86970-70-9; 4-bromobicyclo[3.2.0]hept-2-ene, 38352-98-6; cuprous chloride, 7758-89-6; methyllithium, 917-54-4; 5-bromo-1,3-cycloheptadiene, 64392-84-3; 1,3-cycloheptadiene, 4054-38-0; lithium dimethylcuprate, 15681-48-8; toluene, 108-88-3.

Supplementary Material Available: Figures 1–4, showing representative VPC traces and [P_i], [$\sum P_i$], and [SM] vs. time plots (4 pages). Ordering information is given on any current masthead page.

Ring-Closure Reactions. 21.[1] Intramolecular β-Elimination Competing with Ring Formation from *o*-(ω-Bromoalkoxy)phenoxides over a Wide Range of Ring Sizes

Antonella Dalla Cort,* Luigi Mandolini,* and Bernardo Masci*

Centro CNR di Studio sui Meccanismi di Reazione, Istituto di Chimica Organica dell'Università, P.le A. Moro 2, Rome, Italy

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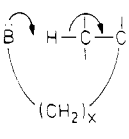
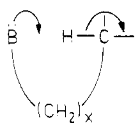
Unimolecular β-elimination of HBr from the CH_2CH_2Br end of o-$^{-}OC_6H_4O(CH_2)_{n-4}Br$ has been interpreted as an E2-type reaction promoted by the distal phenoxide group acting as a base. Combination of careful product analyses with kinetic data has provided rate constants and effective molarities for intramolecularly assisted elimination reactions occurring through 7-, 8-, 9-, 10-, and 14-membered ring transition states. A comparison is carried out with the competing intramolecular substitution reactions leading to ring formation. Attention is called to the specific entropic and geometrical requirements of intramolecular elimination in which the donor–proton-acceptor arrangement is a part of a cyclic structure. The importance of the present results in the general field of intramolecular acid or base catalysis phenomena is discussed.

In spite of the frequent occurrence of β-elimination besides substitution in reactions of basic nucleophiles at saturated carbon, evidence for such a competition in intramolecular reactions is scanty. In a few examples reported by Grob et al.,[2] an internal base such as N, O^-, or S^- was effective in promoting elimination via a six-membered transition state in which the incipient double bond is endocyclic. A different kind of intramolecular β-elimination reaction, namely, the one in which the incipient double bond is exocyclic, has been reported[3] in connection with our studies on the cyclization of 1 and 4 (eq 1 and 2), for which significant amounts of the olefins 3 and 6 were found to accompany the formation of the eight and nine-membered cyclic ethers 2 and 5.



endocyclic



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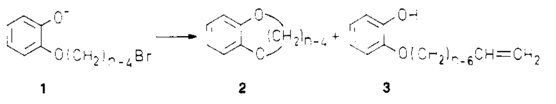
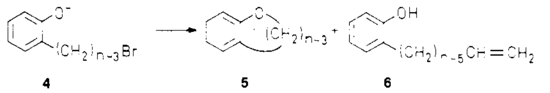


(1)

1 2 3



(2)

4 5 6

In order to provide a proper insight into the factors affecting reactivity in intramolecular proton-transfer reactions, we now report rate data for the intramolecular elimination of HBr from the *o*-(ω-bromoalkoxy)phenoxides (1) in 99% aqueous Me_2SO (v/v) in the range of $n = 7$–10 and 14, as well as an analogous study of the intermolecular reaction of the guaiacolate ion with decyl bromide. An attempt at determining the amount of olefin accompanying the cyclization of 4 ($n = 6$) is also described.

Results

The reactions were carried out in 99% Me_2SO at 25.0 °C. In all cases the initial concentration of 1 was 0.5 mM, i.e., low enough to ensure the intramolecular course of the reaction. Two sets of experiments were carried out. In one set, the anion was generated by the addition of a stoichiometric amount of KOH to the parent phenol, so that the reaction was run in the virtual absence of OH^-. In the other, a 2-fold quantity of base was added. GLC analysis of the reaction mixture showed only two peaks, namely, those of the expected 2 and 3 (comparison with authentic samples). The 3:2 ratio was in all cases independent of the presence of excess KOH (Table I) but was on the other hand markedly influenced by the chain length, which confirms the intramolecular nature of the elimination reactions and rules out any appreciable intermolecular contribution in all cases.

