

(34h) (35%) and an acyclic olefinic alcohol 3h (13%).

**trans-1-Methyl-2-isobutylcyclopentanol (34h)**; bp 104 °C (51 mm); NMR (CCl<sub>4</sub>)  $\tau$  7.90 (br s, 1 H), 8.01–9.05 (m, 10 H), 8.90 (s, 3 H), 9.05 (d, 6 H,  $J$  = 6.0 Hz); IR (neat) 3450 and 1110 cm<sup>-1</sup>. Anal. Calcd for C<sub>10</sub>H<sub>20</sub>O: C, 76.86; H, 12.90. Found: C, 76.98; H, 12.95.

## References and Notes

- (1) A preliminary communication: T. Shono and M. Mitani, *J. Am. Chem. Soc.*, **93**, 5284 (1971).
- (2) (a) M. M. Balzer, Ed., "Organic Electrochemistry", Marcel Dekker, New York, N.Y., 1973, pp 253–444; (b) C. K. Mann and K. K. Barnes, "Electrochemical Reactions in Nonaqueous Systems", Marcel Dekker, New York, N.Y., 1970, pp 177–243; (c) A. J. Fry, "Synthetic Organic Electrochemistry", Harper and Row, New York, N.Y., 1972, pp 207–268; (d) N. L. Weinberg, "Technique of Electroorganic Synthesis", Part II, Wiley, New York, N.Y., 1974, pp 83–269; (e) L. Ebersson and H. Schäfer, *Top. Curr. Chem.*, **21**, 113–124 (1971); (f) A. J. Fry and G. Dryhurst, *ibid.*, **34**, 1–47 (1972); (g) M. R. Rifi and F. H. Coviltz, "Introduction to Organic Electrochemistry", Marcel Dekker, New York, N.Y., 1974, pp 167–247.
- (3) For a review: (a) S. Wawzonek, *Synthesis*, 285 (1971); (b) F. D. Popp and H. P. Schultz, *Chem. Rev.*, **62**, 19 (1962).
- (4) S. Wawzonek and A. Gunderson, *J. Electrochem. Soc.*, **107**, 537 (1960).
- (5) K. Sugino and T. Nonaka, *Electrochim. Acta*, **13**, 613 (1968).
- (6) T. Nonaka, T. Sekine, K. Odo, and K. Sugino, *Electrochim. Acta*, **22**, 271 (1977).
- (7) T. Nonaka and K. Sugino, *Denki Kagaku*, **38**, 105 (1970).
- (8) T. Nonaka and K. Sugino, *Denki Kagaku*, **40**, 66 (1972).
- (9) For a review, see H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 162.
- (10) E. J. Corey and I. Kuwajima, *J. Am. Chem. Soc.*, **92**, 395 (1970).
- (11) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **81**, 247 (1959).
- (12) The stereoconfiguration of the products 19a–c was not established, though IR, NMR, and VPC analyses clearly indicated that each product consisted of a single stereoisomer.
- (13) A. C. Cope, J. M. Grisar, and P. E. Peterson, *J. Am. Chem. Soc.*, **82**, 4299 (1960).
- (14) (a) M. Julia, *Acc. Chem. Res.*, **4**, 386 (1971); *Pure Appl. Chem.*, **15**, 167 (1967); (b) C. Walling and M. S. Pearson, *J. Am. Chem. Soc.*, **86**, 2262 (1964); (c) C. Walling, J. H. Cooley, A. A. Ponaras, and E. J. Racah, *ibid.*, **88**, 5361 (1966), and others cited therein.
- (15) (a) M. Eakin, J. Martin, and W. Parker, *Chem. Commun.*, 206 (1965); (b) H. O. House, R. W. Giese, K. Kronberger, J. p. Kaplan, and J. F. Slmenone, *J. Am. Chem. Soc.*, **92**, 2800 (1970).
- (16) (a) A. Viglani, R. Pasqualucci, G. G. Gallo, and G. Pifferi, *Tetrahedron*, **25**, 573 (1969); (b) A. A. P. Schreiber, *Tetrahedron Lett.*, 4271 (1970).
- (17) E. J. Corey, R. L. Danheiser and S. Chandrasekaran, *J. Org. Chem.*, **41**, 260 (1976).
- (18) U. Ravid and R. Ikan, *J. Org. Chem.*, **39**, 2637 (1974).
- (19) D. S. Breslow, E. Baumgarten, and C. R. Hauser, *J. Am. Chem. Soc.*, **86**, 1286 (1964).
- (20) F. B. Laforge, N. Green, and W. A. Gersdoff, *J. Am. Chem. Soc.*, **70**, 3707 (1948).
- (21) R. B. Moffett and R. L. Shriner, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 562.
- (22) J. Murata and H. Arai, *Kogyo Kagaku Zasshi*, **57**, 578 (1954).
- (23) B. Helferich and T. Malkomes, *Chem. Ber.*, **55**, 705 (1922).
- (24) R. J. Otto, R. A. Clayton, S. M. Robert, and B. H. Vermon, *J. Chem. Eng. Data*, **380** (1971).
- (25) M. Julia, S. Julia, and R. Guégan, *Bull. Soc. Chim. Fr.*, 1072 (1960).
- (26) K. Jamusz, G. Jozef, and K. Katarzyna, *Riechst., Aromen, Koerperpfliegem.*, **19**, 192 (1969); *Chem. Abstr.*, **71**, 102020q (1969).
- (27) M. F. Ansell and D. A. Thomas, *J. Chem. Soc.*, 539 (1961).
- (28) F. Rouessac, P. L. Perchec, and J. M. Conia, *Bull. Soc. Chim. Fr.*, 818 (1967).
- (29) J. M. Conia, *Bull. Soc. Chim. Fr.*, 1392 (1956).
- (30) J. M. Conia and F. Leyendecken, *Bull. Soc. Chim. Fr.*, 830 (1967).
- (31) A. Padwa and D. Eastman, *J. Am. Chem. Soc.*, **91**, 462 (1969).
- (32) P. Beslin, R. Bloch, G. Moinet, and J. M. Conia, *Bull. Soc. Chim. Fr.*, 508 (1969).
- (33) G. Opitz and H. Mildenberger, *Justus Liebigs Ann. Chem.*, **650**, 115 (1961).
- (34) N. Heap and G. H. Whitham, *J. Chem. Soc. B*, 164 (1966).
- (35) Each of the anode and cathode consisted of two cylindric dry-battery carbon rods, of which diameter and length were 0.7 and 10 cm, respectively. The length of the electrodes immersed in the solvent system was 3.0–3.5 cm and the distance between the anode and cathode was 1.0–1.5 cm.
- (36) A sufficient amount of current could not be passed when a divided cell equipped with a ceramic diaphragm was used in the MD solvent.
- (37) The excess of electricity was probably consumed to cause the oxidation of solvents, the heat evolution, and the generation of a small amount of hydrogen. See ref 38 for the anodic oxidation of dioxane.
- (38) T. Shono and Y. Matsumura, *J. Am. Chem. Soc.*, **91**, 2803 (1969).
- (39) J. Doeuve, *Bull. Soc. Chim. Fr.*, **45**, 351 (1929).
- (40) C. Gregoire, *Bull. Soc. Chim. Belg.*, **47**, 241 (1938); *Chem. Abstr.*, **32**, 53839 (1938).
- (41) P. E. Peterson and G. Allen, *J. Am. Chem. Soc.*, **85**, 3608 (1963).
- (42) T. Kato, *Nippon Kagaku Zasshi*, **83**, 752 (1962).
- (43) The electrodes were the same as those described in footnote 35.

