trial was obtained by a nonweighted least-squares fit of $-\log A$ vs. time. The reported rates are the average of two to four trials and are reported in Table I.

Rate of Styrene Addition to 7,10,11-Trimethylacridizinium Perchlorate. Subsequent to the appearance of our communication of steric acceleration[4] a communication by Hart et al.[14] described in some detail the preparation of the above named salt by essentially the method which we used. Our perchlorate, mp 269–270 °C dec (lit.[14] mp > 265 °C), reacted with styrene too fast to give reproducible rate constants at 65 °C using the previously described procedure,[3] although an estimate of the rate constant ($\times 10^3$, min^{-1}) was 700 vs. 5.0 previously observed for the unsubstituted acridizinium ion. At 25 ± 1 °C using the same procedure the observed rate constant was 63×10^{-3} vs. 0.22×10^{-3} min^{-1} estimated for the unsubstituted compound by extrapolation of available $\ln k/T$ vs. $1/T$ plots. A similar estimate of the expected rate of addition of 11-methylacridizinium perchlorate to styrene at 25 °C was 4.9×10^{-3} (min^{-1}).

Rate Studies of Cycloaddition of the Acridizinium Ion and Its 6-Methyl and 11-Methyl Derivatives at Temperatures in the Range 65–110.6 °C. The acridizinium perchlorates were prepared according to previously published[29,30] directions and melting points agreed closely with those reported. The procedures employed in the rate determinations have been discussed in detail.[3] Pseudo-first-order conditions were maintained by using a 10:1 ratio of alkene to acridizinium salt. The rate at the given temperature was followed by loss of the long wavelength absorbance in the visible spectrum of the acridizinium salt. All spectra were measured in a Beckman DB-G UV-visible spectrometer. Temperature controls were maintained by use of vapor baths. Since corrections were not made for fluctuations of atmospheric pressure the temperatures are correct only to ±0.5 °C. In view of the range of reactivities involved the temperature range 65–110.6 °C was near the maximum for convenience, employing this method. The linear correlations and resultant parameters were calculated by means of a nonweighted least-squares program. The statistical treatments and evaluation standards were those recommended by Jaffé.[10] The listed uncertainties in values include two-thirds of all possible deviations.

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Ring-Closure Reactions. 7.[1] Kinetics and Activation Parameters of Lactone Formation in the Range of 3- to 23-Membered Rings[2]

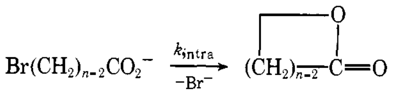
Carlo Galli, Gabriello Illuminati,* Luigi Mandolini, and Pasquale Tamborra

Contribution from the Centro di Studio sui Meccanismi di Reazione del Consiglio Nazionale delle Ricerche, Istituto di Chimica Organica dell'Università, 00185 Rome, Italy.

Received October 8, 1976

Abstract: The ring size (n) range for the quantitative investigation of the lactonization of ω-bromoalkanoic acids with strong bases in 99% aqueous Me_2SO has been considerably extended by the determination of the rate constants for several large rings (n = 13–16, 18, and 23) and for $n = 3$. Also activation parameters have been determined for all the compounds studied so far in the range between 7 and 23 and for $n = 3$. The three-membered ring lactone is a reactive intermediate rather than a final product and is assumed to form in a slow, kinetically detectable step. Extremely high rates are found for the formation of the four-, five-, and six-membered ring lactones and have required the use of an ethyldiisopropylamine-ethyldiisopropylammonium p-toluenesulfonate buffer system in Me_2SO solution and of an appropriate kinetics analysis. The reactivities span six powers of ten, the most reactive compound being the one for $n = 5$ and the least reactive for $n = 8$. They tend to level off in the large ring region and vary within a factor of 2 between $n = 13$ and $n = 23$. The reaction is characterized by a very low k_3/k_5 ratio. The $\Delta H^{\ddagger}$ vs. n profile provides a measure of the strain energy accompanying ring closure. In particular, the highest strains are experienced for $n = 3$ and 8. The entropies of activation provide another clean-cut physical organic demonstration of Ruzicka's hypothesis by undergoing a general and substantial drop as the length of the bifunctional chain increases.

The lactonization of ω-bromo acids is a reaction suitable for quantitative work in the field of ring-closure reactivity. Our previous work[3] has dealt with the kinetics of this reaction in the ring size range n = 7–12, at 50 °C, in 99% Me_2SO solution (eq 1, n = ring size) and with the appropriate intermolecular reference reaction[1] (eq 2) for use in the calculation of the related effective molarities. In order to obtain a deeper understanding of the factors involved in ring closure, in this paper we wish to report rate data which considerably extend the above ring size range by including terms with n = 3, 4, 5, 6, 13,


(1)

$$CH_3(CH_2)_2CO_2^- + CH_3(CH_2)_3Br \xrightarrow[-Br^-]{k_{\text{inter}}} CH_3(CH_2)_2CO_2(CH_2)_3CH_3 \qquad (2)$$

14, 15, 16, 18, and 23. Furthermore, we have been able to include the activation parameters for most compounds, except those with n = 4–6, and for the intermolecular reaction 2.

Earlier studies of similar scope as to ring size range include the cyclization of ω-bromoalkylamines,[4] the lactonization of ω-hydroxy acids,[5] and the formation of catechol polymethylene ethers from the corresponding ω-bromoalkoxy phenoxides.[6] However, the reliability of these early studies suffers from the limited precision of the analytical techniques available at the time and/or from the fact that most data were based mainly on product analysis. Hence, the data reported in the present work combined with those previously described[1,3] provide the most reliable and comprehensive piece of information for a single reaction available for discussion on ring-closure reactivity.

Experimental Section

^{1}H NMR spectra were obtained in CCl_4 solutions on a Jeol C-60 HL spectrometer with Me_4Si as the internal standard. IR spectra were recorded on a Perkin Elmer 257 from 2% solutions in CCl_4. Automatic microtitrations of the bromide ion were performed on a Radiometer SbR2c-AbUlb-TTlc apparatus, employing standard Ag and Hg_2SO_4 electrodes. The cell used for anodic syntheses was a water-jacketed 350-mL flask, fitted with reflux condenser, thermometer, and inlet for the electrodes. These were two identical platinum foils (2.5 × 5 cm), placed about 5-mm apart and connected to a variable dc supply.

