

Ring-Closure Reactions. 19.¹ Kinetics of Formation of Benzo-Crown Ethers by Intramolecular Nucleophilic Substitution. A Comparison between Poly(oxyethylene) and Polymethylene Chains

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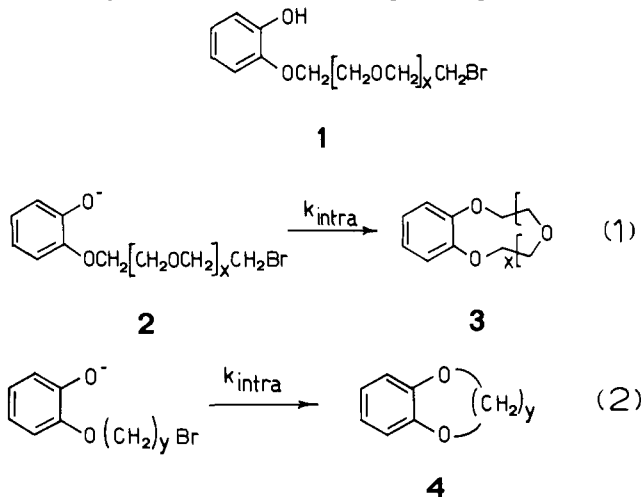
Abstract: Kinetic data have been obtained for the formation of 9-, 12-, 15-, 18-, 21-, 30-, and 48-membered benzo-crown ethers by intramolecular Williamson synthesis in Me₂SO-water (99:1, v/v). Comparison with earlier data for the formation of catechol polymethylene ethers provides an insight into the influence on the ease of ring closure of the replacement of methylene groups by oxygen atoms. Little or no effect occurs at ring size 9. In the next higher homologues the ease of cyclization of the poly(oxyethylene) chains is some 3 times as great as that of the polymethylene chains of similar length, but in the limit of the very long chains the two series behave much in the same way. Interestingly, literature data related to the fast, encounter-controlled reactions between end groups linked by poly(oxyethylene) and polymethylene chains reveal much the same features of the slow, activation-controlled reactions. The general picture fits in with well-established conformational arguments based on the expected strain relief due to replacement of transannular CH...HC interactions with CH...O or O...O interactions. The oxygen atom effect turns out to be a sensitive tool for the detection of even weak strain energies in ring compounds.

Intramolecular interactions of remote groups attached to long chain molecules are currently receiving a great deal of attention in our and in other research groups.²⁻⁵ A major motivation of these studies is to relate cyclization rates to the structure and size of the ring to be formed, as well as to the conformations of the chain connecting the functional groups with the aim at providing a probe for the shape^{3a} and flexibility^{3d,4} of chain molecules in solution. Most of the available studies have dealt with polymethylene compounds, but chains of different nature have also been given some attention. One of these is the poly(oxyethylene) chain.^{4,5} However, in spite of the fact that the physical properties of the poly(oxyethylene) chain, such as the average dimensions in solution, have been widely investigated,⁶ the few available studies on the kinetics of intramolecular reactions of end groups attached to a poly(oxyethylene) chain do not provide definite information as to the ease of the latter to undergo an intramolecular reaction relative to that of the polymethylene chain.

The kinetics of cyclic aromatic ether formation by alkylation of phenoxide ion by a -CH₂Br end group intramolecularly linked by means of orthopolymethylene chains of varying length have been reported by us in a number of cases.^{7,8} We have now extended these studies, using the above functional groups as connected by poly(oxyethylene) chains for lengths corresponding to $x = 1, 2, 3, 4, 5, 8,$ and $14,$ thus leading to benzo-3($x + 2$)-crown-($x + 2$) ethers **3** of varying ring sizes in the range of 9 to 48 atoms (eq 1).

We report here the results of this investigation, as carried out in 99% (v/v) aqueous Me₂SO at 25.0 °C, which permits a close comparison with the kinetic data for cyclization under the same conditions of the corresponding polymethylene compounds (eq

2) recently described over a wide range of ring sizes.⁷



The present study is a continuation of earlier quantitative work⁸ on the effect on cyclization of replacing a methylene group by oxygen (oxygen atom effect).