## Ring-Closure Reactions. 11.<sup>1</sup> The Activation Parameters for the Formation of Four- to Six-Membered Lactones from $\omega$ -Bromoalkanoate Ions. The Role of the Entropy Factor in Small- and Common-Ring Formation<sup>2</sup>

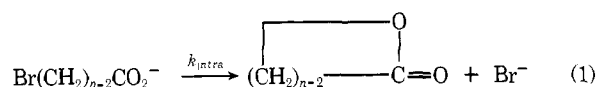
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**Abstract:** Previous work on the kinetics of formation of 3- to 23-membered lactones from  $\omega$ -bromoalkanoate anions in 99% Me<sub>2</sub>SO has been completed with the inclusion of precise rate constants and thermodynamic activation parameters for the formation of four- to six-membered rings. The kinetics were followed by a stopped-flow spectrophotometric technique by the device of introducing a visual indicator into the reaction systems. The pattern observed for the enthalpies of activation leads to the suggestion that they closely follow the strain energies of the rings to be formed. The dependence of the entropy factor upon ring size is discussed in some detail with particular reference to the small- and common-ring regions, for which available literature data for comparison purposes are more abundant.

In recent studies<sup>3</sup> on the kinetics of formation of 3- to 23-membered lactones from  $\omega$ -bromoalkanoate ions in 99% aqueous Me<sub>2</sub>SO (eq 1) accurate rate data and activation parameters have been reported for the formation of most ring compounds in the given range. However, the rate of formation of four-, five-, and six-membered lactones was too high to be



followed by our conventional technique. Only a crude estimation of the rate constants could be made by an indirect

**Table I.** Kinetic Data for the Formation of Four- to Six-Membered Lactones from  $\omega$ -Bromoalkanoate Ions  $\text{Br}(\text{CH}_2)_{n-2}\text{CO}_2^-$  in 99% Aqueous  $\text{Me}_2\text{SO}$ 

