= 8.9), which is similar to the pyrenyl end groups.[14] This is an expression of the old adagium of the alchemists: similia similibus solvuntur.

Acknowledgment. Many thanks are due to George Striker for stimulating discussions on the various aspects of data analysis and for making his deconvolution program available to us. The use of the excellent facilities of the Gesellschaft für wissenschaftliche Datenverarbeitung GmbH Göttingen (GWDG) are gratefully acknowledged.

Registry No. 1,3-Di(1-pyrenyl)propane, 61549-24-4.

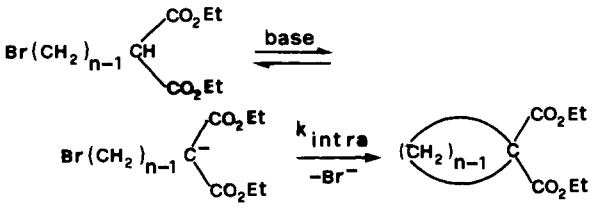
Ring-Closure Reactions. 22.[1] Kinetics of Cyclization of Diethyl (ω-Bromoalkyl)malonates in the Range of 4- to 21-Membered Rings. Role of Ring Strain

Maria Antonietta Casadei, Carlo Galli,* and Luigi Mandolini*

Contribution from the Centro C.N.R. di Studio sui Meccanismi di Reazione, Istituto di Chimica Organica, Università di Roma, 00185 Rome, Italy. *Received May 23, 1983*

Abstract: The kinetics of closure of 1,1-bis(ethoxycarbonyl)cycloalkanes from the anions derived from diethyl (ω-bromoalkyl)malonates have been investigated in Me_2SO at 25 °C. Rate constants and effective molarities (EM) have been obtained for the ring sizes 4–13, 17, and 21. This is the first quantitative study on the kinetics of S_N2 closure of all-carbon rings, which includes small, common, medium, and large rings. The reactivity data span over nine powers of ten, which is the widest reactivity range recorded so far in a cyclization series. Due to the extremely low EM for the 9-, 10-, and 11-membered rings, a special competition technique was developed for these rings. Comparison of the present results with literature data on S_N2 ring-closure reactions reveals structure-dependent reactivity patterns showing varying features, which are qualitatively accounted for on the basis of structure effects on transition-state strain energies. A dissection of the EM data for the malonate cyclization into strain and probability factors was attempted. Perhaps the most interesting result is a definite tendency for transition-state strain energies to parallel cycloalkane strain energies for the 7-membered and larger rings but not for the smaller rings. In the latter cases the ring product no longer appears to be a proper model for comprehending the transition state.

As a continuation of our studies on reactivity in ring-closure reactions[2] and with particular reference to the role of strain on medium-ring formation, we now report on the kinetics of the base-promoted cyclization of diethyl (ω-bromoalkyl)malonates to 1,1-bis(ethoxycarbonyl)cycloalkanes in Me_2SO.



(1)

The existence of a very pronounced medium-ring effect was already apparent from the yield data in a recent work[3] on the synthetic applicability of reaction 1 to the preparation of cyclic compounds over a wide range of ring sizes. In addition to the medium rings (8- to 11-membered) the present kinetic investigation includes the 4-membered small ring, the common rings (5- to 7-membered), and the 12-, 13-, 17-, and 21-membered large rings. In comparison with previous studies in this series,[2] the novel features of the present investigation are (i) cyclization via C–C bond formation by intramolecular alkylation of a carbon nucleophile and (ii) formation of wholly saturated carbocyclic rings.

Methods and Results

The kinetics were carried out in Me_2SO at 25.0 °C by monitoring the disappearance of the strong absorption of the tetramethylammonium salts of the (ω-bromoalkyl)malonic esters at 288 nm (ϵ = 17 100 cm^{-1} M^{-1}). This was carried out by stopped-flow spectrophotometry in the case of the 4-, 5-, and 6-membered rings and by conventional spectrophotometry in all the other cases.

The tetramethylammonium salts were generated in situ by adding the calculated amount of Me_4NOH stock solution to a solution of the malonic ester. The acid–base reaction is virtually quantitative even in the very dilute solutions used in the kinetic runs (ca. (1–2) × 10^{-4} M), so that only the stoichiometric amount of base was required in addition to the amount used up to neutralize the free acidity of the solvent (see Experimental Section). Under the given conditions carbanion production is much faster than cyclization,[4] with the sole exception of the extremely fast reaction leading to the 5-membered ring (vide infra).

As to the small amount of water accompanying the added base, we note that the present reactions, involving highly delocalized carbanionic species, proved to be particularly insensitive to the water content of the medium. We found negligible effects on reactivity on going from neat to 99% Me_2SO in typical cases. A similar insensitiveness to added water has been reported for the rate of methylation with methyl iodide of the potassium salt of dibenzoylmethane in Me_2SO.[5]

The counterion effect has been checked both by replacing K^+ for Me_4N^+ and by adding a large excess of Me_4NBr. In both cases no significant effect on rates was observed,[6] indicating that ion

(1) Part 21: Dalla Cort, A.; Mandolini, L.; Masci, B. *J. Org. Chem.* **1983**, *48*, 3979.
(2) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.
(3) Casadei, M. A.; Galli, C.; Mandolini, L. *J. Org. Chem.* **1981**, *46*, 3127.
(4) In connection with related studies we find that the second-order rate constant for proton abstraction by Me_4NOH from $Cl(CH_2)_5CH(CO_2Et)_2$ in Me_2SO at 25 °C is 2 × 10^6 M^{-1} s^{-1}.
(5) De Palma, V. M.; Arnett, E. M. *J. Am. Chem. Soc.* **1978**, *100*, 3514.
(6) These observations are a part of a detailed study on the effect on ion pairing on reaction 1, which has been reported in a preliminary form at the Sixth IUPAC Conference on Physical Organic Chemistry, Louvain-La-Neuve, Belgium, July 11–16, 1982. See: Galli, C.; Mandolini, L. *Bull. Soc. Chim. Belg.* **1982**, *91*, 432.

