even ques-

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(1) B. Capon, *Quart. Rev., Chem. Soc.*, **18**, 105 (1964).

(2) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, Chapter 1.

(3) See, for example, (a) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, Chapter 7; (b) J. Sicher, *Progr. Stereochem.*, **3**, 202 (1962).

(4) A. C. Knipe and C. J. M. Stirling, *J. Chem. Soc. B*, 67 (1968).

(5) G. M. Bennett, *Trans. Faraday Soc.*, **37**, 794 (1941).

(6) A. G. Davies, M. M. Davies, and M. Stoll, *Helv. Chim. Acta*, **37**, 1351 (1954).

(7) K. Ziegler, A. Lüttringhaus, and K. Wohlgemuth, *Justus Liebigs Ann. Chem.*, **528**, 162 (1937).

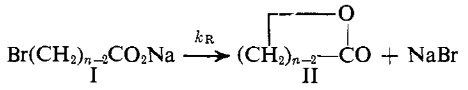
(8) H. Freundlich and coworkers, and G. Salomon, quoted by G. Salomon, *Trans. Faraday Soc.*, **32**, 153 (1936). See also G. Salomon, *Helv. Chim. Acta*, **19**, 743 (1936).

(9) (a) M. Stoll and A. Rouvé, *Helv. Chim. Acta*, **17**, 1283 (1934); **18**, 1087 (1935). (b) The formation of dimeric lactones under the

tionable in some cases, are available, so far information concerning the structural effects on cyclization rate has been obtained mainly from correlations of ring size with yields in cyclic products.[3] This is despite the fact that the available studies have revealed special features in the region of medium rings, particularly the frequent occurrence of a minimum in the tendency to ring closure.

For example, in the cyclization of carboxylic acids as obtained by heating the Th, Ce, or Y salts, Ruzicka[11] found that the minimum yield is experienced at the 10- and 11-membered rings. In the Thorpe reaction, where cyclic ketones are also formed, Ziegler[12] found a minimum in the region $n = 9$–11. Similar results were obtained[13] with the Dieckmann reaction. The ring closure of ω-chloroalkyl sulfides $RS(CH_2)_{n-1}Cl$[14] failed for $n = 8$–13. The lactonization of ω-hydroxyalkanoic acids in benzene–benzenesulfonic acid[9] also showed a deep minimum in ease of cyclization to 8- to 11-membered rings. Another method, due to Stoll[15] and, independently, Hunsdiecker and Erlbach,[16] involves the lactonization of ω-bromoalkanoic acids with K_2CO_3 in boiling butanone. This method was employed by the latter authors to synthesize 10- to 18-membered lactones in good yields but failed for the eight- and nine-membered rings. Stoll and coworkers[6] also attempted a kinetic study in aqueous butanone in two cases, the 12- and the 16-rings, but did not seem to have extended their study down to the medium rings. Similarly, rates of ring closure of some ω-bromoalkylamines have been measured by Freundlich and Salomon.[8] A minimum was again found for the medium rings, but neither its exact location nor the energetic factors involved were obtained because even approximate rate constants could not be obtained in this region.

We are currently engaged in kinetic investigations intended to fill this gap and to establish structure–reactivity relationships in ring-forming reactions on a firmly quantitative basis. In the present paper we wish to report a study on the intramolecular nucleophilic substitution of the sodium salts of ω-bromoalkanoic acids (I, $n = 7$–12) in DMSO–water 99:1 at 50° leading to the formation of 7- to 12-membered lactones (II, $n = 7$–12) (eq 1). First-order rate constants for ring



$$Br(CH_2)_{n-2}CO_2Na \xrightarrow{k_R} (CH_2)_{n-2}\text{—}CO + NaBr \qquad (1)$$

I II

formation (k_R) have been measured for the whole set of substrates. In two cases the second-order rate constants (k_P) for the competing bimolecular dimerization (eq 2) were also evaluated.

$$2Br(CH_2)_{n-2}CO_2Na \xrightarrow{k_P} Br(CH_2)_{n-2}CO_2(CH_2)_{n-2}CO_2Na + NaBr \qquad (2)$$

Results

The ring-closure reaction of a bifunctional compound is made complex by consecutive as well as parallel reactions, as shown by the following equations (monomer = ω-bromoalkanoate ion).