All melting and boiling points are uncorrected.

Materials. Reagent grade Me_2SO (Erba RS, water content less than 0.1%) was thoroughly fluxed with pure argon in order to remove any volatile material. Commercial 1,10-dibromodecane (Fluka), 1,12-dibromododecane (Fluka), γ-bromobutyronitrile (Fluka), δ-valerolactone (Aldrich), and p-toluenesulfonic acid monohydrate (Erba RP) were used as received. Butyl bromide (Erba RP), hexyl bromide (Schuchardt), diisopropylethylamine (Fluka), and butyric acid (Erba RP) were distilled before use. Methyl hydrogen sebacate was available from a previous investigation.[7] 1,20-Dibromoeicosane was prepared by symmetrical anodic coupling[8] of 11-bromoundecanoic acid in 52% yield, mp 64–66 °C from light petroleum (bp 40–70 °C) [lit.[8] mp 66.3–67 °C].

ω-Bromo Acids. 6-Bromohexanoic, 7-bromoheptanoic, 8-bromooctanoic, 9-bromononanoic, 10-bromodecanoic, 11-bromoundecanoic, 15-bromopentadecanoic, and 17-bromoheptadecanoic acids were available from previous investigations.[3,7] Bromoacetic acid (ERBA RP) was crystallized from hexane at 5 °C, mp 47–49.5 °C [lit.[9] mp 49.4 °C]. 3-Bromopropionic acid (ERBA RP) was crystallized from CCl_4, mp 59–60 °C [lit.[10] 62–63 °C].

4-Bromobutanoic acid was obtained by refluxing the corresponding nitrile in 48% hydrobromic acid and isolated by standard methods. The compound was purified by distillation, bp 94–96 °C (1 mmHg), followed by crystallization from hexane at 5 °C, mp 25.5–26.5 °C [lit.[9] 32–33 °C].

5-Bromopentanoic acid was prepared by hydrolysis of the corresponding lactone (δ-valerolactone) in refluxing 48% hydrobromic acid, mp 37–37.5 °C from hexane at 5 °C [lit.[9] 39–40 °C].

12-Bromododecanoic Acid. Treatment of 1,10-dibromodecane with sodium diethyl malonate (1:1 mol ratio) in boiling EtOH, followed by elution of the crude reaction product with $CHCl_3$ on silica gel, gave 10-bromodecyl malonate in 28% yield; ^{1}H NMR δ 4.1 (q, 4 H, CO_2CH_2), 3.4 (t, 2 H, CH_2Br), 3.1 (t, 1 H, methine), 1.9–1.4 (m, 18 H, "central" methylene protons), 1.2 (t, 6 H, CH_3). Hydrolysis and decarboxylation of the monomalonyl derivative, effected by treatment with refluxing 48% hydrobromic acid for 5 h, afforded 12-bromododecanoic acid in 76% yield, mp 50–52 °C from light petroleum (bp 40–70 °C) at 5 °C [lit.[11] mp 53 °C].

13-Bromotridecanoic Acid. Treatment of 1,12-dibromododecane with 1 equiv of KCN in water/ethanol, followed by chromatography on silica gel with $CHCl_3$/light petroleum (bp 40–70 °C), 1:1, gave after a forerun of unreacted 1,12-dibromododecane, 13-bromotridecanenitrile in 31% yield. Hydrolysis of the nitrile with boiling 48% hydrobromic acid gave 13-bromotridecanoic acid in 48% yield, mp 54.5–56 °C from hexane at 5 °C [lit.[11] mp 58 °C].

14-Bromotetradecanoic Acid. This compound was prepared by unsymmetrical anodic coupling, followed by hydrolysis of the methyl ester obtained.

$$CH_3O_2C(CH_2)_8CO_2H + HO_2C(CH_2)_5Br \rightarrow CH_3O_2C(CH_2)_{13}Br + 2CO_2 + H_2$$

A solution of methyl hydrogen sebacate (22 g, 0.1 mol) and 6-bromohexanoic acid (20 g, 0.1 mol) in methanol (250 mL) was treated with a small piece of sodium metal (ca. 300 mg), then electrolyzed at 1.2–1.4 A until the solution turned alkaline to litmus (7 h). During the electrolysis external cooling was adjusted as to keep the temperature at 40–50 °C. In order to isolate the product, the solution was acidified with acetic acid, concentrated on the water bath, diluted with water, and extracted with ether. The ethereal extract was washed with Na_2CO_3 solution, then with water, and dried over Na_2SO_4. Removal of the solvent left a residue (25 g) that was distilled at 1.2 mmHg. After a forerun of 1,10-dibromodecane, several fractions boiling in the range 132–200 °C were combined (14 g) and eluted with benzene/$CHCl_3$, 2:1, on silica gel. Methyl 14-bromotetradecanoate (6.0 g, 19% yield) was obtained as a pure fraction (TLC); IR ν(C=O) 1735 cm^{-1}; ^{1}H NMR δ 3.6 (s, 3 H, CO_2CH_3), 3.4 (t, 2 H, CH_2Br), 2.2 (t, 2 H, CH_2CO), 1.7–1.1 (m, 22 H, "central" methylene protons). The methyl ester was converted to the parent acid in 96% yield by treatment with boiling 48% hydrobromic acid. The acid was purified by crystallization from light petroleum (bp 40–70 °C) at 5 °C, mp 61.5–63 °C [lit.[11] 63 °C].

22-Bromodocosanoic Acid. This preparation was effected by the malonic ester synthesis starting from 1,20-dibromoeicosane, according to the same procedure followed for the preparation of 12-bromododecanoic acid. 20-Bromoeicosyl diethyl malonate was obtained in 34% yield, mp 36–38 °C; ^{1}H NMR δ 4.1 (q, 4 H, CO_2CH_2), 3.4 (t, 2 H, CH_2Br), 3.1 (t, 1 H, methine), 1.8–1.3 (m, 38 H, "central" methylene protons), 1.1 (t, 6 H, CH_3). Hydrolysis and decarboxylation of the latter with 48% hydrobromic acid gave 22-bromodocosanoic acid in 68% yield, mp 84.5–85.5 °C from light petroleum (bp 40–60 °C).