Ring size <i>n</i>	$k_{\text{intra}}, \text{s}^{-1}{}^a$					$k_{\text{intra}}^b$ $\text{s}^{-1}$ , at 50.0 °C	$\Delta H^\ddagger, {}^c$ kcal/mol	$\Delta S^\ddagger, {}^c$ eu	$r^c$
	18.0 °C	26.0 °C	34.0 °C	42.0 °C	50.0 °C <sup>d</sup>				
4	<i>e</i>	0.0582	0.136 <sup>f</sup>	0.280	0.587	~2.6	17.7 ± 0.70	-4.9 ± 2.2	0.9985
5	10.1	21.8	45.1	87.9	170	~310	15.9 ± 0.19	-5.6 ± 0.6	0.9996
6	0.0879	0.210	0.447 <sup>g</sup>	0.922	1.88	~2.9	17.2 ± 0.34	-4.2 ± 1.1	0.9992

<sup>a</sup> Average from 3 to 12 independent runs. Standard deviations from the Eyring plots are in the order of 2.5–4%. <sup>b</sup> Early preliminary estimated values, from ref 3. <sup>c</sup>  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  data calculated from the least-squares slope and intercept of the Eyring plots, whose correlation coefficients ( $r$ ) are shown. The single values from each determination, and not the reported average values, were used in the least-squares method. The magnitude of the errors was estimated as  $\pm 2\sigma$  (95% confidence limit) where  $\sigma$  is the standard error. <sup>d</sup> Since this temperature could not be attained because of technical limitations of the stopped-flow apparatus, the pertinent  $k_{\text{intra}}$ 's were extrapolated from the Eyring plots. <sup>e</sup> The reaction was too slow for precise measurement. <sup>f</sup> At 33.85 °C. <sup>g</sup> At 34.1 °C.

method. As a consequence, no activation parameters were reported for the latter rings, since their determination requires accurate rate measurements. The present investigation was undertaken with the aim of filling this gap, as activation parameters are of great significance for a deeper understanding of the factors controlling reactivity in ring-closure reactions.

In this paper an accurate kinetic study for the formation of four-, five-, and six-membered lactones is reported. A reliable and consistent set of rate constants and activation parameters for the ring-size range 3 to 23 is thus now available. The entropy of activation data are discussed in the light of a comparison with related literature data on the formation of small and common rings. An assessment of the general dependence of the entropy terms for ring closure upon the chain length in the bifunctional precursors is attempted.

### Methods and Results

As shown by our preliminary estimates,<sup>3</sup> the rates of formation of four-, five-, and six-membered lactones lie conveniently in the stopped-flow range, the estimated half-life times at 50 °C being 0.27, 0.002, and 0.24 s, respectively. Commonly available stopped-flow apparatuses are fitted with spectrophotometric detection, but little or no change of absorbance is expected to accompany the lactonization reaction (1). In principle, the kinetics might be followed conductometrically, as a substantial change in conductivity is expected for the reaction at hand. However, stopped-flow apparatuses with conductimetric detection appear to have been used but seldom, and do not seem to be either commercially available or easy to set up.<sup>4</sup> The problem was circumvented by matching a proper visual acid-base indicator to the reaction under study, so that the kinetics could be easily followed by monitoring the disappearance of the indicator itself by ordinary stopped-flow spectrophotometry. The rationale of the method is as follows. Let  $\text{InH}$  be a weak acid whose conjugate base strongly absorbs in some spectral region useful for analytical purposes. By combining the equilibrium constants  $K_n$  and  $K_{\text{InH}}$  for the dissociation of a given bromo acid and of the indicator, respectively, eq 2 is obtained.

$$[\text{In}^-] = \frac{K_{\text{InH}}[\text{InH}]}{K_n[\text{Br}(\text{CH}_2)_{n-2}\text{CO}_2\text{H}]} [\text{Br}(\text{CH}_2)_{n-2}\text{CO}_2^-] \quad (2)$$

That is, if the  $\text{InH}/\text{In}^-$  and  $\text{Br}(\text{CH}_2)_{n-2}\text{CO}_2\text{H}/\text{Br}(\text{CH}_2)_{n-2}\text{CO}_2^-$  pairs are both present in the reaction medium,  $[\text{In}^-]$  is proportional to  $[\text{Br}(\text{CH}_2)_{n-2}\text{CO}_2^-]$  provided that the ratio  $[\text{Br}(\text{CH}_2)_{n-2}\text{CO}_2\text{H}]/[\text{InH}]$  is a constant. This condition was largely fulfilled in the kinetic runs by the devices (1) of running the cyclization reaction of a given  $\omega$ -bromocarboxylate anion in the presence of a substantial amount of the undissociated parent acid; and (2) of using an indicator enough less acidic than the given bromo acid that only a comparatively small, but still analytically appreciable, amount was converted

into its basic form. It can be easily verified that under the above conditions the rate law for the disappearance of the anionic form of the indicator is coincident with that for the cyclization of the  $\omega$ -bromoalkanoate ion. Several indicators were tested for the different substrates. It was found that *m*-nitrophenol was suitable for the cyclization reactions of 4-bromobutanoate and 5-bromopentanoate anions, while 3-bromopropanoate required a more acidic indicator, namely, 2,4-dichlorophenol, owing to the enhanced acidity of 3-bromopropanoic acid as compared to its higher homologues. The results of the kinetic experiments are collected in Table I.