0002-7863/84/1506-1051$01.50/0 © 1984 American Chemical Society

Table I. Yields and Kinetic Data for the Ring-Closure Reactions of Diethyl (ω-Bromoalkyl)malonate Anions in Me_2SO at 25.0 °C

n^a	k_{obsd},[b] s^{-1}	yield,[c] %	k_{intra},[d] s^{-1}	EM,[e] M
4	0.42 ± 0.02	*f*	0.42	1.5
5	(6 ± 1) × 10^2	*f*	6 × 10^2	2.1 × 10^3
6	0.72 ± 0.02	100 ± 1	0.72	2.6
7	(6.3 ± 0.2) × 10^{-3}	99 ± 1	6.3 × 10^{-3}	2.3 × 10^{-2}
8	(8.4 ± 0.4) × 10^{-4}	13 ± 3	1.1 × 10^{-4}	3.9 × 10^{-4}
9[g]			1.2 × 10^{-5}	4.3 × 10^{-5}
10[g]			1.0 × 10^{-6}	3.6 × 10^{-6}
11[g]			2.1 × 10^{-6}	7.5 × 10^{-6}
12	(1.00 ± 0.06) × 10^{-3}	29 ± 2	2.9 × 10^{-4}	1.0 × 10^{-3}
13	(1.15 ± 0.03) × 10^{-3}	46 ± 3	5.3 × 10^{-4}	1.9 × 10^{-3}
17	(2.94 ± 0.12) × 10^{-3}	73 ± 1	2.1 × 10^{-3}	7.5 × 10^{-3}
21	(4.00 ± 0.06) × 10^{-3}	77 ± 4	3.1 × 10^{-3}	1.1 × 10^{-2}
inter[h]	0.36 ± 0.01	78 ± 2	0.28	

[a] Size of the ring to be formed. [b] Average from three to five independent runs. [c] Data from GLC analyses. Runs in duplicate or triplicate. [d] Calculated as k_{obsd}(yield %/100). [e] Calculated as k_{intra}/k_{inter}. [f] Yield assumed to be quantitative. [g] Rate data from competitive experiments. See Table II. [h] The intermolecular model reaction is the alkylation of diethyl butylmalonate anion with butyl bromide. The rate constant k_{inter} is given in M^{-1} s^{-1}.

pairing is unimportant under the conditions of the kinetic runs.

Cyclization of the (ω-bromoalkyl)malonate anions suffers from two main competing processes. One of these is common to all cyclization reactions of bifunctional reactants and is due to stepwise polymerization upon intermolecular head-to-tail condensation. Polymerization is made negligible when the initial substrate concentration is much smaller than the effective molarity, EM, which is defined as k_{intra}/k_{inter} and represents the reactant concentration at which the rate of cyclization (k_{intra}) equals the rate of polymerization (k_{inter}).[2] The other competing reaction is the previously noted spontaneous decay of the carbanionic species. For instance, the absorption of a solution of the diethyl butylmalonate anion is not stable[3] but disappears according to first-order kinetics with half-life times on the order of 15 min. Since the rate of spontaneous decay varies somewhat from run to run, it cannot be accounted for once for all.

Because of the dramatic dependence of the ease of ring closure on chain length, we have found that some members of the present series suffer significantly from competition of the above side reactions, whereas others do not. Accordingly, depending on reactivity the ring-closure reactions described here can be grouped into three categories.

In the first category we find the fast reactions leading to the 4-, 5-, 6-, and 7-membered rings, which are not affected significantly by either of the above competing processes. Whenever carried out, product analysis at the end of the reaction showed quantitative formation of the expected ring product. Cyclization of (4-bromobutyl)malonate, which is the fastest reaction in the series, required excess base to make proton removal significantly faster than cyclization.[4] With [Me_4NOH] < 1 × 10^{-3} M, production of the carbanion absorption is practically instantaneous, and the intensity of absorption at zero time corresponds very nearly to complete ionization of the parent malonic ester. The half-time for the subsequent disappearance of the carbanion absorption reaches the lower limit of 1.1 ms, which is invariant upon further increase of base concentration. Accuracy is not high, as 1.1 ms is close to the mixing time of the instrument.

The 8-, 12-, 13-, 17-, and 21-membered rings belong to the second group. For these rings the initial substrate concentration was low enough to render polymerization relatively unimportant, but competition by the spontaneous decay of the carbanions was in all cases significant. Product analyses after at least ten half-times showed in all cases the yield of ring products to be significantly less than quantitative (Table I). Observed first-order rate constants (k_{obsd}) were then converted into cyclization rate constants (k_{intra}) by means of the equation

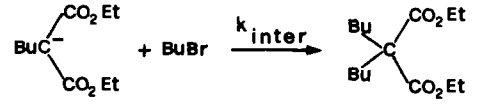
$$k_{intra} = k_{obsd} \times (\text{yield } \%/100) \quad (2)$$

Table II. Cyclization of Diethyl (ω-Bromoalkyl)malonate Anions in Me_2SO: Results of the Competitive Experiments

run no.	i/j^a	t, °C	conditions[b]	C_i,[c] yield %	C_j,[c] yield %	$(k_{intra})_i$[d]/$(k_{intra})_j$	$(k_{intra})_i$[e]/$(k_{intra})_j$
1	17/13	25	bw	13	4.5	3.6 ± 0.5	3.9
2	17/13	25	bw	20	5.8	3.5 ± 0.4	
3	17/13	25	bw	23	6.6	3.6 ± 0.6	
4	13/8	25	bw	13	3.0	4.3 ± 0.2	4.8
5	12/8	25	infl[f]	5.7	2.0	2.9 ± 0.1	2.7
6	12/8	50	infl[g]	15.4	4.9	3.1 ± 0.2	
7	8/9	50	infl[h]	7.6	0.88	8.6 ± 0.2	
8	9/11	50	infl[i]	1.4_5	0.25_5	5.7 ± 0.1	
9	9/10	50	infl[i]	1.3	0.11	12 ± 2	