Anal. Calcd for $C_{22}H_{43}BrO_2$: C, 62.99; H, 10.33; Br, 19.04. Found: C, 62.89; H, 10.34; Br, 18.92.

Kinetic Measurements. These were effected as previously described.[1,3] The experimental data were treated according to standard integrated equations. The rate constants were evaluated graphically from the appropriate plots, which were linear up to 75–85% conversion. In the reactions run in buffer solution, the diisopropylethylammonium cation was prepared in situ by partly neutralizing diisopropylethylamine with the calculated amount of p-toluenesulfonic acid, which behaves as a strong acid in Me_2SO solution.[12]

The Reaction between 5-Bromopentanoic Acid and Diisopropylethylamine. A 0.5 M solution of both reactants in 99% Me_2SO was kept at 50 °C for 1 h. After cooling, the solution was diluted with water and continuously extracted with diethyl ether for several hours. The ether solution was washed, dried over Na_2SO_4, and evaporated to give practically pure (TLC) 5-pentanolide (δ-valerolactone) in 90% yield, bp 111–114 °C (20 mmHg): $n^{21}{}_D$ 1.4601 [lit.[13] $n^{20}{}_D$ 1.4600].

Results

Seven- and Higher-Membered Rings. The kinetics of the cyclization reactions of the potassium salts of the parent ω-bromo acids were followed by micropotentiometric titration of the bromide ion released. In most cases initial concentrations were in the order of 2–6 × 10^{-4} M. The formation of the eight-, nine-, and ten-membered rings required somewhat lower concentrations, namely approximately 1 × 10^{-4} M for the eight- and nine-membered rings, and lower than 2.5 × 10^{-4} M for the ten-membered ring, as previously shown.[3] Under the stated conditions, the contribution of the second-order polymerization was negligible, and a clean first-order behavior was observed.[3]

Table I. Kinetic Data for the Formation of 3- to 16-, 18-, and 23-Membered Lactones from the Anions of the Parent ω-Bromo Acids $Br(CH_2)_{n-2}CO_2H$ in 99% Aqueous Me_2SO

n^a	Temp, °C	k_{intra}, $s^{-1\,b}$	k_{rel} (at 50 °C)	EM, M^c	$\Delta H^{\ddagger}$,^{d} kcal/mol	$\Delta S^{\ddagger}$,^{d} eu	r^d
3	20.0	$(6.50 \pm 0.11) \times 10^{-5}$	21.7	1.23×10^{-2}	22.0 ± 0.24	-2.5 ± 0.76	0.9999
	35.0	$(4.44 \pm 0.03) \times 10^{-4}$					
	50.0	$(2.41 \pm 0.02) \times 10^{-3}$					
4	50.0	2.6	2.4×10^4	1.35×10			
5	50.0	3.1×10^2	2.8×10^6	1.60×10^3			
6	50.0	2.9	2.6×10^4	1.45×10			
7	20.0	$(6.17 \pm 0.17) \times 10^{-4}$	97.3	5.51×10^{-2}	17.4 ± 0.58	-13.6 ± 1.90	0.9987
	35.0	$(3.02 \pm 0.14) \times 10^{-3}$					
	50.0	$(1.08 \pm 0.02) \times 10^{-2}$					
8	40.0	$(3.88 \pm 0.04) \times 10^{-5}$	1.00	5.66×10^{-4}	21.8 ± 0.46	-9.2 ± 1.38	0.9995
	50.0	$(1.11 \pm 0.02) \times 10^{-4}$					
	60.0	$(3.17 \pm 0.06) \times 10^{-4}$					
	70.0	$(9.13 \pm 0.04) \times 10^{-4}$					
9	40.0	$(4.12 \pm 0.05) \times 10^{-5}$	1.12	6.33×10^{-4}	20.3 ± 0.36	-13.9 ± 1.10	0.9996
	50.0	$(1.24 \pm 0.03) \times 10^{-4}$					
	60.0	$(3.11 \pm 0.04) \times 10^{-4}$					
	70.0	$(7.96 \pm 0.07) \times 10^{-4}$					
10	35.0	$(9.19 \pm 0.04) \times 10^{-5}$	3.35	1.90×10^{-3}	17.4 ± 0.32	-20.5 ± 0.98	0.9997
	50.0	$(3.72 \pm 0.11) \times 10^{-4}$					
	65.0	$(1.26 \pm 0.02) \times 10^{-3}$					
11	35.0	$(2.38 \pm 0.08) \times 10^{-4}$	8.51	4.82×10^{-3}	16.4 ± 0.58	-21.9 ± 1.80	0.9986
	50.0	$(9.45 \pm 0.06) \times 10^{-4}$					
	65.0	$(2.80 \pm 0.09) \times 10^{-3}$					
12	20.0	$(6.49 \pm 0.07) \times 10^{-5}$	10.6	6.02×10^{-3}	17.6 ± 0.32	-17.6 ± 1.06	0.9995
	35.0	$(3.07 \pm 0.11) \times 10^{-4}$					
	50.0	$(1.18 \pm 0.02) \times 10^{-3}$					
13	20.0	$(2.82 \pm 0.01) \times 10^{-4}$	32.2	1.82×10^{-2}	15.3 ± 0.54	-22.5 ± 1.76	0.9994
	35.0	$(1.08 \pm 0.07) \times 10^{-3}$					
	50.0	$(3.57 \pm 0.02) \times 10^{-3}$					
14	20.0	$(4.00 \pm 0.03) \times 10^{-4}$	41.9	2.37×10^{-2}	14.8 ± 0.20	-23.6 ± 0.62	0.9999
	35.0	$(1.48 \pm 0.02) \times 10^{-3}$					
	50.0	$(4.65 \pm 0.02) \times 10^{-3}$					
15	20.0	$(3.52 \pm 0.05) \times 10^{-4}$	45.1	2.56×10^{-2}	16.1 ± 0.24	-19.5 ± 0.80	0.9998
	35.0	$(1.44 \pm 0.03) \times 10^{-3}$					
	50.0	$(5.01 \pm 0.07) \times 10^{-3}$					
16	20.0	$(3.60 \pm 0.03) \times 10^{-4}$	52.0	2.94×10^{-2}	16.8 ± 0.28	-17.0 ± 0.94	0.9997
	35.0	$(1.54 \pm 0.06) \times 10^{-3}$					
	50.0	$(5.77 \pm 0.08) \times 10^{-3}$					
18	20.0	$(4.42 \pm 0.08) \times 10^{-4}$	51.2	2.90×10^{-2}	15.4 ± 0.38	-21.2 ± 1.26	0.9995
	35.0	$(1.79 \pm 0.03) \times 10^{-3}$					
	50.0	$(5.68 \pm 0.09) \times 10^{-3}$					
23	40.0	$(3.01 \pm 0.04) \times 10^{-3}$	60.4	3.42×10^{-2}	14.5 ± 0.56	-23.8 ± 1.76	0.9987
	50.0	$(6.70 \pm 0.10) \times 10^{-3}$					
	60.0	$(1.30 \pm 0.03) \times 10^{-2}$					