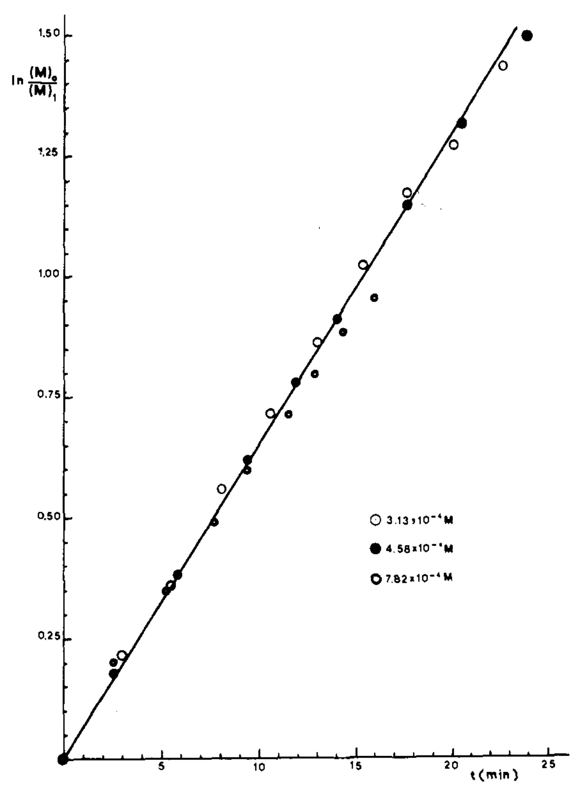


Figure 1. First-order plot for the cyclization of sodium 11-bromoundecanoate. Symbols refer to initial concentrations.

$$\text{monomer} \xrightarrow{k_R} \text{lactone} + Br^- \qquad (3a)$$

$$2\text{monomer} \xrightarrow{k_P} \text{dimer} + Br^- \qquad (3b)$$

$$\text{dimer} \xrightarrow{k_R'} \text{dimeric lactone} + Br^- \qquad (3c)$$

$$\text{monomer} + \text{dimer} \xrightarrow{k_P'} \text{trimer} + Br^- \qquad (3d)$$

In the above scheme, k_R and k_R' denote ring-closure rate constants, and k_P and k_P' polymerization rate constants. Since the polymerization reactions are second order, their relative importance decreases as the concentration of the substrate is decreased. To a first approximation, let us assume at this point that at the concentrations used in this work the occurrence of the higher polymerization processes is negligible.

From the above scheme, the following rate equation can be set, where M and D represent the monomer and the dimer, respectively.

$$-d[M]/dt = k_R[M] + 2k_P[M]^2 \qquad (4)$$

$$-d[D]/dt = k_R'[D] + k_P'[D][M] - k_P[M]^2 \qquad (5)$$

The progress of the reaction was followed by measuring the concentration of the released bromide ions, which were titrated by a sufficiently precise method (see Experimental Section) to let the kinetic experiments run at initial concentrations as low as 1×10^{-4} *M*. In the concentration range 9×10^{-4}–1×10^{-4} *M* the observed kinetics proved to be first order for four out of six salts, *i.e.*, those with $n = 7$, 10, 11, and 12. First-order plots (Figure 1) were found to be linear up to 70–80% conver-

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conditions of the present work has been confirmed by us (unpublished work).

(10) M. M. Davies, *Trans. Faraday Soc.*, **34**, 410 (1938).

(11) L. Ruzicka, M. Stoll, and H. Schinz, *Helv. Chim. Acta*, **9**, 249 (1926).

(12) K. Ziegler, H. Eberle, and H. Ohlinger, *Justus Liebigs Ann. Chem.*, **504**, 94 (1933).

(13) N. J. Leonard and C. W. Schimelpfenig, Jr., *J. Org. Chem.*, **23**, 1708 (1958).

(14) G. M. Bennett and H. Gudgeon, *J. Chem. Soc.*, 1891 (1938).

(15) M. Stoll, *Helv. Chim. Acta*, **30**, 1393 (1947).

(16) H. Hunsdiecker and H. Erlbach, *Ber.*, **80**, 129 (1947).