The rate constants for intramolecular elimination (k^E_{intra}) were calculated as

$$k^E_{intra} = k^S_{intra} 3{:}2 \qquad (3)$$

where k^S_{intra} is the known rate constant for ring closure.[3d]

A similar procedure was applied to the model intermolecular reaction between guaiacolate ion and decyl bromide. Two independent experiments were carried out. In one experiment the concentrations of guaiacol, decyl bromide, and KOH were 1.6, 80, and 1 mM, respectively, and in the other 0.5, 10, and 0.5 mM. In both cases the yield of 1-decene relative to that of *o*-(decyloxy)anisole was the same within experimental errors, namely, $7.4 \pm 0.1 \times 10^{-3}$. The rate constant for the intermolecular elimination (k^E_{inter}) reported in Table I was calculated by combining

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[1] Part 20: Gargano, P.; Mandolini, L. *Gazz. Chim. Ital.* **1982**, *112*, 31.

[2] Fischer, W.; Grob, C. A. *Helv. Chim. Acta* **1978**, *61*, 2336 and references therein cited.

[3] (a) Illuminati, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1974**, *96*, 1422. (b) Illuminati, G.; Mandolini, L.; Masci, B. *J. Org. Chem.* **1974**, *39*, 2598. (c) Illuminati, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1975**, *97*, 4960. (d) Dalla Cort, A.; Illuminati, G.; Mandolini, L.; Masci, B. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1774.

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Table I. Yield and Rate Data for the Competing Substitution (S) and Elimination (E) Reactions of o-$^{-}OC_6H_4O(CH_2)_{n-4}Br$ in 99% Me_2SO at 25.0 °C

n[a]	(E/S) × 100[b]	k^S_{intra},[c] s^{-1}	k^E_{intra},[d] s^{-1}	EM_S,[e] M	EM_E,[f] M
7	2.8 ± 0.2	3.7	0.10	12.5	49
8	9.6 ± 0.3	0.22	0.021	0.75	10
9	35 ± 1	0.026	0.0091	0.088	4.3
10	2.8 ± 0.1	0.0084	0.00023	0.028	0.11
14	4.2 ± 0.1	0.0076	0.00032	0.026	0.15
inter[g]	0.74 ± 0.001	0.284[h]	0.0021		

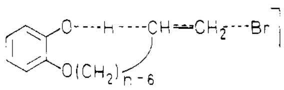
[a] Size of the ring formed in the substitution reaction and in the cyclic transition state of the elimination reaction. [b] Relative yields of elimination vs. substitution product as determined by GLC. Mean values and standard deviation of four to six independent measurements relative to the two different sets of conditions. [c] Rate constants for the intramolecular substitution reaction; data from ref 3d. [d] Rate constants for the intramolecular elimination reaction, as calculated as $k^E_{intra} = k^S_{intra}(E/S)$. [e] Effective molarity for the substitution reaction $EM_S = k^S_{intra}/k^S_{inter}$. [f] Effective molarity for the elimination reaction $EM_E = k^E_{intra}/k^E_{inter}$. [g] Data relative to the intermolecular model reaction between guaiacolate ion and 1-bromodecane, k's in $M^{-1}\ s^{-1}$. [h] Obtained from the k_{obsd} value (0.299 $M^{-1}\ s^{-1}$) times the GLC yield (95/100).

the GLC data with the overall rate constant, $k_{inter} = 0.299$ $M^{-1}\ s^{-1}$. Table I also lists the EM values for the two reactions. These were calculated as k_{intra}/k_{inter}.[4]

Compound 1 ($n = 6$) has not been included in the present investigation, as elimination from it would lead to a vinyl ether. We have therefore considered the cyclization of the closely related compound 4 ($n = 6$) where any possible electronic effect of the ethereal oxygen is obviously absent. The yield of o-allylphenol, if any, was found to be no more than 0.1%, which leads to the estimate of 1 s^{-1} as upper limit for the rate of the elimination reaction via a six-membered transition state.