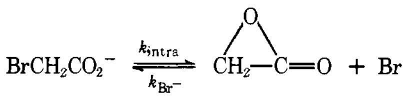
[a] Ring size of the ring to be formed. [b] Runs in duplicate or triplicate. [c] Calculated as k_{intra}/k_{inter}, where k_{inter} refers to the corresponding intermolecular counterpart. All rate constants at 50.0 °C. [d] $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values were estimated from the least-squares slope and intercept of the Eyring plots, i.e., ln k_{intra}/T against $1/T$. The reported errors are expressed as 2σ (95% confidence limit), where σ is the pertinent standard error. The correlation coefficients (r) are also shown.

Rate measurements were effected over a 30° temperature range for all cyclization reactions with the exception of the 23-membered ring, which was examined in the range of 40–60 °C. In this case the low solubility of potassium 22-bromodocosanoate prevented measurements below 40 °C, whilst above 60 °C the cyclization reaction was too fast for precise measurements. In view of reasonably precise activation parameters, care was taken to carry out the kinetic measurements for any given compound in the same stock of mixed solvent, since a slight irreproducibility in the rate constants, within a 10% range, was observed in different batches, probably due to varying composition features of the different stocks of Me_2SO employed. Within these limits of uncertainty, the rate constants for the formation of 7- to 12-membered lactones at 50.0 °C from the present work compare quite well with those previously reported.[3]

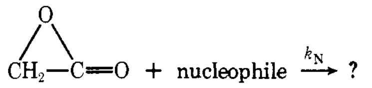
Rate data and activation parameters are reported in Table I.

The Three-Membered Ring. The cyclization of the bromoacetate ion, which is expected to yield a three-membered lactone, requires a separate comment. α-Lactones have been postulated as short-lived intermediates in a variety of transformations,[14] such as α-halo acid hydrolysis, and cannot be isolated under ordinary conditions. We suggest the reaction scheme of eq 3 to apply to the reaction at hand. In the proposed

$$BrCH_2CO_2H + OH^- \rightleftharpoons BrCH_2CO_2^- + H_2O \qquad (3a)$$



$$BrCH_2CO_2^- \underset{k_{Br^-}}{\overset{k_{intra}}{\rightleftharpoons}} \overset{\overset{O}{\diagup\diagdown}}{CH_2{-}C}{=}O + Br^- \qquad (3b)$$



$$\overset{\overset{O}{\diagup\diagdown}}{CH_2{-}C}{=}O + \text{nucleophile} \xrightarrow{k_N} ? \qquad (3c)$$

scheme the conversion of the acid into the corresponding anion

Table II. Rate Data for the Formation of Three- to Seven-Membered Lactones from the Parent ω-Bromo Acid $Br(CH_2)_{n-2}CO_2H$ in 99% Me_2SO at 50 °C in the Presence of Diisopropylethylamine Buffer

n	k_{obsd}, s^{-1} $[B]/[BH^+] = 4.93$[a]	k_{obsd}, s^{-1} $[B]/[BH^+] = 0.146$[b]	k_{rel}^{app}	K_n	k_{rel}
3	$(1.56 \pm 0.07) \times 10^{-3}$		64	3.7×10^{-1}	
4		$(3.69 \pm 0.08) \times 10^{-3}$	3.8×10^{3}	7.1×10^{-3}	2.4×10^{2}
5		$(6.31 \pm 0.29) \times 10^{-2}$	6.4×10^{4}	1.0×10^{-3}	2.9×10^{4}
6	$(7.99 \pm 0.09) \times 10^{-3}$	$(3.19 \pm 0.02) \times 10^{-4}$	3.3×10^{2}	5.7×10^{-4}	2.6×10^{2}
7	$(2.45 \pm 0.02) \times 10^{-5}$[c]		1.0	4.6×10^{-4}	1.0

[a] $[B] = 1.48 \times 10^{-2}$; $[BH^+] = 3.00 \times 10^{-3}$ M. [b] $[B] = 2.08 \times 10^{-3}$; $[BH^+] = 1.42 \times 10^{-2}$ M. [c] The reported value is corrected for solvolysis. The importance of the latter was estimated from hexyl bromide as a model compound, $k_{solv} = 7.5 \times 10^{-6}$ s^{-1}.

(eq 3a) is practically complete. Possible reactions for the last step (eq 3c) are bimolecular S_N reactions with either H_2O or Me_2SO, and/or the conjugate bases therefrom depending on the concentration of base present. It was found that the bromide ion release from bromoacetic acid in the presence of varying amounts of potassium hydroxide follows a strictly first-order behavior. The pertinent rate coefficients are as follows, the relative potassium hydroxide over bromoacetic acid ratio being reported in parentheses: k_{intra} (s^{-1}) = 2.38×10^{-3} (1:1); 2.43×10^{-3} (2:1); 2.41×10^{-3} (4:1). Thus the kinetics are strictly zero order in base. This observation is consistent with the above scheme, provided that the lactone is formed in the rate determining step (eq 3b), and destroyed in the subsequent fast step (eq 3c), i.e., $k_N[\text{nucleophile}] \gg k_{Br^-}\ [Br^-]$. No attempt was made to identify the reaction product(s). Rate measurements were effected at 20.0, 35.0, and 50.0 °C. The related kinetic data are reported in Table I.