[a] The sizes of the two formed rings are *i* and *j*. [b] Runs carried out under batchwise (bw) or influxion (infl) conditions. [c] Data from GLC analyses. [d] Calculated from eq 4. [e] Data from direct spectrophotometric measurements (Table I). [f] $\nu_f = 5.1 \times 10^{-7}$ M^{-1} s^{-1}. [g] $\nu_f = 4.7 \times 10^{-7}$ M^{-1} s^{-1}. [h] $\nu_f = 3.0 \times 10^{-7}$ M^{-1} s^{-1}. [i] $\nu_f = 1.6 \times 10^{-7}$ M^{-1} s^{-1}.

Also in this second group is the intermolecular model reaction between diethyl butylmalonate anion and butyl bromide (eq 3),



(3)

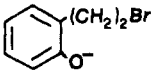
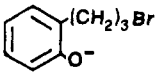
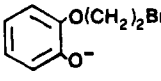
which was carried out under pseudo-first-order conditions in the presence of excess BuBr. The k_{inter} value was reckoned as above on the basis of the nonquantitative yield of diethyl dibutylmalonate (Table I). It was used to calculate the EM values for all the cyclization reactions. From the calculated EM values it can be verified that the initial concentrations used in the kinetic runs are much lower than the EMs for the small and common rings, and at least one order of magnitude lower than the EMs for the 12-membered and larger rings but not for the 8-membered ring. However, in the latter case the main competing process is the spontaneous decay, and the initial concentration is on the order of $^1/_3$ to $^1/_2$ of the EM, so the overall decay of the carbanionic species should be practically first order, which is in agreement with experiment. Rings from 9- to 11-membered, which exhibit the lowest ease of formation, form the last group. In these cases the rate of the absorbance disappearance of 1 × 10^{-4} M substrate solutions was very similar to that of the spontaneous decay, and no trace of the expected ring products could be detected at the end of the reactions. Therefore a special technique was developed to measure the k_{intra} values in these extreme cases. This was based on competitive experiments, in which equimolar amounts of two (ω-bromoalkyl)malonates, M_i and M_j, are allowed to react simultaneously. If the experimental conditions are such as to render the yields of ring products C_i and C_j very small, it can be shown (see Appendix) that during the whole course of reaction the relation

$$[C_i]/[C_j] = (k_{intra})_i/(k_{intra})_j \quad (4)$$

is a satisfactory approximation. An influxion method was required in the competition experiments involving the 9- to 11-membered rings to accumulate the ring products in the reaction medium up to analytically convenient concentration levels. The results of the competitive experiments are listed in Table II.

Runs 1–6 serve as control experiments, yielding relative rates which agree to within ±10% with those from the direct spectrophotometric determinations independent of the technique adopted, i.e., either batchwise or influxion. Given the approximations and the experimental difficulties involved, the agreement leaves little to be desired. Competitive experiments involving the 9-, 10-, and 11-membered rings (runs 7–9) were carried out at 50 °C for analytical convenience. Rates of feed similar to those used in the previous preparative work[3] proved to be convenient. We assume that relative rates at 50 °C in the ring size range of 8–11 are reasonable approximations of relative rates at 25 °C, as suggested

Table III. EM Data, M, for the Formation of 4-, 5-, and 6-Membered Rings by Intramolecular S_N2 Reactions

4	5	6	source
$Br(CH_2)_3C(CO_2Et)_2^-$, 1.5 I	$Br(CH_2)_4C(CO_2Et)_2^-$, 2.1×10^3 II	$Br(CH_2)_5C(CO_2Et)_2^-$, 2.6 III	this work
$Br(CH_2)_3NH_2$, ca. 0.2 IV	$Br(CH_2)_4NH_2$, ca. 7×10^3 V	$Br(CH_2)_5NH_2$, ca. 1×10^2 VI	ref 8
$Cl(CH_2)_3O^-$, ca. 4 VII	$Cl(CH_2)_4O^-$, ca. 6×10^4 VIII	$Cl(CH_2)_5O^-$, ca. 2.8×10^2 IX	ref 8
$Br(CH_2)_2CO_2^-$, 2.99 X	$Br(CH_2)_3CO_2^-$, 8.67×10^2 XI	$Br(CH_2)_4CO_2^-$, 9.59 XII	ref 10
	 1.3×10^5 XIII	 6.6×10^3 XIV	ref 11
		 3.9×10^3 XV	ref 11

by runs 5 and 6. By means of the known $(k_{intra})_8$ value at 25.0 °C as determined spectrophotometrically, relative rates were converted into the k_{intra} and EM values reported in Table II for the 9-, 10-, and 11-membered rings. Clearly, these data are only of limited precision, because of the extreme experimental conditions. We believe, however, that they reflect correct reactivity levels and are quite adequate for the purposes of the present work.

Discussion

The plot of log k_{intra} against ring size (Figure 1) shows reactivity data spanning over nearly nine powers of ten, which is the widest reactivity range reported so far in a cyclization series.[2] In their kinetic work on the base-promoted ring closure of (ω-halogenoalkyl)malonic esters in *tert*-butyl alcohol and in ethanol, Knipe and Stirling[7] reported that the rate of formation of the 3-membered ring was too fast to measure and assigned a minimum value of 100:1 to the relative rates of closure of 3- and 5-membered rings. In view of the extremely high rate of formation of the 5-membered ring in Me_2SO, the rate of formation of the 3-membered ring is also very likely to be too fast to measure in this medium. If the rough factor of 100 for the relative rate of formation of 3- over 5-membered ring holds for Me_2SO as well, then the formation of the 3-membered ring turns out to be faster than that of the 10-membered ring by a spectacular factor of 10^{11}!