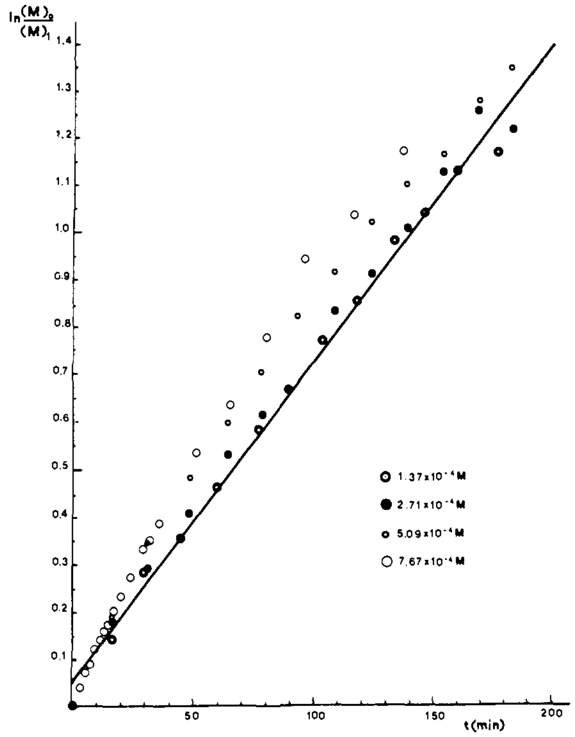

Figure 2. Deviations from a first-order kinetic correlation for the cyclization of sodium 8-bromooctanoate from four independent runs. Symbols refer to initial concentrations.

Table I. Kinetic Data for the Ring-Closure Reaction of the Sodium Salts of Some ω-Bromoalkanoic Acids, $Br(CH_2)_{n-2}CO_2H$, in DMSO–Water (99:1, v/v) at 50°

Acid	n[a]	10^4k_R, sec^{-1}	10^4k_R, sec^{-1}	k_P, $M^{-1}\ sec^{-1}$	k_R/k_P,[e] M
6-Bromohexanoic	7	98[b]			0.27
7-Bromoheptanoic	8	1.02[c]	1.04[d]	0.034[d]	0.0029
8-Bromooctanoic	9	1.13[c]	1.06[d]	0.038[d]	0.0029
9-Bromononanoic	10	3.43[b]			0.0095
10-Bromodecanoic	11	8.70[b]			0.024
11-Bromoundecanoic	12	10.8[b]			0.030

[a] Number of members (ring size) in the lactone to be formed. [b] Errors are in the order 2–4%, as determined by three independent runs. [c] Obtained from runs at the lowest concentrations (1×10^{-4} M) of the substrate and subject to errors in the order of 5%. [d] Obtained by means of eq 10. [e] Calculated on the assumption that the same average value, $k_P = 0.036$ M^{-1} sec^{-1}, applies to all tested compounds.

sion, and the rate constants proved to be reproducible and independent of the initial concentrations, the latter being changed by factors of 2 and 3. As to the salts with $n = 8$ and 9, which are the least reactive in the lot, linear first-order plots were observed (Figure 2) only for runs performed at the lowest possible concentrations (*ca.* 1×10^{-4} M). The rate data are reported in Table I.

The observed first-order kinetics were taken as evidence for the relative unimportance, under the stated conditions, of even the first polymerization terms in the above rate equations. This conclusion was confirmed by vpc product analysis for the reactions of 8-bromooctanoic and 11-bromoundecanoic acids, as shown in Table II.

In a 8.79×10^{-4} M solution, the 12-membered ring lactone is already formed in 100% yield without any interfering side reactions. However, at similar concentrations (7.16×10^{-4} M) the nine-membered ring lactone is only formed in 49% yield. The reaction appears to lead predominantly to the lactone (and the kinetics to be first order) only at substantially lower concentrations (*i.e.*, 1.09×10^{-4} M).

Table II. Yields of Lactone for the Cyclization of 8-Bromooctanoic and 11-Bromoundecanoic Acid (as sodium salts) in 99% DMSO at 50° as Determined by Vpc Analysis

Acid	n	Concn (10^4 M)	Yield,[a] %
8-Bromooctanoic	9	1.09	93
8-Bromooctanoic	9	7.16	49
11-Bromoundecanoic	12	8.79	100

[a] Experimental error is ±4%.