Four-, Five-, and Six-Membered Rings. When the bromo acid precursors of the four-, five-, and six-membered lactones were treated with the stoichiometric amount of KOH at 50 °C, cyclization was too fast to be followed by our conventional techniques. The amount of bromide ion released was found to correspond to complete reaction after ca. 30 s.

It was found that in the presence of the weak base diisopropylethylamine (B) rather than KOH, the reaction rate had significantly slowed down, according to the reaction scheme

$$Br(CH_2)_{n-2}CO_2H + B \overset{K_n}{\rightleftharpoons} Br(CH_2)_{n-2}CO_2^- + BH^+ \qquad (4a)$$

$$Br(CH_2)_{n-2}CO_2^- \xrightarrow{k_{intra}} \text{lactone} + Br^- \qquad (4b)$$

in which preequilibrium (eq 4a) is only slightly shifted to the right. Diisopropylethylamine was chosen because of its low nucleophilicity due to steric crowding. The base was effective in promoting lactonization of the bromo acids, as shown by the fact that 5-bromopentanoic acid was converted to 5-pentanolide (δ-valerolactone) in 90% yield under preparative conditions (see Experimental Section). When the cyclization reactions of the given bromo acids were carried out in the presence of excess base and excess conjugate acid BH^+, i.e., under buffered conditions, the kinetics were found to be strictly first order. For the sake of comparison, the kinetics of cyclization of bromoacetic and 6-bromohexanoic acids to the three- and seven-membered lactones, respectively, were also studied in the presence of diisopropylethylamine buffer. The experimental data are collected in Table II. The observed first-order rate coefficients (k_{obsd}) were found to be dependent on the buffer ratio $[B]/[BH^+]$. Since the cyclization reactions to the four- and five-membered rings were very fast even in buffer solution, a low buffer ratio, namely $[B]/[BH^+] = 0.146$, was used for precise measurement. In contrast, the occurrence of a "spontaneous" side reaction with the solvent, slowly producing free bromide ions, required a high buffer ratio ($[B]/[BH^+] = 4.93$) to speed up the slow cyclization reaction of 6-bromohexanoic acid to the seven-membered lactone (see Table II, footnote *c*).

The rates of the six-membered ring formation could be measured in both buffer solutions. This allowed the apparent reactivity data (k_{rel}^{app}) reported in Table II to be calculated on a single scale. However, the reactivity data as obtained in buffer solution are affected to a certain extent by the varying acidities of the substrates. A correction for the latter effect requires the equilibrium constant K_n for the equilibrium (eq 4a) to be known. The K_n values could be crudely estimated by assuming that acidities of the bromo acids in 99% Me_2SO correlate linearly with the corresponding K_a values in water, according to the equation

$$\log K_n = m \log K_a + \text{constant} \qquad (5)$$

The closest available K_a values (at 18–25 °C)[15] include the following acids: CH_3CO_2H (1.78×10^{-5}); $BrCH_2CO_2H$ (1.29×10^{-3}); $Br(CH_2)_2CO_2H$ (1.02×10^{-4}); $Cl(CH_2)_3CO_2H$ (3.0×10^{-5}); and $Cl(CH_2)_4CO_2H$ (2.04×10^{-5}). It was assumed that the K_a values for 4-bromobutanoic and 5-bromopentanoic acid can be considered equal to those of the corresponding chloro derivatives. Furthermore, the acidity of 6-bromohexanoic acid was set equal to that of acetic acid. In order to evaluate the slope, m, K_n values for at least two bromo acids are required. The latter were calculated as follows. According to the scheme in eq 4, the observed first-order rate constant, k_{obsd}, in buffer solution is related to k_{intra} by means of the equation

$$k_{obsd} = \alpha k_{intra} \qquad (6)$$

where α is the degree of dissociation of the bromo acid in the given buffer solution. When applied to the cyclization reactions of bromoacetic and 6-bromohexanoic acids, for which both k_{obsd} and k_{intra} are known, eq 6 gives $\alpha = 0.65$ and 2.3×10^{-3}, respectively.

Introduction of these α values into the equation

$$K_n = \alpha[BH^+]/(1 - \alpha)[B] \qquad (7)$$

which is the expression of the equilibrium constant for the acid–base reaction (eq 4a), gives $K_3 = 0.37$ and $K_7 = 4.6 \times 10^{-4}$. Hence, the slope in eq 5 could be calculated as $m = 1.56$. It is worth noting that a greater sensitivity of the acidity of the bromo acids to electronic effects in 99% Me_2SO than in water, i.e., $m > 1$, could be anticipated since little or no stabilization of the carboxylate ions by hydrogen bonding is expected in the former solvent. Knowledge of m allowed us to calculate K_4, K_5, and K_6 values (Table II), which were used to correct apparent reactivity data as obtained in buffer solutions. Since the condition $[RCO_2H] \gg [RCO_2^-]$ is fulfilled by the bromo acid precursors in the given buffer solutions, the simple equation,

$$k_{rel} = k_{rel}^{app}/(K_n)_{rel} \qquad (8)$$

which applies to each pair of cyclization reactions run in the same buffer solution, could be used. Corrected ring-closure rate constants relative to ring size 7 are reported in Table II as k_{rel}. The latter were multiplied by 1.08×10^{-2}, i.e., the cyclization rate constant of 6-bromohexanoate anion at 50.0 °C, to give the corrected cyclization rate constants of the anion reported in Table I. It can be seen that corrections for the varying acidity of the parent bromo acids are relatively unimportant in the case of the five- and six-membered rings. In contrast, the four-membered ring formation required a correction in the order of a power of ten. The kinetic measurements for the given rings were effected at one temperature only, namely at 50.0 °C. Since quite accurate rate constants are required for the determination of meaningful activation parameters, no attempt was made to carry out rate measurements at different temperatures.