Results

The parent *o*-[ω-bromopoly(oxaalkyl)]phenols **1** were prepared by unambiguous synthetic routes (see Experimental Section), so that contamination by oligomers of close molecular weight can be ruled out. It is worth noting that, as far as we are aware, benzo-48-crown-16 (**3**, $x = 14$) is the largest ring compound for which rate data have been obtained starting from an open chain precursor of well-defined molecular weight.

Rate measurements and product analyses were carried out spectrophotometrically as previously reported,⁷ with the sole significant difference that, instead of KOH, Me₄NOH was used as the base to generate in situ the anions **2** from the parent phenols **1**. The choice of a tetraalkylammonium ion as a counterion with which ion pairing is presumably negligible permits the reactivity of the free anions to be determined in the absence of any interference due to the operation of the template effect, which has been found to be significant in the presence of alkali and alkaline earth cations.⁹ Consistent with this idea is the finding that added

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Table I. Kinetic Data for the Ring-Closure Reaction of $o\text{-OC}_6\text{H}_4\text{OCH}_2[\text{CH}_2\text{OCH}_2]_x\text{CH}_2\text{Br}$ in 99% Me_2SO at 25.0 °C

ring size	x	$k_{\text{obsd}},^a \text{ s}^{-1}$	yield, ^a %	$10^3 k_{\text{intra}},^b \text{ s}^{-1}$	EM, ^c M
9	1	$1.62 \pm 0.02 \times 10^{-2}$	65.1 ± 0.3	10.5	0.116
12	2	$7.87 \pm 0.08 \times 10^{-3}$	94.0 ± 1.0	7.4	0.081
15	3	$9.02 \pm 0.01 \times 10^{-3}$	90.1 ± 1.1	8.1	0.089
18	4	$8.11 \pm 0.24 \times 10^{-3}$ ^d	90.4 ± 0.6	7.3	0.080
21	5	$6.85 \pm 0.08 \times 10^{-3}$ ^e	88.7 ± 0.0	6.1	0.067
30	8	$3.81 \pm 0.08 \times 10^{-3}$ ^f	90.7 ± 0.9	3.5	0.038
48	14	$1.89 \pm 0.03 \times 10^{-3}$ ^g	81.8 ± 1.8	1.5 _s	0.017

^a Average from two to four independent runs. ^b Calculated as $(\text{yield}/100)k_{\text{obsd}}$. ^c Calculated as $k_{\text{intra}}/k_{\text{inter}}$, where $k_{\text{inter}} = 9.1 \pm 0.2 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$ refers to the intermolecular model reaction, namely the alkylation of guaiacolate ion with $\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_2\text{Br}$ under the same conditions. ^d In the presence of 0.2 M Et_4NBr k_{obsd} was 7.85×10^{-3} . ^e In the presence of 0.05 M Me_4NBr k_{obsd} was 5.81×10^{-3} . ^f In the presence of 0.2 M Et_4NBr k_{obsd} was 3.29×10^{-3} . ^g In the presence of 0.2 M Et_4NBr k_{obsd} was 1.68×10^{-3} .

Me_4NBr or Et_4NBr up to 0.2 M hardly affects the rates of cyclization¹⁰ in typical cases, as shown in Table I, where rate and yield data are listed.

In addition to the spectrophotometric determinations, product analysis was carried out by isolation of the reaction product at the end of the reaction under conditions very close to those of the kinetic runs in one typical case, namely, the cyclization of **1**, $x = 8$. Benzo-30-crown-10 (**3**, $x = 8$) was isolated in 81% yield, in reasonable agreement with the spectrophotometric determination. As Table I shows, yields of ring products are usually fairly high, with the sole exception of the 9-membered ring.¹¹

The second-order rate coefficient for the reaction between the guaiacolate ion and $\text{EtOCH}_2\text{CH}_2\text{Br}$ was determined under the same conditions. This reaction was chosen as the intermolecular analogue of the ring-closure reaction at hand, and the determined k_{inter} value ($9.1 \pm 0.2 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$) was used for the calculation of the effective molarity (EM) for all terms of the series. Under the same conditions the specific rate k_{inter} for reaction between the guaiacolate ion and butyl bromide, which was chosen as a model for reaction 2, is $0.295 \text{ M}^{-1} \text{ s}^{-1}$. Thus, butyl bromide alkylates the guaiacolate ion 3.2 times more rapidly than $\text{EtOCH}_2\text{CH}_2\text{Br}$ does. This again emphasizes the need for an appropriate choice of the monofunctional reagents used to model the inherent reactivity of the functional groups in the bifunctional substrates undergoing cyclization. This is particularly so when small differences in EM values are to be compared, as happens to be the case in the present work.