The reactivity profile for the malonate cyclization (Figure 1) is highly structured. There is a sharp maximum lying at ring size 5, which invariably exhibits the highest ease of formation in cyclization reactions via intramolecular nucleophilic substitution.[8] The next homologues at either side lie at a reactivity level which is a good two orders of magnitude below that of the 5-membered ring. From the 6-membered ring onward the reactivity drops dramatically until it reaches a very pronounced minimum in the medium-ring region. On going from the medium- to the large-ring region the reactivity increases, showing the expected leveling off tendency in the region of chains of 15–20 atoms.[2]

Measurement of the EMs in the medium-ring region is the major achievement of the present investigation. Indeed, the EM values on the order of 10^{-5}–10^{-6} M measured for ring size 9–11 are by far the lowest values ever recorded.[2] They refer to cyclization reactions which should be run at concentrations of less than 10^{-6} M in order to proceed free from polymerization!

It is of interest to compare the log (EM) profile for the malonate cyclization with the corresponding profiles for the formation of catechol polymethylene ethers[9] from o-$^-OC_6H_4O(CH_2)_{n-4}Br$ in 99% Me_2SO at 25 °C and of lactones[10] from $Br(CH_2)_{n-2}CO_2^-$ in 99% Me_2SO at 50 °C. The three profiles are shown in Figure

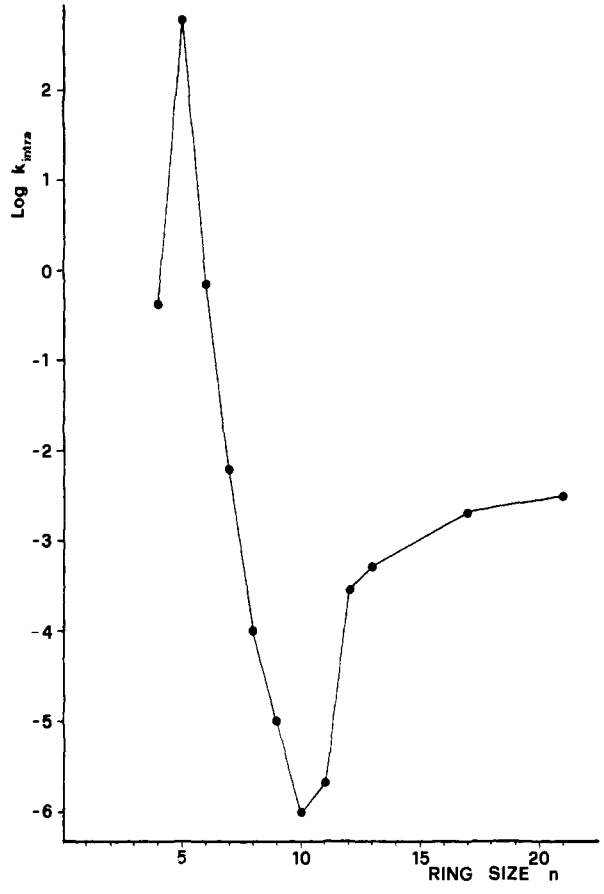


Figure 1. Reactivity plot for the cyclization of diethyl (ω-bromoalkyl)-malonate anions in Me_2SO at 25.0 °C.

2. The different shapes and the relative positions of these profiles are easily understood on the basis of the simple rule that replacement of one or more CH_2 groups by trigonal carbons and/or oxygens significantly decreases transannular and torsional interactions. Such structure effects largely disappear in the large-ring region. The EM values for the malonates lie at the lower limit of the range 0.1–0.01 M, where most of the available EM data related to the formation of large rings has been found to cluster.[2]

The EM values for the formation of the 4-, 5-, and 6-membered rings in the malonate series are listed in Table III together with the corresponding data for other intramolecular nucleophilic substitutions. The 4-membered ring requires little comment, as its EM is similar to the values for the formation of the other 4-membered rings. The EM for closure of the 5-membered ring lies close to the lower limit of the range of 10^3–10^5 M spanned

(7) Knipe, A. C.; Stirling, C. J. M. *J. Chem. Soc. B* **1968**, 67.
(8) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.
(9) Dalla Cort, A.; Illuminati, G.; Mandolini, L.; Masci, B. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1774.
(10) Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* **1977**, *99*, 2591.

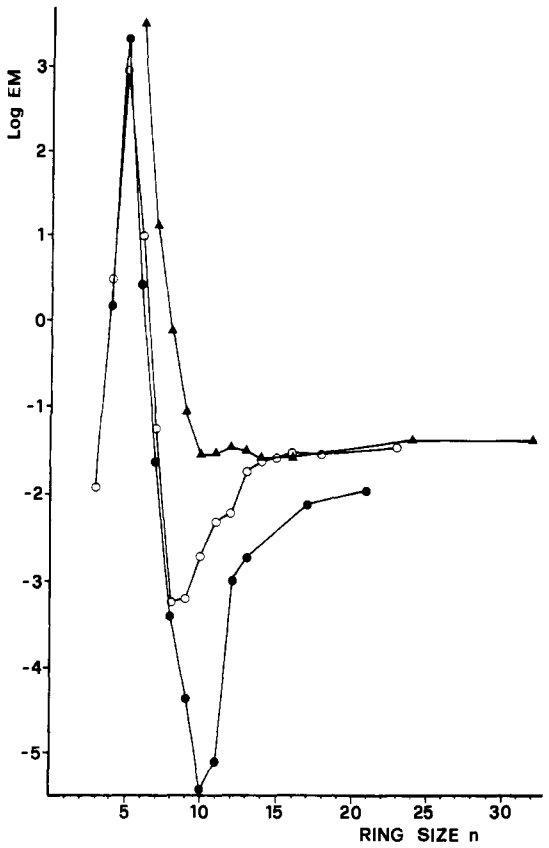
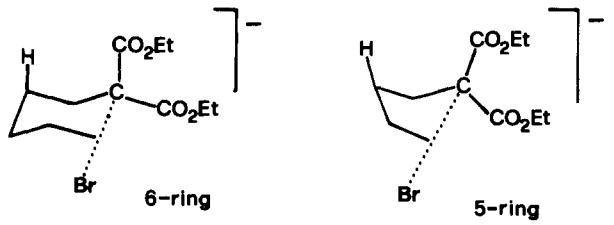