The Intermolecular Reaction. The S_N2 reaction between potassium butanoate and butyl bromide was studied in the same solvent. This reaction, which leads to butyl butanoate in virtually quantitative yield, provides a reasonably general intermolecular model for the lactonization reaction, as was recently shown.[1] The kinetic measurements were effected at three different temperatures, over a 30° range. Kinetics data were obtained as follows: k_{inter} (L mol^{-1} s^{-1}) = $(6.73 \pm 0.09) \times 10^{-2}$ (at 35.0 °C); $(1.96 \pm 0.06) \times 10^{-1}$ (at 50.0 °C); $(5.67 \pm 0.12) \times 10^{-1}$ (at 65.0 °C); $\Delta H^{\ddagger} = 14.1 \pm 0.42$ kcal/mol; $\Delta S^{\ddagger} = -18.4 \pm 1.3$ eu; $r = 0.9992$. The k_{inter} value (at 50.0 °C) was employed for the calculation of the effective molarities (EM),[16] reported in Table I, which are defined by the k_{intra}/k_{inter} ratios, and represent an absolute measure of the ring-closure tendency of bifunctional substrates.

Discussion

The cyclization rate constants at 50.0 °C (from Table I) are plotted in Figure 1. The ease of ring formation is extremely sensitive to chain length. On going from the three- to the five-membered lactone the rate constant increases by five powers of ten, the four-membered ring being formed at an intermediate rate. The five-membered ring is located at a sharp maximum. Then the velocity decreases rapidly down to the eight-membered ring, which is formed more than 10^6-fold less easily than the five-membered one, an approximate drop of two powers of ten being observed per added methylene group. The eight-membered ring is located with the next higher homologue at the reactivity minimum.[3] The ease of ring closure then increases again with increasing ring size, until a substantial leveling off is observed for the large rings. Rate data in the range 13-23 lie well within a factor of 2.

Several features of the above data are noteworthy. First of all the k_3/k_5 ratio, i.e., 1.4×10^{-5}, is very low for lactone formation, in fact it is the lowest reported so far[17] for ring-closure reactions. We believe that a major factor for this value is the additional strain introduced by the sp^2 carbonyl carbon to the strained three-membered cyclic transition state. Furthermore, lack of a stabilizing conjugative substituent effect in the transition state is another possible factor as suggested by Stirling et al.[17] in other series.

It has already been observed that ring closure to the five-membered ring is by far the fastest in the whole set. It is also a very fast reaction on an absolute scale, the estimated half-life being 2.4 ms at 50.0 °C. Nevertheless the corresponding effective molarity (Table I and right hand scale in Figure 1) is one to two orders of magnitude lower than those reported for such analogous five-membered ring formation reactions proceeding via intramolecular nucleophilic displacement as the cyclization reactions of: (i) $H_2N(CH_2)_3Br$ (EM = 1.4×10^4 M);[18] (ii) $^-O(CH_2)_4Cl$ (EM = 8.1×10^4 M);[18] (iii) *o*-$^-OC_6H_4CH_2CH_2Br$ (EM = 1.3×10^5 M).[19] This behavior is fully consistent with our previous hypothesis,[3] i.e., that transition states leading to lactones with less than nine atoms in the ring, which contain the ester function in the less stable cis confomation, suffer from a destabilizing factor when compared with higher homologues and open-chained counterparts in which the ester function is trans.[20] The estimated difference in the free energies of the two extreme conformations, i.e., 3.8 kcal/mol,[20] corresponds to a kinetic factor of about 400 at 50 °C. If the transition state leading to the five-membered lactone is assumed to be affected by a significant fraction, say, two-thirds or so, of the above free energy difference, a rate depressing factor of one to two powers of ten can be accounted for.

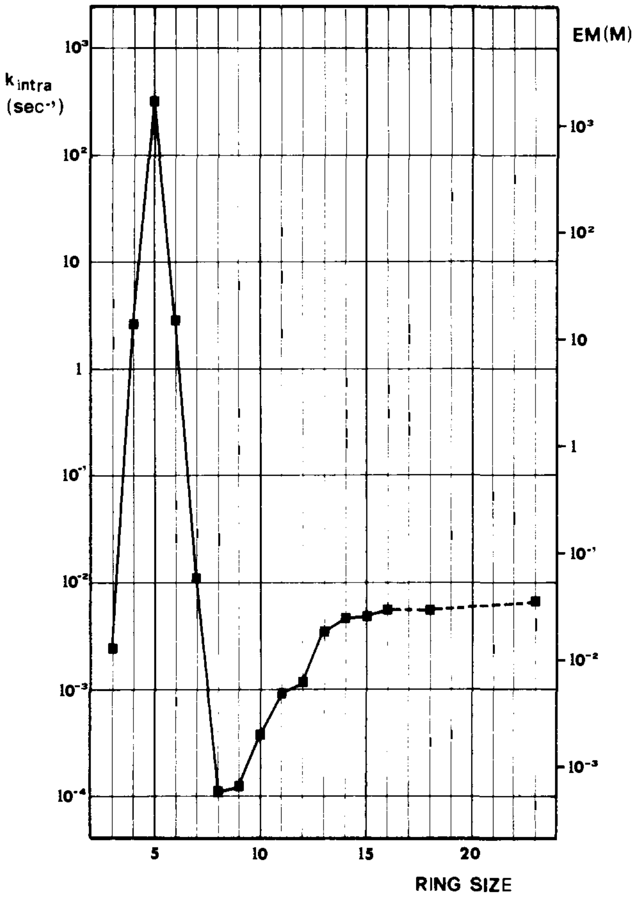


Figure 1. Reactivity plot for the formation of lactones in 99% Me_2SO at 50 °C from the parent ω-bromoalkanoate ions. In the right-hand scale the effective molarities (EM) are reported (see text).