Discussion

Apart from a small inversion on going from the 12- to 15-membered ring, the rates of formation of the benzo-crown ethers regularly decrease upon increasing the length of the open-chain precursors. The overall effect is moderate, the observed reactivity range from ring size 9 to ring size 48 being included within a factor of 10. It is worth noting that no maximum is shown at ring size 18, which seems to be in contrast with Mattice's Monte-Carlo

(10) Many examples can be found in the literature indicating that cancellation of activity coefficients between transition state and reactants in reactions involving an ion and a neutral molecule sometimes extend to surprisingly high salt concentrations. See: Hammett, L. P. "Physical Organic Chemistry"; MacGraw-Hill: New York, 1970; 2nd ed, p 211 and references therein cited.

(11) The situation is very nearly the same as that obtained in the cyclization reaction of eq 2 in 99% Me_2SO at 25 °C, where the yield was 67% for the nine-membered ring and about 90% for the higher homologues.⁷ This phenomenon, also observed in many other instances,^{8a,12} was attributed to the operation of an intramolecularly assisted β -elimination reaction of the E2 type competing with the formation of the strained medium rings. It seems very likely that this is also the case with the present reaction, but no attempt has been made to isolate the o -(1,4-dioxahexen-5-yl)phenol presumably formed.

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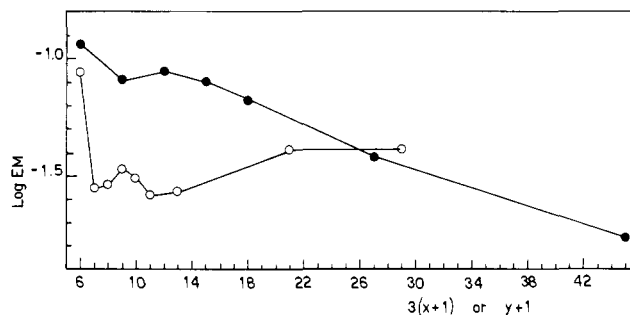
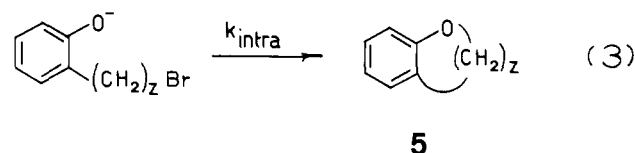


Figure 1. Log EM values for the ring-closure reaction of $o\text{-OC}_6\text{H}_4\text{OCH}_2[\text{CH}_2\text{OCH}_2]_x\text{CH}_2\text{Br}$ (●) and $o\text{-OC}_6\text{H}_4\text{O}(\text{CH}_2)_y\text{Br}$ (○) in 99% Me_2SO at 25.0 °C as a function of the number of single bonds [$3(x+1)$ or $y+1$] in the chain connecting the chain termini.

calculations,^{5b} showing that formal cyclization of poly(oxyethylene) chains to the macrocyclic oligomers $(\text{CH}_2\text{CH}_2\text{O})_r$ is most readily achieved when $r = 6$ among all the even r 's ranging from 4 to 20.

Figure 1 provides a comparison between EM values for the present reaction and those for the cyclization of the corresponding polymethylene compounds, reaction 2. At ring size 9, which is the smallest one for which a comparison is possible, the EM values are remarkably similar in both series. In the next higher homologues the ease of cyclization of the poly(oxyethylene) chains is decidedly greater than that of the polymethylene chains of similar length¹³ by a factor of about 3. The magnitude of the above oxygen atom effect tends to vanish when the ring size becomes greater. In the neighborhood of ring size 30 the two series behave much in the same way.