Discussion

If the H atom undergoing transfer from C to O is included in the computation,[5] the number of the ring atoms n in the transition state for elimination (7) is the same as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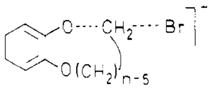
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that for substitution (8). The log k_{intra} profiles for the two reactions as a function of n are shown in Figure 1. In both reactions, rates decrease on increasing chain length. The rate profiles, owing to the relief of medium ring strain brought out by the presence of the o-phenylenedioxy unit,[6] do not show the rate minimum found in the medium-ring region of other series.[4] The EM profile for elimination (Figure 2A), apart from $n = 6$, lies above the EM profile for substitution, in contrast to what observed with the related log k profiles (Figure 1). This again emphasizes the importance of the effective molarity (EM) as an appropriate measure of the efficiency of intramolecular reactions.[4] Although the intramolecular elimination has a higher EM for all the investigated n's larger than 6, it does not predominate over substitution for any member of the series because it is inherently slower than the latter by more than 2 orders of magnitude.

The EM_E/EM_S ratio (Figure 2B) is no greater than 0.2 for $n = 6$, but increases regularly from 3.9 to 49 for n from 7 to 9, and drops to an essentially constant value of ca. 5 for $n = 10$ and 14. Apparently, this is still a manifestation of a medium-ring effect, i.e., a phenomenon that is in some way related to medium-ring strain, suggesting that 7 is less strained than 8 when $n > 6$. But the entropy factor must also be taken into account. Cyclization reactions involve a more or less complete freezing of the internal rotors of the freely rotating chain of the precursor. It has been found[6] that on increasing the chain length, the $\Delta S^{\ddagger}$ values exhibit a drop of some 4 eu per methylene group for chains up to about eight single bonds and a much less pronounced dependence for longer chains. Such an entropy loss of ca. 4 eu corresponds to a reactivity drop of nearly 10 per added methylene group in the shorter chains.

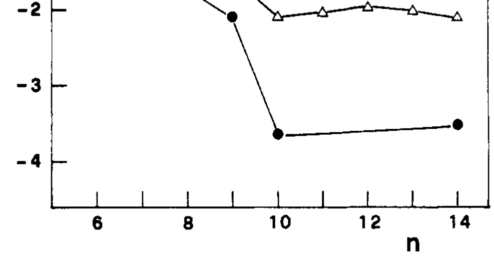

Figure 1. log k_{intra} profiles for competing intramolecular elimination and substitution from o-$^{-}OC_6H_4O(CH_2)_{n-4}Br$ in 99% Me_2SO at 25.0 °C as a function of the size n of the cyclic transition states. The point for the elimination reaction where $n = 6$ is an estimate for the upper reactivity limit.

Reaching 8 from 1 involves freezing of $n - 3$ rotors. The same number of rotors is frozen in 7, namely, $n - 4$ in the ring structure, and 1 in the partially formed exocyclic double bond. But forming a double bond also freezes one rotor in the corresponding intermolecular reaction. As a consequence, the EM_E values are referred to a reaction where one less rotor is frozen with respect to the competing substitution reaction. Thus, on a purely entropic basis, elimination is favored over substitution by a factor of ca. 10 for all n's up to about 12.

On the basis of the above arguments, the advantage of elimination over substitution can be entirely accounted for as an entropy phenomenon for n = 7, 8, and 10 but not

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(4) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.

(5) The size of the cyclic transition states containing hydrogen is sometimes designated by (n + 1/2), where n is the number of heavy atoms. See, for instance: Bell, R. P.; Timimi, B. A. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1518.

(6) Illuminati, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1977**, *99*, 6308.