Figure 2. EM profiles for the formation of 1,1-bis(ethoxycarbonyl)-cycloalkanes (●), lactones (○), and catechol polymethylene ethers (▲). Data from the present work and from ref 9 and 10.

by the EMs for the formation of 5-membered rings. At ring size 6 a larger spread of values is observed, the EM value for the cyclization of the malonic ester derivative being by far the lowest. A proper discussion of these data requires consideration of the entropy contributions to ring closure. Cyclization of II involves the freezing of four internal rotors, but freezing of only two rotors is required by the ring closure of XIII. Remembering that the entropic contribution of a rotor amounts to some 4.5 eu,[11,12] which corresponds to a reactivity factor of nearly 10, one can entirely account for the two-order-of-magnitude difference between the EM values of the two compounds as an entropy effect. A different situation is observed in the case of the formation of the 6-membered rings. If compounds XIV and XV are taken as reference and the gross reactivity factor of 10 per internal rotor is applied, then the EM of III is concluded to be lower than expected by one to two powers of ten. A possible explanation might be based on the hypothesis that the transition state for the ring closure of the (ω-bromoalkyl)malonates is loose[13] and, therefore, that unusually low EM values are to be expected for this series.[12] But this is in disagreement with the finding that the EM of II turns out to be normal when allowance is made for the number of internal rotors involved. Hence we rather prefer to interpret the low EM value of III as due to transition-state strain. Such strain might result from interaction between the quasi-axial ethoxycarbonyl function and the quasi-axial hydrogen on the β-carbon.[14] This interaction, which is likely to be much less severe in the 5-membered transition state, might be on the order of the conformational energy of ca. 1 kcal/mol of the CO_2Et group of (ethoxycarbonyl)cyclohexane.[15]



Transition-State Strain vs. Cycloalkane Ring Strain. Since the early Ruzicka hypothesis,[16] the stability of the ring being formed has been recognized as a major factor affecting the ease of ring closure. Because of the limited availability of equilibrium data for the formation of ring compounds, it has been a common practice to compare reactivity data for ring closure to strain energy data of the cycloalkanes, which are the only series of ring compounds for which such data are available over a wide range of ring sizes. The malonate cyclization described in the present work permits a closer comparison with the cycloalkane strain energies, as it also involves closure of only sp^3-carbon chains. Indeed, the reactivity minimum exactly corresponds to the maximum in the cycloalkane strain energies[17] (vide infra). In view of the well-recognized importance of entropy factors on cyclization, the use of $\Delta H^{\ddagger}$ data in place of $\Delta G^{\ddagger}$ data for comparison with strain energies would be more appropriate, but activation parameters for the malonate cyclization could not be obtained due to the limited precision of kinetic data. Nevertheless, a gross separation between enthalpy and entropy factors can be attempted as follows.

According to transition-state theory the EM can be written as

$$\mathrm{EM} = \exp\left(-\frac{\Delta H^{\ddagger}_{\mathrm{intra}} - \Delta H^{\ddagger}_{\mathrm{inter}}}{RT}\right)\exp\left(\frac{\Delta S^{\ddagger}_{\mathrm{intra}} - \Delta S^{\ddagger}_{\mathrm{inter}}}{R}\right) \quad (5)$$

On the basis of the available activation parameters for ring-closure reaction series, it has been found[18] that to a reasonable approximation the quantity $\Delta S^{\ddagger}_{\mathrm{intra}} - \Delta S^{\ddagger}_{\mathrm{inter}}$ for a chain of r single bonds is given in eu by $30 - 4.5r$ for all r's smaller than 8 and levels off to a constant value of −6 for longer chains of up to 20–25 atoms.[19] If this relationship also holds for the reaction series at hand, then the quantity $\Delta H^{\ddagger}_{\mathrm{intra}} - \Delta H^{\ddagger}_{\mathrm{inter}}$ may be calculated for each term of the series for which the EM is known as

$$\Delta H^{\ddagger}_{\mathrm{intra}} - \Delta H^{\ddagger}_{\mathrm{inter}} = -RT \ln (\mathrm{EM}) + T(30 - 4.5r) \quad (6)$$

when $r < 8$ and

$$\Delta H^{\ddagger}_{\mathrm{intra}} - \Delta H^{\ddagger}_{\mathrm{inter}} = -RT \ln (\mathrm{EM}) - 6T \quad (7)$$

when $r \geq 8$. The results of these calculations are given in kcal/mol for the various ring sizes (in parentheses): 4.7 (4), −0.9 (5), 1.7 (6), 3.1 (7), 4.2 (8), 4.2 (9), 5.6 (10), 5.2 (11), 2.3 (12), 1.9 (13), 1.1 (17), 0.9 (21). These values show quite a reasonable pattern for quantities which are expected to provide a measure for the strain energies of transition states for cyclization relative to that for the intermolecular reaction. Apart from the smaller rings, there is a definite tendency for transition-state strain energies to parallel cycloalkane strain energies (Figure 3), the former being roughly one-half of the latter. This points to a close resemblance between transition states and ring products and puts on a more quantitative basis the basic postulate of the Ruzicka hypothesis.