The present finding compares well with our earlier results on the subject.⁸ The oxygen atom effect observed in comparing the reactions of eq. 2 and 3, which showed a well-defined maximum in the medium ring region with a top value of 5.6 at ring size 9 and the tendency to vanish in the large-ring region, was explained as a strain relief phenomenon. At ring size 16, which was the



largest investigated one, the ease of formation of the diether was 1.4 times as large as that of the monoether, suggesting that appreciable strain may still be present in such a large ring. In the present case, in view of the cumulative action of the several oxygen atoms in the benzo-crown ethers **3**, the oxygen atom effect is distinctly greater in the large-ring region and is still significant for ring sizes up to more than 20.

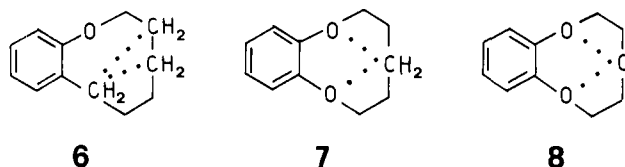
In contrast, the close similarity in the ease of formation of the 9-membered rings in series **3** and **4** apparently violates the rule that the oxygen atom effect should be a maximum in the strained medium rings. A reasonable explanation for this discrepancy, as well as a deeper insight into the origin of the oxygen atom effect, may be obtained on the basis of the arguments presented by Dale¹⁴ in a comprehensive review on the conformational consequence of replacing methylene groups by oxygen in acyclic and cyclic compounds. A substantial body of experimental evidence led Dale

(13) These findings appear to be in contrast with the results obtained by Sisido et al.^{5a} in a kinetic study of the nucleophile-assisted hydrolysis of a terminal p -nitrophenyl ester group attached to a 4-pyridyl group by means of poly(oxyethylene) chains of varying length. By comparing their data with early yield data on the lactonization of ω -hydroxyalkanoic acids in benzene solution (Stoll, M.; Rouv , A. *Helv. Chim. Acta* **1935**, *18*, 1087) the unexpected conclusion was reached that the supposedly more flexible poly(oxyethylene) chain was less effective than the polymethylene one in promoting the intramolecular reaction of the end groups. Because the above comparison was based on mechanistically different reactions as carried out in two basically different solvents, we believe that the present work provides a more reliable assessment of the oxygen atom effect on ring closure reactions and of its dependence upon chain length.

(14) Dale, J. *Tetrahedron* **1974**, *30*, 1683.

to point out that 1,4- and 1,5-CH...O interactions are less unfavorable than the corresponding CH...HC interactions, and that the 1,4-O...O interaction is unquestionably attractive, as shown by the unequivocal gauche preference for CC bonds in 1,2-dimethoxyethane and poly(oxyethylene). Although little or no evidence as to the strain energies of cyclic ethers and polyethers relative to those of the corresponding polymethylene compounds is available, we expect transannular CH...HC repulsions in ring compounds to be relieved when replaced by CH...O or O...O interactions, and the magnitude of this effect to be a maximum for the medium rings, where severe transannular interactions are a major source of strain. Conversely the effect is predicted to decrease as the size of the ring becomes greater, and eventually to vanish in the limit of the very large rings, a portion of which should closely resemble the inner portion of a long alkane chain.

As long as the stability of the cyclic transition state in a ring-closure reaction is related to the stability of the ring to be formed, the above arguments apply as well to a discussion of the oxygen atom effect on rates of cyclization. Substitution of x methylene groups of diethers **4** with an equal number of oxygen atoms in suitable positions to give the corresponding benzo-crown ethers **3** transforms two 1,4-CH...O and $(x - 1)$ 1,4-CH...HC into 1,4-O...O interactions, and $2(x - 1)$ 1,5-CH...HC into 1,5-CH...O interactions. Thus, relief of unfavorable CH...HC repulsions takes place when $x \geq 2$, i.e., when the ring size is 12 or larger. On the other hand, when $x = 1$ (ring size 9) only two presumably weak interactions between CH and oxygen lone pairs are relieved, as shown in structures **7** and **8**. Therefore it seems



that formation of rings **7** and **8** from the open-chain precursors is accompanied by comparable strain energies, which is not only consistent with the close similarity of the EM values, but also with the suggestion¹¹ that similar extents of the olefin-forming side reaction compete with the formation of the given rings. The situation is different when rings **6** and **7** are compared. Relief of one 1,5- and one 1,4-CH...HC transannular interaction upon substitution of the benzyl methylene of **6** by oxygen is clearly responsible for the significant oxygen atom effect observed in this case.