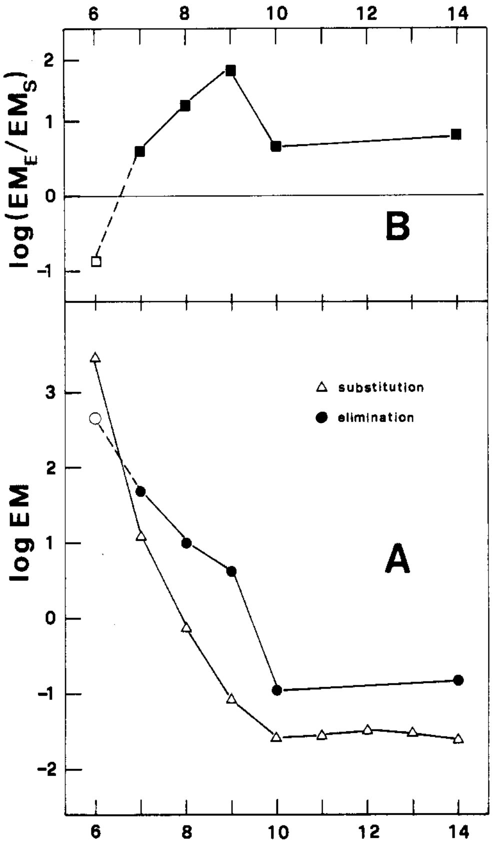

Figure 2. log EM profiles for competing intramolecular elimination and substitution from o-$OC_6H_4O(CH_2)_{n-4}Br$ in 99% Me_2SO at 25.0 °C as a function of the size n of the cyclic transition states (plot A). The point for the elimination reaction where $n = 6$ is an estimate for the upper reactivity limit. Plot B gives the vertical differences between the two profiles.

$n = 9$ and 14. For $n = 9$ the EM_E/EM_S ratio of 49 seems too large to be explained by entropy alone, and for $n = 14$ we believe it unlikely that one less rotor can account for an EM_E/EM_S ratio as large as 5, in view of the substantial insensitiveness of $\Delta S^{\ddagger}$ to chain length in the large-ring region.[4] Thus we tend to conclude that for $n = 9$ and 14, 7 is less strained than 8.

The peculiar steric and geometrical requirements for proton transfer,[7] requiring a linear C···H···O arrangement, may provide an explanation of much of the observed phenomena. Such an arrangement may have more or less stringent requirements, but in any case it is expected to introduce a larger bending strain in the smaller size transition states.[7] On the other hand, a strain relief is presumably brought out by the presence of the hydrogen atom being transferred, which provides a "bare" region in the cyclic structure. It seems reasonable to expect that such a strain relief should be the largest in the most strained medium-sized transition states.

The crossing of the profiles in Figure 2A can be explained on the basis of the above effects, if one assumes that a C···H···O arrangement can hardly be accommodated without severe distortion from linearity in a six-membered ring structure and that a ring size of seven is already large enough to accomodate a bent arrangement of acceptable energy. The more favorable conditions for linearity in the higher homologues coupled with the observation that the eight- and nine-membered transition states for intramolecular substitution are the most strained in the series[6] explain why the advantage of elimination over substitution is largest for $n = 8$ and 9.

Large rings are viewed as essentially strainless, but the presence of weak residual strains in the region of rings of some 15 atoms has been detected.[6,8] That the EM_E is some five times larger than the EM_S when $n = 14$ suggests that incorporation of the C···H···O moiety in a ring structure large enough to permit a linear geometry further reduces the already weak ring strains and explains why the EM_E for $n = 14$ lies at the upper limit of the narrow range of 0.1–0.01 M where EM values for the formation of large rings have been found to cluster.[4,8]

Intramolecular Elimination vs. Intramolecular Acid or Base Catalysis. The present study can be viewed as a systematic investigation of an intramolecular base-catalyzed reaction, where the ring-size range is the widest among all the series investigated so far and where the ring size in the transition state is unequivocally known, because there is no ambiguity deriving from the intervention of bridging solvent molecules which can possibly play a role in hydroxylic solvents. We may now wonder whether the results from the present work are of some relevance to an understanding of intramolecular acid or base catalysis phenomena in general.[9,10]

In accordance with the hypothesis that the entropic advantage of intra- over intermolecular reactions should be low for reactions passing through loose transition states,[11] the low efficiency of internal acid or base catalysts relative to that of internal nucleophiles has been ascribed to the inherent looseness of transition states in acid–base reactions.[9,11]