In order to gain a better insight of the kinetics for the least reactive salts leading to the eight- and nine-membered rings, a more detailed analysis is appropriate. At about 1×10^{-4} M concentrations, a least-squares treatment yielded k_R values of 1.02×10^{-4} ($r = 0.9958$) and 1.13×10^{-4} sec^{-1} ($r = 0.9969$) for $n = 8$ and 9, respectively. The correlation coefficients are quite satisfactory if we consider that the experimental errors become relatively large at the very low concentrations used. In more concentrated solutions nonrandom upward deviations relative to the expected straight line are observed, the experimental points corresponding to shorter half-lives. For example, for the ring closure of 8-bromooctanoic acid the $t_{0.5}$ value was 94 min at 1.37×10^{-4} M and decreased to 68 min at 7.67×10^{-4} M. The observed deviations are not very large but well outside the experimental errors. They can be accounted for in terms of the superimposition of a second-order term due to a competing dimerization. Generally speaking, the second term of (4) is negligible when the following condition is met.

$$k_R/2k_P \gg [M] \tag{6}$$

However, since the eight- and nine-membered rings are formed at relatively slow rates at the lowest accessible concentration range, k_R and $k_P[M]$ may become of the same order of magnitude (eq 7). Also, large rings are

$$k_R/2k_P \simeq [M] \tag{7}$$

known to be formed more rapidly than medium rings,[3] and dimeric lactones have been isolated in good yields on attempted preparations of medium ring lactones.[9] This means that, for $n = 8$ and 9

$$k_R' > k_R \tag{8}$$

and, by condition (7)

$$k_R' > k_P[M] \tag{9}$$

If k_R' is sufficiently larger than $k_P[M]$, the term $k_P'[D]\cdot[M]$ of (5) also vanishes because the polymerization rates, k_P and k_P', are likely to be close to each other.

We thus conclude that in the investigated concentration range for which condition (7) is assumed to be valid, reaction 3d for the formation of the eight- and nine-membered rings can be neglected and reaction 3c is kinetically unimportant being relatively fast. In this case the rate of disappearance of the substrate ($-d[M]/dt$) can be set equal to the rate of bromide ion release

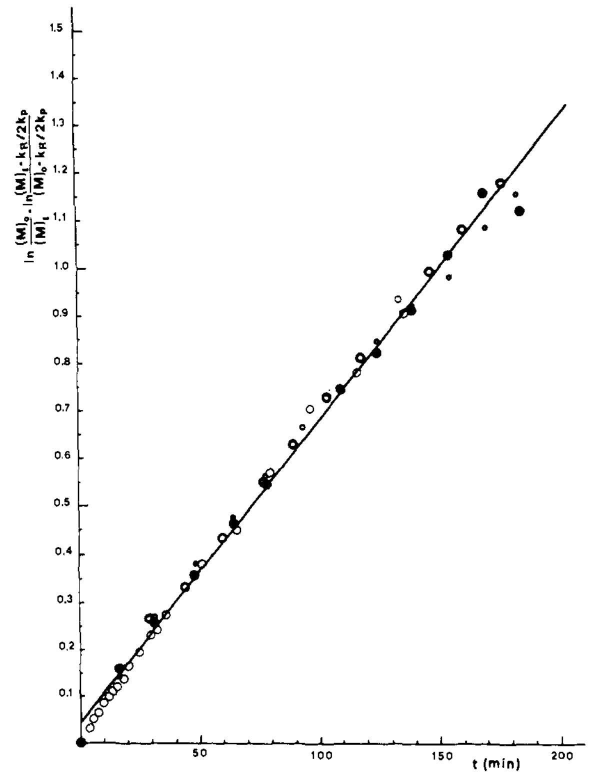

Figure 3. Fit of the kinetic data for the cyclizaton of sodium 8-bromooctanoate to a mixed first- and second-order treatment. The symbols are the same as for Figure 2.