We have already commented on the reactions leading to cyclic ethers **4** and **5** as cyclization series in which much, but not all, of the strain factor responsible for the appearance of a deep reactivity minimum in the medium ring region of other series has largely disappeared.^{8b} Thus, the reactivity vs. ring size profiles of these series were considered as approaching that of a strainless cyclization reaction. However, the influence of significant strain factors, neatly detectable in the medium-ring region and still appreciable in the lower large-ring region, causes a downward shift in the reactivity values of these rings and is very likely responsible for the upward trend observed in the reactivity profiles on going from the lower to the higher large rings. As the latter feature is lacking in the reactivity profile of reaction 1 (Figure 1), this reaction can be viewed as a further step toward a hypothetical cyclization reaction in which the reactivity between the chain ends is solely governed by the expected monotonic drop of activation entropy upon increasing the chain length.^{8b} The remarkable flatness of the EM profile in the neighborhood of ring size 15 is decidedly suggestive of the presence of but a mere vestige of a medium-ring effect.

Activation vs. Encounter Controlled Intramolecular Processes. An important property of linear molecules is the chain flexibility,^{3d,4,15} a property which arises from internal rotations around the single bonds. One must distinguish between dynamic and static

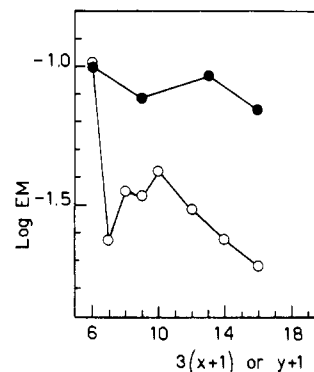


Figure 2. Log EM values for intramolecular electron-transfer reactions in $\text{PICH}_2[\text{CH}_2\text{OCH}_2]_x\text{CH}_2\text{PI}\cdot$ (●) and $\text{PI}(\text{CH}_2)_y\text{PI}\cdot$ (○) in DMF at 20 °C as a function of the number of single bonds [$3(x + 1)$ or $y + 1$] in the chain connecting the chain termini (data from ref 4).

flexibility; whereas the former depends on the rate of conformational changes, the latter is bound to the equilibrium distribution of chain conformations and is therefore a time-independent property. Szwarc and his co-workers⁴ have proposed to view the rates of intramolecular reactions of end groups attached to chain molecules as a way of probing the flexibility of such chains. Accordingly, the specific rate P of intramolecular electron transfer between N -phthalimide (PI) terminal groups connected by $-(\text{CH}_2)_y-$ or $-\text{CH}_2(\text{CH}_2\text{OCH}_2)_x\text{CH}_2-$ chains was measured in several solvent systems and argued to be virtually controlled by the frequency of encounters between chain ends. Some of their data are plotted in Figure 2 in terms of EM values calculated as P/k_{ex} , where k_{ex} refers to the intermolecular exchange between $\text{BuPI}\cdot$ and BuPI . It is apparent from Figure 2 that, provided $x > 1$, the frequency of electron exchange for poly(oxyethylene) chains is some two or three times as fast as that for alkane chains with a similar number of skeleton atoms. This behavior was taken as evidence for a higher dynamic flexibility of the oxygen-containing chain with respect to the all-carbon one.