At ring size 4, however, only a meager portion of the 26 kcal/mol strain energy of cyclobutane shows up in the transi-

(11) Illuminati, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1975**, *97*, 4960. *Ibid.* **1977**, *99*, 6308.
(12) (a) Page, M. I.; Jencks, W. P. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1678. (b) Page, M. I. *Chem. Soc. Rev.* **1973**, *2*, 295.
(13) An explanation based on transition-state looseness has been put forth by Kirby[8] to account for the low EM of XII.
(14) An additional possible source of strain is a 1,3-diaxial-type interaction across the bond being formed. We are indebted to a referee for calling our attention to this point.
(15) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. "Conformational Analysis"; Wiley-Interscience: New York, 1956; p 44.
(16) Ruzicka, L. *Chem. Ind. (London)* **1935**, *13*, 2.
(17) Skinner, H. A.; Pilcher, G. *Q. Rev. Chem. Soc.* **1963**, *17*, 264.
(18) Mandolini, L. "Abstracts of the EUCHEM Conference on Ring Closure and Related Topics"; Castel Gandolfo, Italy, Aug 28–Sept 1, 1978.
(19) A different equation, namely, $\Delta\Delta S = 34.901 - 2.868r$ has been proposed by De Tar and Luthra.[20]

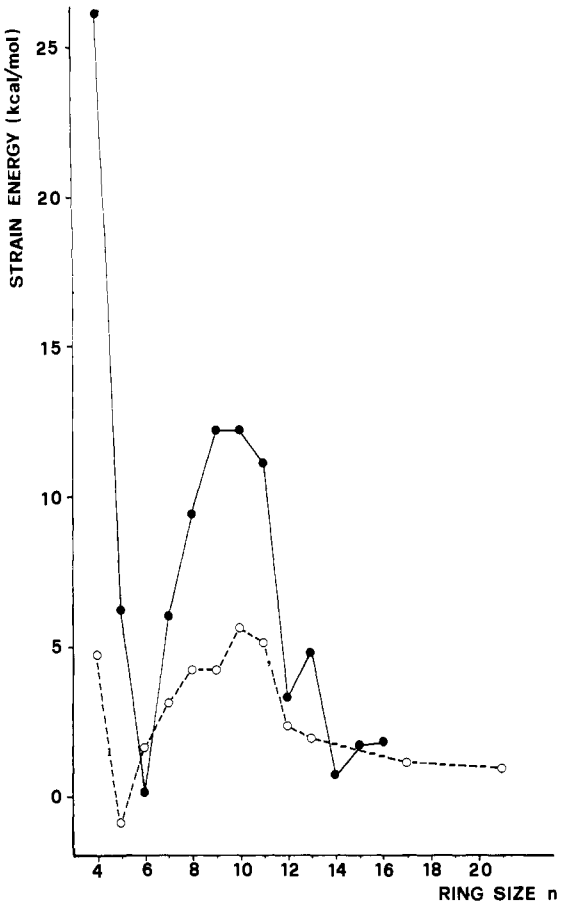


Figure 3. Comparison of transition-state strain energies for the cyclization of diethyl (ω-bromoalkyl)malonate anions (O) with cycloalkane strain energies (●).

tion-state strain energy, and at ring size 5 not even a small fraction of the 6.5 kcal/mol strain energy of cyclopentane is found in the transition state. These observations are consistent with the suggestion by De Tar and Luthra[20] that "product rings are not always suitable models of the transition states" in S_N2 ring closure reactions which lead to the smaller rings. Although De Tar and Luthra's hypothesis was aimed at including rings up to 7-membered, we believe that it strictly applies to ring sizes up to 5. We also suggest that it should be viewed as a general rule for all S_N2 ring-closure reactions.

Experimental Section

UV spectrophotometric measurements were carried out either on a Beckman DB GT or on a Varian DMS 90 instrument with a thermostated cell compartment. Fast reactions were followed on a Durrum stopped-flow spectrophotometer, Model D-110, matched with a Biomation Model 805 waveform recorder and a Hewlett-Packard storage oscilloscope, Model 1207B. A Hewlett-Packard 5830A flame ionization GC and a CARLO ERBA Fractovap ATC-F preparative GC equipped with a thermal conductivity detector were used.

Materials. Reagent grade Me_2SO (ERBA RPE) was thoroughly purged with pure argon, degassed under vacuum for 1 h, and distilled from $NaNH_2$ as described by Bordwell et al.[21] The distilled solvent was again degassed under vacuum and eventually stored under argon in a brown automatic buret protected from CO_2 and moisture with guard tubes. The Me_4NOH stock solution in 93% aqueous Me_2SO was prepared and handled as before.[22] The "free acidity" of the purified Me_2SO, as determined by a spectrophotometric titration method[23] using diethyl butylmalonate as the reference compound, was found to be 7×10^{-5} M.