(d[Br⁻]/d*t*) and the kinetics are expected to be fully described by (4). It may be worth noting that had the reaction scheme included reaction 3d the process could not be unambiguously followed by analyzing for the Br⁻ ions. Equation 4 may be rearranged to

$$\frac{\mathrm{d}[\mathrm{M}]}{[\mathrm{M}]^2 + k_\mathrm{R}[\mathrm{M}]/2k_\mathrm{P}} = -2k_\mathrm{P}\mathrm{d}t$$

which on integration between limits by standard methods yields

$$\ln\frac{[\mathrm{M}]_0}{[\mathrm{M}]_t} + \ln\frac{[\mathrm{M}]_t + k_\mathrm{R}/2k_\mathrm{P}}{[\mathrm{M}]_0 + k_\mathrm{R}/2k_\mathrm{P}} = k_\mathrm{R}t \qquad (10)$$

Equation 10 is a mixed first- and second-order rate equation which reduces to the familiar first-order equation when condition (6) holds.

The kinetic data for the reaction of the ω-bromoalkanoates with $n = 8$ and 9 were applied to (10). A trial-and-error calculation method (see Experimental Section) gave the best k_R and k_P values (Table I).

The data fit much better to (10) than to a simple first-order equation, as shown for the reaction of the 8-bromoalkanoate ion on comparing Figures 2 and 3. Similar results are obtained for the 7-bromo analog.

In the last column of Table I values for the ratio $k_\mathrm{R}/k_\mathrm{P}$ were calculated by using the same value $k_\mathrm{P} = 0.036\ M^{-1}\ \mathrm{sec}^{-1}$ for all the investigated substrates. Such values are consistent with the experimental observations and with the above interpretations. In particular, in the concentration range 1×10^{-4}–9×10^{-4} *M* condition (6) is fulfilled only by those substrates displaying clean first-order kinetics ($n = 7$, 10,[17] 11, and 12). For the least reactive substrates ($n = 8$ and 9), the $k_\mathrm{R}/k_\mathrm{P}$ value becomes small enough and comparable to [M]. Under such conditions, *i.e.*, (7), the reaction kinetics are still mixed first and second order; condition (6) is approached only at the lowest concentrations used (1×10^{-4} *M*).

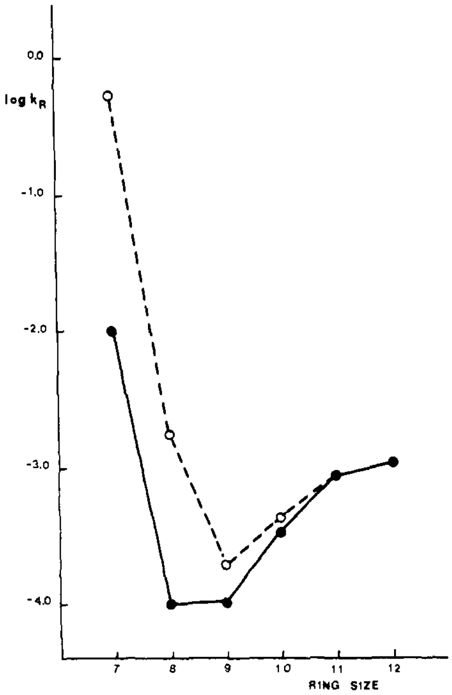

Figure 4. Reactivity plot for the cyclization of some sodium ω-bromoalkanoates in 99% DMSO at 50.0° (●); (○) a hypothetical reactivity calculated assuming $\Delta\Delta G^{\ddagger}_n = (2/3)\Delta\Delta G^\circ_n$, where $\Delta\Delta G^\circ_n$ is given by eq 11 and 2/3 is an arbitrary factor (see text).

Discussion

The ease of ring closure results from a combination of entropy and energy terms. The former term is expected to decrease with increasing chain length,[18] so that larger rings should form with lower entropies of activation. The energy term represents the sum of unfavorable interactions set up as the chain approaches the ring-shaped transition state. In dealing with medium rings (8- to 11-membered) it is usual to discuss ring strain in terms of transannular interactions, bond angle deformations, and bond opposition forces due to eclipsing of atoms along the ring.[3] To the extent that the activation energy for ring closure reflects the stability of the ring to be formed, the lowest yields generally occurring in the region of the most strained 9-, 10-, and 11-membered rings[3] are accounted for on this basis.