We now note that the similarities between the reactivity profiles reported in Figures 1 and 2 are remarkable, the EM values for chains of equal nature and length being very similar in the two different reactions. Noteworthy is the lack of oxygen-atom effect also in the encounter-controlled reaction when the terminal groups are connected by five-atom chains. Also in this case the oxygen atom in $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2-$ replaces the only methylene in $-(\text{CH}_2)_5-$ not involved in interactions with 1,5- and/or 1,4-CH groups. Thus it is very tempting to explain the oxygen atom effect as a phenomenon related to relief of strain due to 1,5- and 1,4-CH...HC repulsions also in the case of encounter-controlled reactions. Although two distinct models have been proposed to account for the progress of "fast" and "slow" intramolecular reactions, both kinds of processes appear to be affected much in the same way by structure.

The above discussion indicates that if flexibility is to be regarded as an intrinsic property of a chain that is independent of chain length, any conclusion drawn by kinetic data referring to chain molecules belonging to a limited chain length range is not safe. Alternatively, the statement that for certain chain lengths the poly(oxyethylene) chains are more flexible than the polymethylene ones can still be accepted, provided that one chooses to include in the flexibility concept any strain factor resulting from transformation of an extended conformation to a ring-shaped conformation.

Experimental Section

Most techniques and apparatuses were previously reported.⁷

Materials. Diethylene glycol (Erba RP), triethylene glycol (Erba RP), tetraethylene glycol (Fluka), and catechol (Erba RP) were reagent grade commercial samples. 2-Bromoethyl ethyl ether (Aldrich) was distilled at reduced pressure over anhydrous K_2CO_3 . Hexaethylene glycol dibromide and triethylene glycol dichloride were available from a previous investigation.¹⁶ The dibromides of di-, tri-, and tetraethylene glycol were

prepared by reaction of the glycols with PBr_3 and pyridine. Workup with water- CCl_4 followed by removal of the solvent gave the pure (TLC) dibromides in 50–56% yield.

Nonaethylene Glycol Dibromide. Excess triethylene glycol and triethylene glycol dichloride were reacted in the presence of NaOH according to Krespan.¹⁷ Distillation of the reaction mixture gave crude nonaethylene glycol, bp ca. 240 °C (0.4 mmHg). Treatment of the latter with PBr_3 -pyridine as above, followed by column chromatography on silica gel with AcOEt, gave pure nonaethylene glycol dibromide in 12.7% overall yield.

Pentadecaethylene Glycol Dibromide. Pentadecaethylene glycol was prepared as above from pentaethylene glycol, pentaethylene glycol dibromide, and NaOH. After removal under vacuum of excess pentaethylene glycol, the residue was treated with PBr_3 and pyridine in the usual way. Chromatography of the crude material on alumina with AcOEt-benzene 1:1 followed by AcOEt gave pure (TLC) pentadecaethylene glycol dibromide in 8.3% yield. All the dibromides gave ^1H NMR spectra consistent with the expected structure.

***o*-Hydroxyphenyl ω -Bromopoly(oxaalkyl) Ethers.** The preparation of *o*-hydroxyphenyl 3,6,9,12-tetraoxa-14-bromotetradecyl ether (**1**, $x = 4$) has been reported in a previous paper.^{9a} The other compounds were prepared in a similar way from the proper poly(ethylene glycol) dibromide, catechol, and KOH in the molar ratio of 1:4:1. Purification of the crude products was carried out by column chromatography. Details of the chromatographic conditions and yields of isolated pure products are as follows: *o*-Hydroxyphenyl 3-oxa-5-bromopentyl ether (**1**, $x = 1$): silica gel, CHCl_3 , 8% yield. *o*-Hydroxyphenyl 3,6-dioxa-8-bromooctyl ether (**1**, $x = 2$): silica gel, CHCl_3 -MeOH 49:1, 16% yield. *o*-Hydroxyphenyl 3,6,9-trioxa-11-bromoundecyl ether (**1**, $x = 3$): silica gel, CHCl_3 -MeOH 49:1, 18% yield. *o*-Hydroxyphenyl 3,6,9,12,15-penta-oxa-17-bromohexadecyl ether (**1**, $x = 5$): silica gel, benzene-AcOEt 1:1,

20% yield. *o*-Hydroxyphenyl 3,6,9,12,15,18,21,24-octa-oxa-26-bromohexacosyl ether (**1**, $x = 8$): alumina, benzene-AcOEt 1:3, 31% yield. *o*-Hydroxyphenyl 3,6,9,12,15,18,21,24,27,30,33,36,39,42-tetra-oxa-44-bromotetratetracontyl ether (**1**, $x = 14$): alumina AcOEt-EtOH 20:1, 16% yield.