### Discussion

Inspection of Table I shows that previously estimated values agree with the present data (at 50 °C) in their order of magnitude. The most serious discrepancy is observed for the four-membered ring, whose rate of formation as obtained in the present work is some four times lower than that previously reported. This fact was not completely unexpected, since our previous estimates involved a rather crude correction for the unknown acidities of the parent bromo acids in 99%  $\text{Me}_2\text{SO}$ . The correction was more significant for 3-bromopropanoic acid than for the higher homologues, owing to the greater acidity of the former.<sup>3</sup> However, even this extreme case adds little new to the reactivity picture as a whole, since the latter spans over six powers of ten in the investigated ring-size range of 3 to 23.<sup>3</sup>

The enthalpies of activation from the present work are plotted in Figure 1 together with all the available data for the other ring sizes and for the intermolecular model reaction, viz., the alkylation of butanoate ion with butyl bromide. The behavior of  $\Delta H^\ddagger$  values in the whole ring-size range is qualitatively in agreement with expectations. In particular, the steep drop on going from the three- to the five-membered ring, followed by a similarly steep increase up to the eight-membered medium ring, is consistent with widely accepted ideas on the dependence of ring strain upon ring size in the small- and common-ring region, and beyond.<sup>5</sup> It is unfortunate that, in the absence of either thermochemical data or theoretical calculations, the strain energies of the formed lactones are not available. Thus, whether a linear strain energy relationship<sup>6</sup> holds or not in the ring-closure series at hand cannot be at present verified. However, there is little doubt that  $\Delta H^\ddagger$  values are indeed related to the strain energies of the formed rings.

It is worth noting that the enthalpies of activation for the formation of the five- and six-membered rings are higher by some 2–3 kcal/mol than the corresponding value for the strainless intermolecular model reaction. In contrast, in an analogous ring-closure reaction, viz., the formation of cyclic aralkyl ethers via intramolecular nucleophilic substitution,<sup>7</sup> the transition states leading to the five- and six-membered rings were found to be essentially strainless. This observation adds further experimental support to the view<sup>3,8</sup> that a significant

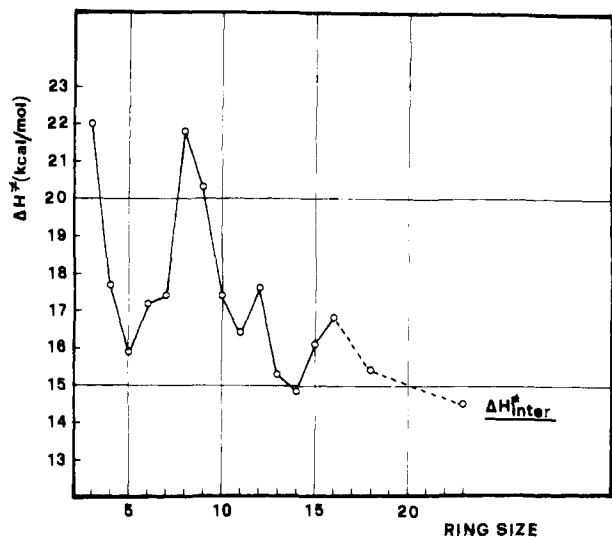


Figure 1. Plot of  $\Delta H^\ddagger$  vs. ring size for the formation of lactones. The  $\Delta H^\ddagger$  value for the intermolecular model reaction is also reported. (Data from the present work and from ref 3.)

fraction of the conformational energy of the cis form of the ester function, which is 3.8 kcal/mol less stable than the trans form,<sup>9</sup> affects the transition states leading to the five- and six-membered lactones, in which the ester group is required to be cis because of geometric reasons.