The reactivity data for lactone formation (Table I) are plotted as a function of the ring size in Figure 4. The data cover two powers of ten, and the plot has the familiar shape of the yield *vs.* ring size relationships as obtained in related reactions.[3b] The very steep drop in rate of ring closure that is observed on passing from the seven-ring to the eight-ring is followed by a shallow increase up to the 12-membered ring. A characteristic feature of these data is the occurrence of a reactivity minimum lying at the eight- and nine-rings. Thus in the present reaction the minimum is located at a ring

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(17) In this case concentrations not higher than 4×10^{-4} *M* were used.

(18) L. Ruzicka, *Chem. Ind. (London)*, **54**, 2 (1935).

size smaller by about two units with respect to those previously reported in the literature. Keeping in mind that the entropy of activation for the formation of an eight-membered ring should be more favorable than that for a nine-membered one, the former appears to be the most strained term in the series. This is also in contrast with the observed strains (heats of combustion) in cycloalkanes which reach a maximum with cyclodecane.[3b] That the lactone structure is specifically responsible for the displacement of maximum strain down to the eight-ring is suggested by comparison with Huisgen and Ott's[19] kinetic data for the ring opening of lactones. The rings with $n \leq 8$ were found to hydrolyze 10^3–10^5 times as fast as the higher homologs ($n \geq 10$), the nine-ring showing intermediate reactivity. In particular, within the medium rings, the eight- and nine-membered lactones are much more reactive than the 10- and 11-membered ones. The ring-closure and ring-opening reactions are thus related to each other by a roughly inverted reactivity order. Out of the factors controlling the two reactions, at least one, *i.e.*, the stability of the lactone, is expected to be common to both, though acting in opposite directions. The lactone structure is indeed involved in the transition state of the former reaction and in the initial state of the latter. On the base of such physical properties as dipole moments and boiling points Huisgen and Ott showed that the lactone ring should contain the ester function in the less stable, more polar cis conformation for a ring size seven or less and in the more stable, less polar trans conformation when the ring size is ten or higher. In the intermediate sizes eight and nine the two conformations are in equilibrium, the cis being predominant in the eight-ring, the trans in the nine-ring. The kinetic data for hydrolysis were easily explained on this basis, the greater reactivity of cis lactones being related to the higher energies of the initial states.

In lactone formation, the transition state can be assumed to be ring shaped whereas the ground state is open chained. Only the stability of the former will be affected by the cis/trans conformation of the ring to be formed. Consequently, the rate of formation of the lactone ring will suffer from a depressing factor which can be related to the contribution of the less stable cis-like conformation, depending on ring size. In order to assess the influence of the conformation on lactone formation, conformational free energy changes relative to ring size 12 (100% trans, $\Delta\Delta G° = 0$) can be obtained on the basis of the lactone hydrolysis data[19] ($\Delta\Delta G° =$ 3.8 kcal/mol for ring size seven assumed to be 100% cis). For any given ring size in the range 7–12 we have

$$\Delta\Delta G°_n = 3.8(\mu_n - 1.86)/2.59 \qquad (11)$$

where μ_n is the dipole moment (in D units) for that particular ring, 1.86 is the μ value for the trans conformation (ring size 12) and 2.59 is the difference μ(cis) − μ(trans). Although the $\Delta\Delta G°$ values thus obtained are not meaningful as such in the ring-closure reaction, they can be used as a basis for arbitrary sets of relative rate correction factors. The result is given by the dotted line of Figure 4 for a given set of rate correction factors. The line provides a qualitative illustration of the shape of the diagram were the rate-depressing influence of the cis conformation relieved in the transition state. We conclude that the conformational cis/trans effect in lactone formation is indeed a possible factor responsible for the shift of the reactivity minimum toward the eight-membered ring.

Table III. Physical Constants of ω-Bromo Acids

Acid	Bp, °C (mm)	Mp, °C	Lit. mp, °C
6-Bromohexanoic	150 (5)	33–34	35[a]
7-Bromoheptanoic	121–125 (5)	30.5–32.5	29–30[20]
8-Bromooctanoic		38.5–40	37[23]
9-Bromononanoic	173–174 (5)	35–36.5	34[23]
10-Bromodecanoic	205 (21)	38.5–41.5	43[23]
11-Bromoundecanoic		51.5–53	50[23]

[a] C. S. Marvel, D. W. MacCorquodale, F. E. Kendall, and W. A. Lazier, *J. Amer. Chem. Soc.*, **46**, 2838 (1924).