All compounds were liquids at room temperature and gave the expected ^1H NMR spectra. Bromine content was -0.5% for compound **1**, $x = 14$, and within $\pm 0.3\%$ of theory in the other cases.

Benzo-30-crown-10 (**3**, $x = 8$) was prepared by cyclization of **1**, $x = 8$, in Me_2SO solution in the presence of Me_4NOH . The reaction was run under nitrogen in a 250-mL, three-necked flask charged with Me_2SO (70 mL). The reagents were added separately and simultaneously to the well-stirred solvent, heated at 40 °C, by means of two motor-driven syringes. One syringe was charged with 1 mmol of **1**, $x = 8$, in 10 mL of Me_2SO , and the other with 1.1 mmol of Me_4NOH in 10 mL of Me_2SO - H_2O 9:1. When the addition was over (4 h), ice-cold water was added, and the mixture was continuously extracted with diethyl ether for several hours. After removal of the solvent, the residue was freed from a small amount of Me_2SO by distillation under vacuum and then was chromatographed on silica gel with AcOEt-MeOH 25:1 to give the desired product in 81% yield, mp 37–38 °C, from heptane. ^1H NMR was as expected; $M^+ m/e$ 488. Anal. Calcd for $\text{C}_{24}\text{H}_{40}\text{O}_{10}$: C, 59.00; H, 8.25. Found: C, 59.61; H, 8.44.

Kinetics. Rate measurements were carried out in 99% Me_2SO by following the disappearance of the phenoxide absorption at 314 nm. The reactions were started by adding by a microsyringe a calculated amount of Me_4NOH stock solution (2×10^{-2} M in 98% Me_2SO) into a 10-mm quartz cuvette containing a very dilute (ca. 1×10^{-4} M) substrate solution in 99% Me_2SO . Clean first-order kinetics were observed up to high conversions. In all cases the infinity spectra showed a residual phenoxide absorption.⁷ Yields of cyclic products in the kinetic runs were calculated as the fraction of phenoxide absorption disappeared in the course of the reaction. The intermolecular model reaction was studied under pseudo-first-order conditions in the presence of a 50- to 200-fold excess of $\text{EtOCH}_2\text{CH}_2\text{Br}$.

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Degenerate Thermal Rearrangement of 1,3-Dimethylenecyclopentane. Evidence for Partially Stereospecific Biradical Formation and Closure in a 1,3 Shift¹

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Abstract: Pyrolysis of 1,3-bis(dideuteriomethylene)cyclopentane at 370 °C resulted in a first-order degenerate rearrangement in which the 1,3- and 3,3-shift products were formed in a 2:1 ratio, respectively, indicating the intermediacy of an effectively orthogonal 2,2'-bis(allylmethane) biradical. Pyrolysis of *trans*- and *cis*-4,5-dimethyl-1,3-dimethylenecyclopentane (**T** and **C**) gave 1,3- and 3,3-shift products with stereochemistry consistent with predominant conrotatory-bevel ring opening to produce the orthogonal diradical directly. Pyrolysis of optically active **T** gave the 1,3-shift products with 20.8% inversion of configuration of the migrating carbon indicative of partial stereospecific closure of the biradical. Comparative pyrolysis of optically active **T** and its bis(dideuteriomethylene) derivative revealed no secondary kinetic deuterium isotope effect, but an alteration in the extent of racemization of starting material and amounts of 1,3- and 3,3-shift products indicates a product-determining isotope effect. These data provide further evidence for an intermediate.

Because of their simplicity, unimolecular thermal isomerization reactions raise significant questions to experimentalists and theorists. Unaffected by polar solvents and catalysts, these reactions may be among the few in which questions about structure and

energy of transition states and intermediates can be focused solely on the molecule of interest and not solvents etc. Nonetheless there is controversy about the mechanism for these reactions since the Benson diradical hypothesis² and quantum chemical calculation³

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