Ruzicka's hypothesis,<sup>10</sup> according to which the longer the chain joining the two ends of the bifunctional precursor, the lower the probability of ring closure, has found a general confirmation in our quantitative work on cyclic aralkyl ether formation via intramolecular Williamson synthesis,<sup>7,11</sup> where a general decrease of  $\Delta S^\ddagger$  values on increasing ring size was observed. It is further confirmed on inspection of Figure 2, where the diagram of  $\Delta S^\ddagger$  vs. ring size for lactone formation indeed shows a general trend toward more negative  $\Delta S^\ddagger$  values with increasing ring size. However, a closer inspection reveals  $\Delta S^\ddagger$  data not closely conforming to the general behavior. In addition to the peculiar irregular pattern as observed in the medium- and large-ring region, which has been already discussed in some detail,<sup>3</sup> in the ring-size range of three to six  $\Delta S^\ddagger$  values span over about 3 eu, thus displaying a substantial insensitiveness to chain length. Similar apparent anomalies have been reported<sup>12</sup> and strongly emphasized by Stirling<sup>13</sup> in a comparison of three- vs. five-membered ring formation. Table II lists Stirling's data (reactions 1-5) together with available data from this (reactions 9 and 10) and other laboratories. Inspection of Table II indeed shows that, although a general trend toward more negative entropy values with increasing ring size is apparent, significant irregularities do exist. A major remark in this respect is that the precision of the data is a crucial problem in the determination of activation parameters. Maximum errors<sup>14</sup> in the activation entropy for kinetic studies of ordinary accuracy are in the order of  $\pm 2$  eu, but still higher errors are probably not uncommon. Other things being equal, it is likely that a combination of errors of the above magnitude in opposite directions for a pair of consecutive homologues in a cyclization reaction may even produce an artifactual inversion in the most unfavorable cases. This observation draws attention to the need for caution in the interpretation of the above  $\Delta S^\ddagger$  data. However, the observed anomalies are believed to be significant in view of their general occurrence for certain ring sizes in structurally similar reactions. In this connection the following points will be clarifying. In the first place, a representative value of ca. 4.5 eu has been estimated for the entropy contribution of the internal rotation around a C-C single bond.<sup>15,16</sup> Thus, were all internal rotations completely

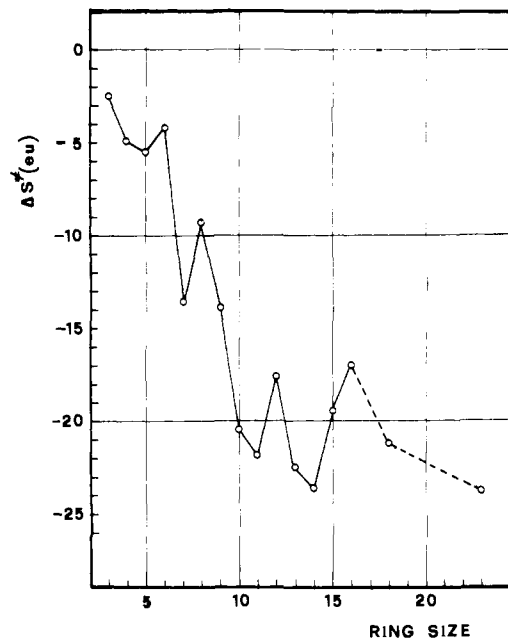


Figure 2. Plot of  $\Delta S^\ddagger$  vs. ring size for the formation of lactones. (Data from the present work and from ref 3.)

frozen upon cyclization, a constant drop of 4.5 eu per added methylene group would be expected in a given cyclization series. However, as Benson and O'Neal<sup>15</sup> have pointed out, compensating entropy terms due to different degrees of "looseness" in the low-frequency out-of-plane bending motions of the various ring structures can reduce the entropy loss upon cyclization by unpredictable amounts depending on both nature and size of the ring to be formed. They have been suggested to be responsible for the substantial leveling off of  $\Delta S^\ddagger$  values observed in the large-ring region.<sup>11b</sup>

Secondly, the entropy contributions due to solvent reorganization on going from the initial to the transition state ( $\Delta S^\ddagger_{\text{solv}}$ ) must also be considered. The fact that interactions of a series of solutes with polar solvents may occur with extraordinarily large changes in enthalpy and entropy components, with little or no net change in free energy, is a well-recognized phenomenon.<sup>17</sup> Thus, varying extents of solvent interaction with either the initial or transition states, or both, in a ring-closure series can possibly result in significant changes in the  $\Delta S^\ddagger_{\text{solv}}$  term. For sufficiently long chains, say, of more than five carbon atoms or so, it is likely that the structure of the solvation shells around the chain ends are independent of each other, and constant throughout. However, for shorter chains the mutual polar interactions of the end groups should result in significant changes of initial state solvation, depending on chain length. This effect is expected to be particularly significant in reactions of charged substrates in polar solvents, where a reduced extent of initial state solvation is likely to occur in the short-chain compounds.

The  $\Delta S^\ddagger$  pattern obtained for the lactonization reaction can be rationalized in the light of the above arguments, if one assumes that the initial state solvation of the very first members of the series is substantially lower than that of the higher ones, probably on account of a reduced availability of negative charge on the carboxylate group in the former compounds. Since on going from the initial to the transition state the anionic end undergoes a substantial desolvation, a positive  $\Delta S^\ddagger_{\text{solv}}$  term is expected. Therefore, the formation of small rings is likely to be accompanied by a lower  $\Delta S^\ddagger_{\text{solv}}$  contribution. As a result, the entropies of activation turn out to be more negative than what they would be in the absence of specific solvation effects by larger amounts, the shorter the chain of the bi-