Without entering the merits of the above hypothesis, we note that much of the supporting evidence is based on EM values of reactions passing through five- and six-membered transition states, i.e., involving ring sizes for which proton transfer is expected to be disfavored on enthalpic grounds. We also note that when larger ring sized transition states are involved, no evidence for a markedly different behavior of the two reaction types is apparent, as shown by the two reaction series compared in this work, and that no entropic handicap shows up in the general behavior of intramolecular proton transfer with respect to intramolecular nucleophilic attack. It might be objected that this is due to a "tight" transition state for proton transfer from carbon, at variance with proton transfer from oxygen or nitrogen, but inspection of EM data from Kirby's review[9] shows that there seems to be no general tendency for intramolecular proton transfer to occur more efficiently from carbon than from oxygen or nitrogen.

We conclude, therefore, that when allowance is made for the different number of internal rotors involved and for the geometrical requirements of proton transfer disfavoring the smaller sized cyclic transition states, an intramolecular base-catalyzed reaction and a nucleophilically assisted intramolecular reaction display much of the same features, irrespective of the supposedly different transition-state looseness.

Experimental Section

Most techniques and apparatuses were previously described.[3d]

Materials. All materials, except those listed below, were reagent-grade commercial samples. Compounds **2**,[3a,12] **3** ($n = 8$

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[7] Gandour, R. D. *Tetrahedron Lett.* **1974**, 295.

[8] Illuminati, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1981**, *103*, 4142.

[9] Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.

[10] Capon, B. In "Proton-Transfer Reactions"; Caldin, E., Gold, V, Eds.; Chapman and Hall: London, UK, 1975.

[11] (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.

and 9)[3a] **5**, (n = 6),[3c] and the parent phenols of compounds **1**[3a,12] and **4**, (n = 6)[3c] were available from previous investigations.

6-Bromo-1-hexene and 10-bromo-1-decene were obtained from 5-hexen-1-ol and 9-decen-1-ol, respectively, and PBr_3, and purified by elution with light petroleum on silica gel; their structures were confirmed by ^1H NMR spectra.

Compounds 3 (n = 7, 10, and 14) were prepared by adding a concentrated KOH solution (3 mmol) to a boiling solution of catechol (15 mmol) and the proper ω-bromo-1-alkene (3.1 mmol) in ethanol. The crude products were eluted with benzene on silica gel. *o*-Hydroxyphenyl 2-propenyl ether (**3**, n = 7) was obtained in 31% yield; *o*-hydroxyphenyl 5-hexenyl ether (**3**, n = 10) in 63% yield; *o*-hydroxyphenyl 9-decenyl ether (**3**, n = 14) in 60% yield.

***o*-Methoxyphenyl decyl ether** was prepared as above from 2-methoxyphenol, 1-bromodecane, and KOH. The compound was purified by microdistillation in vacuo, mp 31–31.5 °C.

The structure of compounds **3** and that of *o*-methoxyphenyl decyl ether was confirmed by ^1H NMR spectra and by elemental analyses (C, H). These were within ±0.3% of theory in all cases except for **3** (n = 10) where C was +0.47%.

Product Analysis. The base–solvent system was as previously reported.[13,14] Yields of elimination products were determined under conditions analogous to those of the kinetic runs.[3d] The calculated amount of KOH stock solution (2×10^{-2} M) was added to the thermostated solution (50 mL) of the substrate(s). After at least 10 half-lives the mixture was diluted with water, extracted with several portions of pentane, and worked up as usual. After careful evaporation of the solvent,the residue was analyzed by GLC on a 1-m column packed with 2% SE-30 plus 0.5% FFAP on silanized Chromosorb W 60–80 and/or a 1-m column packed with 3% Apiezon on silanized Chromosorb W 60–80. *o*-Methoxyphenyl decyl ether was checked to be formed in high yields (95 ± 5%) in the conditions of the kinetic runs.

Kinetic Measurements. The reaction between *o*-methoxyphenoxide ion and 1-bromodecane was followed as prevously described[14] under pseudo-first-order conditions in the presence of a 50-fold excess of 1-bromodecane.