Diethyl malonate (ERBA RPE) and butyl bromide (ERBA RPE) were purified by distillation. The diethyl (ω-bromoalkyl)malonates $Br(CH_2)_{n-1}CH(CO_2Et)_2$ with n = 6–13, 17, and 21 and the 1,1-bis(ethoxycarbonyl)cycloalkanes $(EtO_2C)_2\bar{C}(CH_2)_{n-1}$ with n = 6, 7, 8, 12, 13, 17 and 21 were available from a previous investigation.[3] Diethyl butylmalonate,[24] diethyl dibutylmalonate,[24] and diethyl (3-bromopropyl)malonate[7] were prepared according to literature methods and purified by preparative GLC on a 200 cm × 6 mm 15% SE-30 on Chromosorb 60–80 W column. Diethyl (4-bromobutyl)malonate was prepared by the following route. To minimize the formation of 1,1-bis(ethoxycarbonyl)cyclopentane, alkylation of the sodium derivative of malonic ester was carried out with $Br(CH_2)_4Cl$ in EtOH. After distillation of the chloro derivative (bp 150–159 °C (18–20 torr); lit.[25] bp 145–148 °C (10 torr)) a Finkelstein exchange of Br for Cl with LiBr in refluxing acetone[7] gave $Br(CH_2)_4CH(CO_2Et)_2$, purified by preparative GLC as before. ^1H NMR (CCl_4) δ 4.1 (q, 4 H, CO_2CH_2), 3.4 (t, 2 H, CH_2Br), 3.1 (t, 1 H, methine), 1.9–1.5 (m, 6 H, "central" methylene protons), 1.2 (t, 6 H, CH_3).

Rate Measurements. Kinetic runs were started by fast addition of the Me_4NOH stock solution to the thermostated solution of the reactant contained in a 10-mm quartz cuvette. The disappearance of the malonate anion absorption was monitored at 288 nm. First-order plots were linear up to 75–85% reaction and the rate constants were found to be independent, whenever tested, of a 5-fold change in initial substrate concentration. The intermolecular alkylation with BuBr of the anion derived from diethyl butylmalonate was carried out under pseudo-first-order conditions with at least a 30-fold excess of BuBr.

Competitive experiments as carried out according to the influxion procedure were performed with two identical 5-mL hypodermic syringes driven by a Sage Instrument syringe pump, Model 355. Typically, one syringe was loaded with 0.38 mmol of Me_4NOH in 5 mL of Me_2SO, and the other with 0.19 mmol of each of the two substrates in 5 mL of Me_2SO. The reactor was a 100-mL three-necked flask, immersed in a thermostatic bath, kept under a slight argon overpressure, and fitted with silicone septa through which needles were inserted. These were connected to the syringes by Teflon tubing. The reactor was loaded with 40 mL of Me_2SO to which enough Me_4NOH had been added to neutralize the solvent "free acidity". The reactants were added simultaneously to the well-stirred reaction medium at constant speed over a 4-h period. Analysis of the reaction mixture was than carried out as described below.

Product Analyses. These were carried out on scaled-up kinetic experiments. At the end of the reaction the proper internal standard (usually eicosane) was added, and the reaction mixture was diluted with brine and crushed ice. The mixture was then extracted at least six times with small portions of $CHCl_3$. The combined extracts were washed with water, dried over Na_2SO_4, and eventually concentrated to a small volume for GLC analysis. This was carried out either on a 250 cm × 3.2 mm 2% OV 17 on 80–100 Chromosorb GAW DMCS or on a 100 cm × 5.0 mm 2% FFAP-SE 30 column, operated in the range of 100–250 °C, depending on substrate molecular weight.

Appendix

Cyclization of a bifunctional monomer M is accompanied by stepwise polymerization, competition between the two processes being determined by the initial concentration of M and by its EM.[26] The system is kinetically complex, but a substantial simplification is obtained from the assumption of functional group reactivity (k_{inter}) independent of molecular weight.[27] Then

$$-d[M]/dt = k_{intra}[M] + k_{inter}[M][\sim\sim CH_2Br] \quad (8)$$

where $\sim\sim CH_2Br$ represents any unreacted end group, irrespective of the length of the chain. When [M] >> EM, cyclization is negligible with respect to polymerization and eq 8 reduces to the simple form

$$-d[M]/dt = k_{inter}[M][\sim\sim CH_2Br] \quad (9)$$

If in a competition experiment the initial concentrations (or the rates of feed in influxion experiments) of the two reacting monomers M_i and M_j are equal and such as to make cyclization very small with respect to polymerization, then

(20) De Tar, D. F.; Luthra, N. P. *J. Am. Chem. Soc.* **1980**, *102*, 4505.
(21) Mathews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006.
(22) Illuminati, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1981**, *103*, 4142.
(23) Mandolini, L.; Masci, B.; Roelens, S. *J. Org. Chem.* **1977**, *42*, 3733.
(24) Dolique, R. *Ann. Chim. (Paris)* **1931**, *15*, 440, 443.
(25) Sayles, D. C.; Degering, E. F. *J. Am. Chem. Soc.* **1949**, *71*, 3161.
(26) Galli, C.; Mandolini, L. *Gazz. Chim. Ital.* **1975**, *105*, 367.
(27) Billmeyer, F. W. "Textbook of Polymer Science"; Wiley: New York, 1971; p 264.

$$-d[M_i]/dt = k_{inter}[M_i][\sim\sim CH_2Br] \quad (10a)$$

and

$$-d[M_j]/dt = k_{inter}[M_j][\sim\sim CH_2Br] \quad (10b)$$

from which

$$d[M_i]/dt = d[M_j]/dt \quad (11)$$

or

$$[M_i] = [M_j] \quad (12)$$

during the whole course of the reaction. Now, since

$$d[C_i]/dt = (k_{intra})_i[M_i] \quad (13a)$$

and

$$d[C_j]/dt = (k_{intra})_j[M_j] \quad (13b)$$

one obtains

$$d[C_i]/d[C_j] = (k_{intra})_i[M_i]/(k_{intra})_j[M_j] \quad (14)$$

from which eq 4 follows, remembering eq 12 and integrating between limits.