Table II. Entropy Data for Closure of Small and Common Rings

Reaction no.	Substrate	Ring size $n$	Solvent	$\Delta S^\ddagger$ , eu
1 <sup>a</sup>	H <sub>2</sub> N(CH <sub>2</sub> ) <sub><math>n-1</math></sub> Cl	3	50% dioxane	-15
		5		-13
2 <sup>a</sup>	C <sub>6</sub> H <sub>5</sub> NH(CH <sub>2</sub> ) <sub><math>n-1</math></sub> Br	3	60% EtOH	-11
		4		-11
		6		-17
		5		-15
3 <sup>a</sup>	C <sub>6</sub> H <sub>5</sub> NH(CH <sub>2</sub> ) <sub><math>n-1</math></sub> Cl	3	50% dioxane	-17
		5		-15
4 <sup>a</sup>	H <sub>2</sub> NC(C <sub>6</sub> H <sub>5</sub> )H(CH <sub>2</sub> ) <sub><math>n-2</math></sub> Cl	3	50% dioxane	-7
		5		-10
5 <sup>b</sup>	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> S(CH <sub>2</sub> ) <sub><math>n-1</math></sub> Cl	3	80% EtOH (w/w)	-24
		5		-20
6 <sup>c</sup>	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub><math>n-1</math></sub> OBs	5	EtOH	-10.4
		6		-15.1
7 <sup>d</sup>	C <sub>6</sub> H <sub>5</sub> C(=O)(CH <sub>2</sub> ) <sub><math>n-2</math></sub> Cl	4	80% EtOH, Ag <sup>+</sup>	-16.0
		5		-15.8
		6		-20.4
		7		-23.1
8 <sup>d</sup>	(CH <sub>3</sub> ) <sub>2</sub> CHC(=O)(CH <sub>2</sub> ) <sub><math>n-2</math></sub> Cl	5	80% EtOH, Ag <sup>+</sup>	-18.2
		6		-20.8
		7		-22.6
		6		+6.2
9 <sup>e</sup>	<i>o</i> -OC <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub><math>n-4</math></sub> Br	6	75% EtOH	+1.2
		7		+4.1
10 <sup>f</sup>	<i>o</i> -OC <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub><math>n-3</math></sub> Br	5	75% EtOH	+5.3
		6		-3.2
		7		-3.0
		6		-6.9
11 <sup>g,h</sup>	HO(CH <sub>2</sub> ) <sub><math>n-3</math></sub> OCH <sub>3</sub>	5	CCl <sub>4</sub>	-10.8
		6		-12.7
		7		-20.6
12 <sup>g,i</sup>	H <sub>2</sub> N(CH <sub>2</sub> ) <sub><math>n-3</math></sub> NH <sub>3</sub> <sup>+</sup>	5	Gas phase	-12.7
		6		-20.6

<sup>a</sup> Data from ref 11a. <sup>b</sup> Data from ref 11b. <sup>c</sup> Data from S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, **3**, 1 (1958). Kinetic data for additional members of the series are available, but they refer to direct solvolytic displacement rather than to participation of the neighboring methoxyl oxygen. <sup>d</sup> Data from D. J. Pasto and M. P. Serve, *J. Am. Chem. Soc.*, **87**, 1515 (1965). Carbonyl oxygen participation is probably uncertain for compounds with  $n = 7$ , which show little anchimeric assistance. <sup>e</sup> Data from ref 11a.  $\Delta S^\ddagger$  values up to ring size 24 are also available (ref 11b). <sup>f</sup> Data from ref 7.  $\Delta S^\ddagger$  values up to ring size 10 are also available. <sup>g</sup> Entropy data reported are  $\Delta S^0$  values for the formation of the hydrogen bonded cyclic forms. The bridging hydrogen atom was included in the calculation of ring sizes. <sup>h</sup> L. P. Kuhn and R. A. Wires, *J. Am. Chem. Soc.*, **86**, 2161 (1964). <sup>i</sup> R. Yamdagni and P. Kebarle, *ibid.*, **95**, 3504 (1973).

functional precursor. A similar explanation was presented<sup>7</sup> for the apparently inverted order in the five- and six-membered rings of reaction 10 (Table II). In reactions of neutral substrates occurring via polar transition states in polar solvents (reactions 1–8, Table II) an increased transition state solvation, rather than a reduced initial state solvation, was suggested in order to account for a more unfavorable activation entropy in three- vs. five-membered ring formation.<sup>12</sup> However, Table II shows that in these reactions the entropy term for the formation of the five-membered ring is invariably less negative than that of the six-membered one, indicating that for neutral substrates solvation effects are relatively less important than for negatively charged compounds (see Table I and reaction 10 in Table II), where an inverted order is observed for the corresponding ring sizes. This view is further substantiated by the "normal" behavior of the entropy data for five- and six-membered ring formation via intramolecular hydrogen bonding either in nonpolar solvent or in the gas phase (reactions 11 and 12 in Table II, respectively).