Registry No. **1** (n = 7), 87013-13-6; **1** (n = 8), 87013-14-7; **1** (n = 9), 87039-21-2; **1** (n = 10), 87013-15-8; **1** (n = 14), 87013-16-9; **3** (n = 7), 1126-20-1; **3** (n = 10), 87013-17-0; **3** (n = 4), 87039-22-3; guaiacolate ion, 54976-95-3; 1-bromodecane, 112-29-8; *o*-methoxyphenyl decyl ether, 87013-18-1.

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(12) Mandolini, L.; Masci, B. *J. Org. Chem.* **1977**, *42*, 2840.

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The Four-Membered-Ring Chemical Shift Anomaly

Joseph B. Lambert,*[1a,2] Stephen M. Wharry,[1a] Eric Block,*[1b,c,2] and Ali A. Bazzi[1b]

Departments of Chemistry, Northwestern University, Evanston, Illinois 60201,
University of Missouri—St. Louis, St. Louis, Missouri 63121, and State University of New York at Albany,
Albany, New York 12222

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Anomalously large downfield shifts have been observed for carbon-13 and other nuclei that are α to sulfonyl or carbonyl groups in four-membered rings. These anomalies are signified by deviations in chemical shift plots for four–seven-membered rings of a functionalized or substituted series vs. the parent cyclic hydrocarbons. Plots are nearly linear for the α ^{13}C shifts for all ring sizes of various cyclic hydrocarbons and thioethers. Small deviations are observed for α ^{13}C shifts of the four-membered ethers, amines, sulfoxides, and phosphoramidates. Large deviations, signifying an anomaly, are observed for the α ^{13}C shifts of the four-membered ketones, lactams, lactones (nuclei α to carbonyl), and sulfones. The ^{15}N shifts in the lactams, the endocyclic ^{17}O shifts in the lactones, and the exocyclic ^{17}O shifts in the sulfones also appear to be anomalous for the four-membered rings.

The resonances of carbon atoms that are adjacent to a sulfide group normally are shifted downfield 20–25 ppm on oxidation to either the sulfoxide or the sulfone, as a result of the increased electron-withdrawing power of these latter functional groups. Block and co-workers[3] observed that this pattern holds for open-chain systems and for rings of three–eleven members, with the exceptions of four-membered rings. In thietans, oxidation of the sulfide to the sulfone group causes a 40-ppm downfield shift of the α carbon. The sulfoxide is about 25 ppm downfield from the sulfide. Block found that this anomaly for four-membered rings is quite general: sulfones are shifted unusually far downfield with respect to sulfides and consequently no longer coincide with the homologous sulfoxide resonance.

In order to define the physical basis for the four-membered-sulfone anomaly, we have now examined a much wider range of four-membered rings. We report that the anomaly is found for functionalities other than sulfones and for nuclei other than ^{13}C, but for only the four-membered ring.

Results

Ring size has a significant effect on ^{13}C shieldings within the homologous series of saturated hydrocarbons $(CH_2)_n$ (**1**).[4] The chemical shift (δ) moves monotonically downfield from the three-membered ring (−2.6 ppm) to the four- (23.3 ppm), five- (26.5 ppm), six- (27.8 ppm), and seven-membered ring (29.4 ppm). The very high-field location for the three-membered ring may be attributed to bond and group anisotropies associated with the geometry of the

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[1] (a) Northwestern University. (b) University of Missouri—St. Louis. (c) Present address: State University of New York at Albany.

[2] This work was supported by the National Science Foundation (J.B.L., Grant CHE80-25601; E.B., Grant CHE80-01490) and the donors of the Petroleum Research Fund, administrated by the American Chemical Society (E.B.).

[3] Block, E.; Bazzi, A. A.; Lambert, J. B.; Wharry, S. M.; Andersen, K. K.; Dittmer, D. C.; Patwardhan, B. H.; Smith, D. J. H. *J. Org. Chem.* **1980**, *45*, 4807–4810. Dittmer, D. C.; Patwardhan, B. H.; Barthlomew, J. T. *Org. Magn. Reson.* **1982**, *18*, 82–86.

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