Registry No. I, 88083-55-0; II, 88083-56-1; III, 88083-57-2; $BuC(CO_2Et)_2^-$, 14851-09-3; BuBr, 109-65-9; $Br(CH_2)_6C(CO_2Et)_2^-$, 88083-58-3; $Br(CH_2)_7C(CO_2Et)_2^-$, 88083-59-4; $Br(CH_2)_8C(CO_2Et)_2^-$, 88083-60-7; $Br(CH_2)_9C(CO_2Et)_2^-$, 88083-61-8; $Br(CH_2)_{10}C(CO_2Et)_2^-$, 88083-62-9; $Br(CH_2)_{11}C(CO_2Et)_2^-$, 88083-63-0; $Br(CH_2)_{12}C(CO_2Et)_2^-$, 88083-64-1; $Br(CH_2)_{16}C(CO_2Et)_2^-$, 88083-65-2; $Br(CH_2)_{20}C(CO_2Et)_2^-$, 88083-66-3; $Br(CH_2)_4Cl$, 6940-78-9; LiBr, 7550-35-8; diethyl 1,1-cyclobutanedicarboxylate, 3779-29-1; diethyl 1,1-cyclopentanedicarboxylate, 4167-77-5; diethyl 1,1-cyclohexanedicarboxylate, 1139-13-5; diethyl 1,1-cycloheptanedicarboxylate, 6557-83-1; diethyl 1,1-cyclooctanedicarboxylate, 76999-11-6; diethyl 1,1-cyclododecanedicarboxylate, 76999-15-0; diethyl 1,1-cyclotridecanedicarboxylate, 37689-04-6; diethyl 1,1-cycloheptadecanedicarboxylate, 76999-16-1; diethyl 1,1-cycloheneicosanedicarboxylate, 76999-17-2; diethyl dibutylmalonate, 596-75-8; diethyl sodiomalonate, 996-82-7; diethyl (4-chlorobutyl)malonate, 18719-44-3.

Specific Acid Catalysis in the Decomposition of Trialkyltriazenes

Richard H. Smith, Jr.,[1] Cheryl L. Denlinger, Robert Kupper, Steven R. Koepke, and Christopher J. Michejda*†

Contribution from the LBI-Basic Research Program, Chemical Carcinogenesis Program, NCI-Frederick Cancer Research Facility, Frederick, Maryland 21701. *Received April 11, 1983*

Abstract: The acid-catalyzed decomposition of 1,3-di-*n*-butyl-3-methyltriazene (**1**) in aqueous buffer was investigated. Determination of the kinetics over a pH range of 10.4 to 12 indicated that the reaction is acid catalyzed. Variation of buffer concentration, at constant ionic strength, produced an insignificant variation in the rate constant. The determination of kinetics of the decomposition of **1** in nine different buffers, ranging in pK_a from 9.6 to 12.7, also gave negligible variation in the rate constants. The solvent isotope effect for the reaction, k_H/k_D, was 0.62. These data strongly support the conclusion that the reaction is specific acid catalyzed. This implies that the reaction involves fast, reversible protonation of the triazene followed by the rate-determining heterolysis of the protonated species to *n*-butyldiazonium ion and *n*-butylmethylamine. A product study of the decomposition supported the conclusion that *n*-butyldiazonium ion was formed during the reaction. The kinetics of the reaction of 1,3,3-trimethyltriazene (**2**) in various buffers also supported the notion of specific acid catalysis in the decomposition of that triazene. The decomposition of 1,3-dimethyl-3-acetyltriazene (**3**) was very slow in comparison to the others, requiring strongly acidic solutions for the reaction to occur (k_{obsd} 7.67×10^{-4} s^{-1} at pH 1.05). 1,3-Dimethyl-3-carbethoxytriazene (**4**) decomposed about 7 times more rapidly than **3** at pH 1.80 but was much more stable than the trialkyltriazenes at that pH.

The study of the chemistry of triazenes has been confined almost entirely to 1-aryl-3,3-dialkyltriazenes. These substances have been shown to be potent carcinogens[2] while some members of the series have been shown to be useful in chemotherapy of cancer.[3] Trialkyltriazenes, however, have not been studied, primarily because no reliable methods for their synthesis have been devised. This is no longer the case since general synthetic methods have been developed by our laboratory.[4,5] These new substances have been shown to have substantially different characteristics from their aryldialkyl analogues. Thus, while trialkyltriazenes are stable in nonhydroxylic solvents, they have been found to be very unstable in aqueous solution. In contrast to the aryldialkyltriazenes, which require metabolic activation, the trialkyltriazenes are potent, directly acting bacterial mutagens.[6] Moreover, some of these substances have been found to be highly selective cytotoxic agents against human tumor cells which are deficient in DNA alkylation repair systems. They are much less toxic toward normal human cells.[7] These data hold promise that suitably substituted members of this series might be useful in chemotherapy. The biological data suggest strongly that trialkyltriazenes decompose to alkylating agents capable of reacting with DNA. It is reasonable to suppose that these agents are alkyldiazonium ions.

In an earlier paper we suggested that the trialkyltriazenes decomposed in aqueous buffers by a general acid catalyzed re-

† The contents of this publication do not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

(1) Present address: Department of Chemistry, Western Maryland College, Westminster, MD 21157.

(2) Preussmann, R.; Ivankovic, S.; Landschütz, L.; Gimmy, J.; Flohr, E.; Griesbach, U. *Z. Krebsforsch.* **1974**, *81*, 285.
(3) Shealy, Y. F.; Montgomery, J. A.; Laster, J. R., Jr. *Biochem. Pharmac.* **1962**, *11*, 674.
(4) Sieh, D. H.; Wilbur, D. J.; Michejda, C. J. *J. Am. Chem. Soc.* **1980**, *102*, 3883–3887.
(5) Smith, R. H., Jr.; Michejda, C. J. *Synthesis* **1983**, 476–477.
(6) Sieh, D. H.; Andrews, A. W.; Michejda, C. J. *Mutat. Res.* **1980**, *73*, 227–235.
(7) Scudiero, D.; Smith, R. H.; Sieh, D. H.; Michejda, C. J., to be published.

0002-7863/84/1506-1056$01.50/0 © 1984 American Chemical Society