To sum up, while a simple reasoning would suggest that the activation entropy for ring closure should drop by about 4.5 eu per methylene group, additional factors, such as different degree of looseness in the cyclic transition states and varying  $\Delta S^\ddagger_{\text{solv}}$  terms can possibly play a significant role. As a result, the behavior of  $\Delta S^\ddagger$  values in a ring-closure series may indeed be a somewhat scattered one. This may be particularly intriguing when data for only a few members of a series are available, as deviations from Ruzicka's postulate may appear. However, the general trend toward more negative  $\Delta S^\ddagger$  values

with increasing ring size can be easily recognized when series with a significant number of members are considered.

### Experimental Section

**Materials.** The  $\omega$ -bromo acids were available from a previous investigation.<sup>3</sup> 2,6-Dichlorophenol (Fisons) was redistilled before use. *m*-Nitrophenol (Fisons) was used as received. Me<sub>2</sub>SO (Fisons AR) was stored over 4A molecular sieves for several days, then carefully fractionated at 32–36 °C (0.2–0.3 mmHg) from powdered NaNH<sub>2</sub>. The mixed solvent for the kinetic runs was prepared, stored, and handled as previously reported.<sup>8</sup> The  $1.3 \times 10^{-3}$  M solution of Me<sub>4</sub>N<sup>+</sup>OH<sup>-</sup> in 99% aqueous Me<sub>2</sub>SO was prepared by proper dilution of commercial 10% aqueous Me<sub>4</sub>N<sup>+</sup>OH<sup>-</sup> (Fisons).

**Kinetics.** The kinetics were followed by stopped-flow spectrophotometry, by means of an all quartz-glass apparatus, having the mixing chamber and observation tube (2-mm optical path) immersed in the thermostat bath, whose temperature was controlled within  $\pm 0.05$  °C. It was analogous to that previously described,<sup>18</sup> with the sole significant difference that the monitoring light beam was conveyed by flexible light guides, rather than through quartz cones. One syringe contained a freshly prepared solution of a given bromo acid ca.  $2.5 \times 10^{-3}$  M in 99% Me<sub>2</sub>SO, plus a known amount of the proper indicator, and the other a solution of Me<sub>4</sub>N<sup>+</sup>OH<sup>-</sup> ca.  $1.3 \times 10^{-3}$  M in the same solvent, so that after mixing of the reactant solutions an approximately 1:1 mixture of bromo acid and its conjugate base was formed. The concentrations of the indicators were adjusted empirically in order to have 95–97% transmittance at zero time at the wavelengths corresponding to the absorption maxima of the basic forms of the indicators, i.e., 440 nm for *m*-nitrophenol and 330 nm for 2,4-dichlorophenol. The concentrations in the kinetic solutions were as follows: *m*-nitrophenol,  $7.0 \times 10^{-3}$  and  $3.0 \times 10^{-3}$  M for the five- and six-

membered rings, respectively; 2,4-dichlorophenol,  $5.0 \times 10^{-3}$  M for the four-membered ring. The progress of the reactions was monitored by following the increase of transmittance at the above wavelengths. The time scale of the oscilloscope was chosen as to include 6 to 8 half-lives in a single trace. The experimental data were treated according to the Guggenheim method,<sup>19</sup> with  $\Delta$  values in the order of 2–3 half-lives. In all cases the linearity of the kinetic plots was good, and no systematic drift was present.

**Acknowledgment.** The author wishes to thank Professor E. F. Caldin for offering the research facilities and for stimulating discussions, and the British Council for a maintenance grant. Thanks are also due to Professor G. Illuminati for helpful suggestions during the preparation of the manuscript.

#### References and Notes

- (1) Part 10: L. Mandolini, B. Masci, and S. Roelens, *J. Org. Chem.*, in press.
- (2) Most of the experimental work on which this article is based has been carried out at the Fast Reaction Group of the University of Kent at Canterbury, U.K., directed by Professor E. F. Caldin, where the author spent two months, October and November 1975, as a visiting research fellow. A preliminary account of this work was presented at the Organic Reaction Mechanism Group, The Chemical Society, Exeter, U.K., July 1976.
- (3) C. Galli, G. Illuminati, L. Mandolini, and P. Tamborra, *J. Am. Chem. Soc.*,