The influence of the above cis/trans effect on the position and shape of the reactivity minimum has already been discussed.[3] In the large ring region the relative insensitiveness of cyclization rates on ring size is not completely unexpected, since approximate rate studies[4-6] and yield data[21] indicate a substantial leveling off of ring-closure tendency in the large-ring region. It is of interest that the alternating effects appearing in the yield profiles for typical cyclization reactions (see Figure 2) do not show up in our reactivity profile (Figure 1). Such effects have been considered an inherent property of the methylene chains connecting the functional groups.[22] However, it must be borne in mind that yield data, even when obtained under strictly comparable conditions, could reflect factors other than relative reactivities. It is well known that many physical properties of the cyclic compounds, particularly those related to the solid state, show interesting zig-zagging behavior.[23] For example, in the Hunsdiecker lactonization reaction (Figure 2, curve A) yields have been based on the

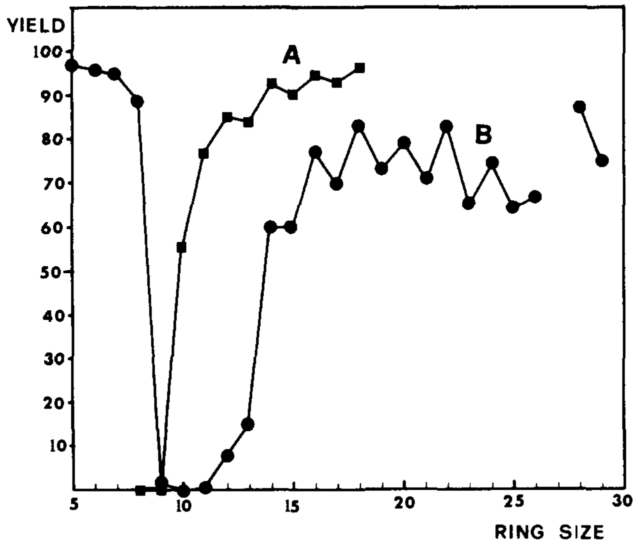


Figure 2. Yield data as a function of ring size for typical cyclization reactions: (A) Hunsdiecker lactonization of ω-bromo fatty acids (data from H. Hunsdiecker and H. Erlbach, *Chem. Ber.*, **80**, 129 (1947)); (B) Ziegler cyclization of dinitriles (data from K. Ziegler and W. Hechelhammer, *Justus Liebigs Ann. Chem.*, **528**, 114 (1937)).

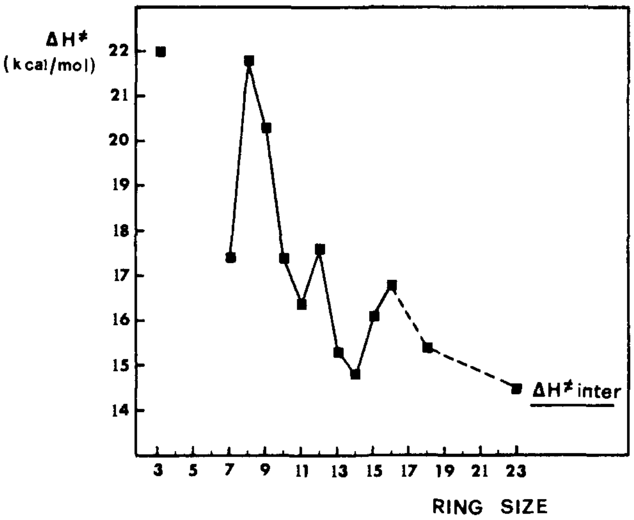


Figure 3. Enthalpies of activation vs. ring size for the formation of lactones. $\Delta H^{\ddagger}$ value for the corresponding intermolecular reaction is also shown.

amounts of lactones recovered by crystallization of the crude reaction products from methanol at low temperature. Hence solubility differences of the lactones could possibly affect yield data to some extent.

Except for the four-, five-, and six-membered rings for which activation parameters are not available as yet, reactivities could be dissected into strain ($\Delta H^{\ddagger}$) and probability ($\Delta S^{\ddagger}$) terms (Figures 3 and 4, respectively). Comparison of the enthalpies of activation for the ring-closure reactions ($\Delta H^{\ddagger}_{\text{intra}}$) with that for the intermolecular counterpart ($\Delta H^{\ddagger}_{\text{inter}}$) which can be taken as the "strainless" reference reaction provides a quantitative estimate of the strain energy accompanying ring closure. The latter can be seen to be strongly dependent on the size of the ring to be formed. Accordingly, a high $\Delta H^{\ddagger}$ value is observed for the formation of the highly strained α-lactone, which amounts to a strain energy of about 8 kcal/mol, as obtained from the difference $\Delta H^{\ddagger}_{\text{intra}} - \Delta H^{\ddagger}_{\text{inter}}$. A similar strain is observed for the formation of the eight-membered ring, which appears to be the most strained term in the medium-ring region, as previously suggested.[3] In this case, the unfavorable enthalpy term can be viewed as due to a superposition of a general medium-ring effect onto the conformational cis effect, the latter being absent in the higher homologues. The $\Delta H^{\ddagger}$ vs. n profile, though irregular, does exhibit a pattern which seems to be too markedly structured to be merely due to experimental uncertainty. The appearance of a sequence of three maxima that are apart from each other by four methylene units, i.e., at $n = 8$, 12, and 16, is hardly fortuitous. The enthalpy of activation generally decreases on increasing ring size, the difference $\Delta H^{\ddagger}_{\text{intra}} - \Delta H^{\ddagger}_{\text{inter}}$ being vanishingly small for the 23-membered ring. This finding is consistent with the view that large rings are substantially strainless, and that many properties of ring compounds approach the values of their open-chained counterparts in the limit of the large-ring region.[21a]

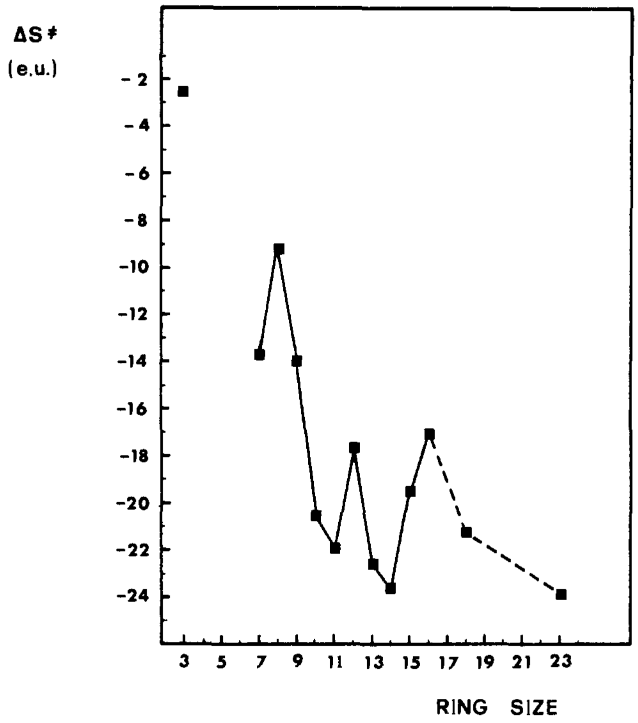


Figure 4. Entropy of activation vs. ring size for the formation of lactones.