It should be noted that the replacement of a methylene group of a carbon chain by a heteroatom or a trigonal group is known to increase the ring-closure reactivity and that relief of transannular interactions and/or bond-opposition forces are held responsible for these effects.[3] One should expect that the replacement of the structural moiety $-CH_2CH_2-$ (I) in cycloheptane and cyclododecane by $-OCO-$ (II) to give the corresponding lactones would lead to a greater release of unfavorable interactions in the more strained seven-membered ring.[3] Available data are scanty, but one comparison can be made by considering the moiety $-CH_2N^+H_2-$ (III) as essentially close to I. In the ring closure of ω-bromoalkylamines,[8] the transition state should approach a situation similar to III and, of course, in lactone formation the transition state should be similar to II.

If we neglect the difference in selectivity of the two reactions and compare the ring-closure reactivity ratios for the formation of 7- and 12-membered rings, ${}_{7}k_{\mathrm{R}}/{}_{12}k_{\mathrm{R}}$, we find, from the available data, that such a ratio is 9 for lactone formation (this work) and 83 for cyclic ammonium ion formation.[8] This is just the opposite to what is expected, *i.e.*, a greater ${}_{7}k_{\mathrm{R}}/{}_{12}k_{\mathrm{R}}$ ratio for lactones than for cyclic ammonium ions, and indicates that a factor other than the well-established interactions[3] usually considered to affect the ease of ring closure must operate in the opposite direction. This conclusion agrees with the above view that the cis/trans conformational effect is an important contributing factor in determining the observed overall reactivity picture, in lactone formation.

Experimental Section

Materials. 8-Bromooctanoic acid (K & K), 10-bromodecanoic acid (K & K), and 11-bromoundecanoic acid (Fluka) were commercial samples. 11-Undecanolide[16] (bp 125–127° (18 mm) [lit.[16] bp 124° (14 mm)], $n^{20}\mathrm{D}$ 1.4722), 8-octanolide[19] (bp 89–95° (16 mm) [lit.[19] bp 72–73° (11 mm)], $n^{23}\mathrm{D}$ 1.4597), and 7-bromoheptanoic acid[20] were prepared by literature methods. 6-Bromohexanoic acid was prepared by refluxing ε-caprolactone (Fluka) in an acetic acid–hydrobromic acid mixture and isolated by standard methods. 9-Bromononanoic acid was prepared from methyl hydrogen sebacate[21] by Cason and Welba's[22] modification (procedure P) of the Hunsdiecker[23] reaction. All bromo acids were purified by distillation and/or recrystallization from hexane at 5°. Their physical constants are collected in Table III. All melting points are uncorrected.

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(19) R. Huisgen and H. Ott, *Tetrahedron*, 6, 253 (1959).

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(21) L. J. Durham, D. J. McLeod, and J. Cason, *Org. Syn.*, **38**, 55 (1958).

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Kinetic Experiments. The solvent was prepared by exactly placing 10 ml of CO_2 free bidistilled water into a 1-l. volumetric flask, that was then made up to the mark with reagent grade DMSO (Merck). The mixed solvent was stored in an automatic buret under pure nitrogen and in the dark, and it was protected from CO_2 and moisture with guard tubes. The solvent was found to react with primary alkyl bromides, slowly producing free bromide ions even at room temperature. Thus stock solutions of bromo acids were kept in the refrigerator and brought to room temperature before use. Blank experiments ($t_{0.5} \simeq 34$ hr at 50° with either butyl bromide or dodecyl bromide) showed that the rate of the side reaction amounted to no more than 5% of the slowest cyclization rate, so that corrections were unnecessary. This was confirmed by product analysis (see below).

The preparation and purification of the soap-like sodium salts of the bromo acids are difficult and cumbersome. The salts were better generated *in situ* by neutralization of the acids with the stoichiometric amount of NaOH. Owing to the low solubility of NaOH in DMSO, a 0.0240 *N* CO_2 free NaOH stock solution was prepared in a mixed solvent containing 12% of water.