- 99, 2591 (1977).
- (4) P. A. Tregloan and G. S. Laurence, *J. Sci. Instrum.*, **42**, 869 (1965).
- (5) As a general reference see J. Sicher, *Prog. Stereochem.*, **3**, 202 (1962).
- (6) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, p 672.
- (7) G. Illuminati, L. Mandolini, and B. Masci, *J. Am. Chem. Soc.*, **97**, 4960 (1975).
- (8) C. Galli, G. Illuminati, and L. Mandolini, *J. Am. Chem. Soc.*, **95**, 8374 (1973).
- (9) R. Huisgen and H. Ott, *Tetrahedron*, **6**, 253 (1959).
- (10) L. Ruzicka, *Chem. Ind. (London)*, **54**, 2 (1935).
- (11) (a) G. Illuminati, L. Mandolini, and B. Masci, *J. Am. Chem. Soc.*, **96**, 1422 (1974); (b) *ibid.*, **99**, 6308 (1977).
- (12) (a) R. Bird, A. C. Knipe, and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 1215 (1973); (b) R. Bird and C. J. M. Stirling, *ibid.*, 1221 (1973).
- (13) C. J. M. Stirling, *J. Chem. Educ.*, **50**, 844 (1973).
- (14) Limits of uncertainty more realistic than the usually reported probable or standard errors should be considered. This is the reason why we have estimated the uncertainty on both  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  as  $\pm 2\sigma$  (see footnote c, Table I). However, a 99% confidence limit of  $\pm 3\sigma$  could have been taken as well.
- (15) H. E. O'Neal and S. W. Benson, *J. Chem. Eng. Data*, **15**, 266 (1970).
- (16) M. I. Page and W. P. Jencks, *Proc. Natl. Acad. Sci. U.S.A.*, **68**, 1678 (1971); M. I. Page, *Chem. Soc. Rev.*, **2**, 295 (1973).
- (17) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969, pp 418–425.
- (18) G. Davies, *Inorg. Chem.*, **10**, 1155 (1971).
- (19) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism", 2nd ed, Wiley, New York, N.Y., 1961 p 49.

## Convenient and Stereoselective Route to Basic Frameworks for Synthesis of Unsymmetrical Pentacyclic Triterpenes<sup>†</sup>

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**Abstract:** Convenient and stereoselective synthesis of 10-ethoxy-3-methoxy- (**1**) and 3-ethoxy-10-methoxy-6b $\beta$ ,12b $\alpha$ ,14a $\alpha$ -trimethyl-5,6,6a $\alpha$ ,6b,7,8,12b,13,14,14a-decahydropicene (**2**), key intermediates for synthesis of alnusenone (**8**) and friedelin (**9**), respectively, has been described. The key step in both syntheses is an intramolecular cycloaddition of the *o*-quinodimethanes **33**, derived from the benzocyclobutenes **32a** and **32b**, to the olefinic system in their side chain to form the corresponding pentacyclic compounds (**4** and **6**). This paper also describes a short but nonstereoselective synthesis of the pentacyclic compounds **4** and **6**.

There are many reports on elegant syntheses of the pentacyclic triterpenes.<sup>2</sup> Key reactions in the synthesis of these natural products are a construction of the pentacyclic ring system, which has a correct stereochemistry, and a stereoselective introduction of methyl groups to the angular positions. Using the enolate trapping method,<sup>3</sup> Stork<sup>4</sup> and Ireland<sup>5</sup> have established the stereoselective total synthesis of lupeol and germanicol, respectively. Recently, Ireland reported the total synthesis of friedelin (**9**) from a pentacyclic diaromatic diether **2**, having the trans-anti-trans BCD ring structure and the correct array of angular methyl groups, as a useful key intermediate.<sup>6</sup> Alnusenone (**8**) has also been prepared by the same authors<sup>7</sup> from the pentacyclic diaromatic compound (**1**).

Since we have found previously that intramolecular cycloaddition<sup>8</sup> of *o*-quinodimethanes in the synthesis of estrone<sup>9</sup> and atisine intermediate<sup>10</sup> could proceed stereoselectively and regioselectively, we investigated a new and simple synthesis

of pentacyclic triterpenoids in connection with our interest<sup>11–13</sup> in the synthetic application of cycloaddition of *o*-quinodimethanes derived from benzocyclobutenes.<sup>14</sup> This paper reports a simple synthesis of two key intermediates **1** and **2**, which have been transformed into alnusenone (**8**) and friedelin (**9**) by Ireland described above.

Our plan was designed on the fact that the portion surrounded by a dotted line in the pentacyclic compounds (cf. **1**) corresponds to an isoprene unit. The first idea is that the pentacyclic ring system (**3**), which is a basic framework of the key compounds in the total synthesis of alnusenone and friedelin by Ireland, would be formed in one step by an intermolecular double cycloaddition of the bis-*o*-quinodimethane (**26b**), generated from the bisbenzocyclobutene (**25b**), with isoprene. The second approach involves the intramolecular cycloaddition of the *o*-quinodimethane (**33**), having an olefinic group at an appropriate position, derived from the benzocyclobutene (**32**). In these trials, we used the 1-substituted 1-cyanobenzocyclobutenes because 1-substituted 1-methylcyclobutenes are transformed into the *o*-methylstyrene derivatives by [1.5]-sigmatropic hydrogen migration<sup>15</sup> in *o*-quinodimethane gen-

<sup>†</sup> A part of this work has been published as a communication; see T. Kametani, Y. Hirai, F. Satoh, and K. Fukumoto, *J. Chem. Soc., Chem. Commun.*, 16 (1977).