As to entropies of activation, the general trend confirms the intuitive notion that the mutual approach of the two ends of a molecular chain is the less probable the longer the chain, as first suggested by Ruzicka.[24] The $\Delta S^{\ddagger}$ parameter drops from the value of -2.6 eu of the three-membered ring to the value of -23.8 eu of the 23-membered homologue. Figure 4 exhibits a similar pattern as that observed in Figure 3. The similarity between the two plots is striking. This could at first sight suggest the existence of an isokinetic relationship,[25] i.e., a linear correlation between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. However, such a relationship is unlikely, since different interaction mechanisms[25] are expected to operate for the different compounds of the reaction series at hand. A plot of $\Delta H^{\ddagger}$ against $\Delta S^{\ddagger}$ (not shown here) indeed shows a random scatter. Nevertheless, a mutual compensation of divergent $\Delta H^{\ddagger}$ and $-T\Delta S^{\ddagger}$ changes renders the effect on $\Delta G^{\ddagger}$ less pronounced than those on either enthalpy and entropy components, particularly in the large-ring region.

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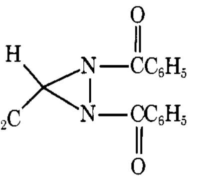
Unsaturated Carbenes from Primary Vinyl Triflates. 7. Reaction with Azoarenes[1,2]

Peter J. Stang* and Michael G. Mangum

Contribution from the Department of Chemistry, The University of Utah, Salt Lake City, Utah 84112. *Received October 18, 1976*

Abstract: Reaction of triflate $(CH_3)_2C{=}CHOTf$ with azobenzene and *tert*-butylazobenzene in glyme with *t*-BuOK at −20 °C gives 2-indazoles in good yield; no benzimidazoles were observed. The azobenzene adduct was identified by spectral means and oxidation to azobenzene-*o*-carboxylic acid. Reaction occurs via interaction of the triflate-derived carbene $(CH_3)_2C{=}C{:}$ with the azoarenes and represents a simple, single-step entry into this interesting class of 10-π-electron heterocyclic system.

Carbenes readily add to olefins and alkynes to give cyclopropanes and cyclopropenes, respectively.[3] Similarly, carbenes are known to interact with heteronuclear multiple bonds and particularly with C=N and N=N bonds.[4] Reaction of carbenes with azo linkages is especially interesting for it can lead to novel heterocyclic compounds. The first such reaction was the interaction of carboethoxycarbene, derived from ethyl diazoacetate, with azodibenzoyl reported by Mueller[5] to give diaziridine **1**, and for a number of years thereafter carbene additions to azo compounds were interpreted in terms of such diaziridine adducts.[6] It was not until the 1960's that Breslow[7] and Fahr[8] reexamined these reactions and showed that the actual product was not a diaziridine **1**, but an oxadiazoline **2**. In fact, interaction of carbenes with azo compounds generally falls in two categories, depending on the structure of the azo substrate, as shown in Scheme I. Azodicarbonyls (or azodicarboxylic esters) generally yield[9] oxadiazolines **3** and/or hydrazones **4**, whereas azoarenes usually give [10] dihydroindazoles, **5**, and/or azomethyne imines, **6**.



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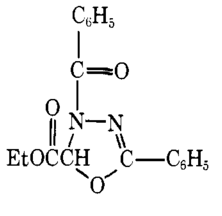

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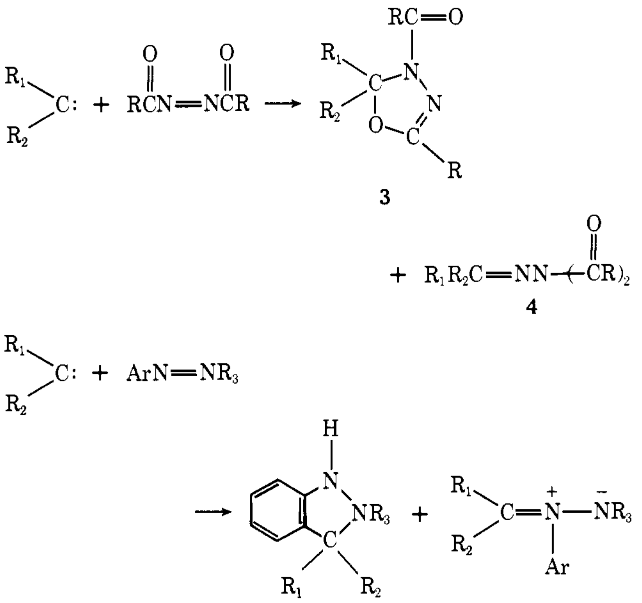
Recently besides normal carbenes there has been increasing interest in unsaturated carbenes,[11] **7** and **8**, generated by α elimination from vinyl halides,[12] **9**, or vinyl triflates,[13] **10**, and base-promoted decomposition of *N*-nitrosooxazolidones,[14] **11**.

Scheme I. Reaction of Carbenes with Carbonyl Azo Compounds and Azoarenes



These carbenes also readily interact with olefins[11] as well as alkynes,[15] but little or no work has been done in the possible reaction of these species with heteronuclear multiple bonds and in particular azo compounds. There is but a single report,[16] with no product identification, but only a 1:1 adduct claimed, on the interaction of an unsaturated carbene, **7**, with an azo compound, namely azobenzene, and a single report[17] on the