The reaction mixtures were generally prepared by placing 40 ml of the solvent and about 0.15–1.15 ml of the NaOH standard solution in a 50-ml volumetric flask (the small variations in water content of the reaction medium for different runs had a negligible effect on the rate constants). After thermal equilibration at 50.0 ± 0.1° the calculated volume of a standard solution of bromo acid was rapidly added with shaking. The resulting concentration of salt was in the range of 1×10^{-4}–9×10^{-4} *M*. Ten to 15 samples were usually withdrawn at convenient time intervals, quenched with 15 ml of 1 *N* H_2SO_4 (prepared in bidistilled water), and potentiometrically titrated with silver nitrate (4×10^{-4}–4.7×10^{-4} *N*) using Radiometer Ag P401 and Hg_2SO_4 K601 electrodes. Better results were obtained when the reference electrode was connected to the titration vessel through a saturated KNO_3 bridge. Microtitrations were performed with a Radiometer SBR2c-TTT1c-ABU1b apparatus, fitted with a 2.500-ml microburet. End points were determined graphically from the recorded titration curves. These were found to be significantly flattened by high percentages of DMSO in the titration medium, so that small samples of kinetic solutions were usually analyzed. Under optimum conditions, *i.e.*, initial concentrations not less than 4×10^{-4} *M* and volume of samples not greater than 2 ml, titration errors were smaller than 1%, as shown by blank experiments.

Calculation Methods for Mixed First- and Second-Order Kinetics. The determination of the intra- and intermolecular rate constants (k_R and k_P, respectively) for both 7-bromoheptanoic and 8-bromooctanoic acids salts by means of (10) was carried out as follows. Initial concentrations ($[M]_0$) and graphically determined initial rates $(-d[M]/dt)_0 = (d[Br^-]/dt)_0$ for different runs were introduced into the equation

$$-\frac{1}{[M]_0}\left(\frac{d[M]}{dt}\right)_0 = k_R + 2k_P[M]_0$$

to yield approximate rate constants k_R^* and k_P^*, from which a trial value for the ratio $k_R^*/2k_P^*$ was obtained for each substrate. This was introduced into the linear equation 10 together with all time–concentration data from four independent runs. A least-squares treatment, as carried out with the aid of an "Olivetti 101" desk computer, gave the slope (k_R) and the correlation coefficients (r). This treatment was repeated several times with different ($k_R^*/2k_P^*$) values, and each time slightly different k_R and r values were obtained. With each k_R value thus determined, the corresponding intermolecular rate constant (k_P) was calculated by means of the expression

$$k_P = (k_R/2)(k_R^*/2k_P^*)^{-1}$$

The results are shown in Table IV. It was assumed that the best values for the rate constants are the ones associated with the highest correlation coefficient obtained. Such values are indicated in italics.

Table IV. Cyclization of Sodium 8-Bromooctanoate. Analysis of Kinetic Data as Mixed First and Second Order, by Means of Eq 10. Results of the Trial-and-Error Calculation Method

$10^4k_R^*/2k_P^*$, *M*	r	10^4k_R, sec^{-1}	10^2k_P, M^{-1} sec^{-1}
9.0	0.99570	1.003	5.5
11.0	0.99677	1.031	4.6
13.0	0.99711	1.052	4.0
14.0	*0.99715*	*1.060*	*3.8*
15.0	0.99712	1.067	3.6
17.0	0.99693	1.079	3.2
19.0	0.99665	1.089	2.9

Product Analysis. The procedure used was according to the following typical experiment. A 1.09×10^{-4} *M* solution of sodium 8-bromooctanoate in 99% DMSO (110 ml) was prepared in the usual way and kept at 50° for 10 half-lives to ensure complete reaction, then cooled and slowly mixed with the same volume of water. After addition of a calculated amount of durene as an internal standard, the mixture was continuously extracted for 6 hr with pentane. The pentane solution was then washed with water, dried (anhydrous Na_2SO_4), and carefully concentrated to a very small volume. Gas chromatographic analysis of the residue was carried out with an "Erba Mod. C" instrument, fitted with a 3% butanediol succinate on a Chromosorb column, operating at 74°. The chromatogram consisted only of the peak due to the durene marker and one with the retention time of the expected 8-octanolide. Relative peak areas were compared with those obtained from standard solutions of durene and 8-octanolide. The reliability of the procedure was checked by blank experiments. The method was also applied to sodium 11-bromoundecanoate; in this case hexadecane was used as the internal standard and the column was operating at 120°.