The Effect of Ring Size on Reactivity: The Diagnostic Value of 'Rate Profiles'

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Dedicated to Professor *Rolf Huisgen* on the occasion of his 85th birthday

The rates of cycloalkyl phenyl sulfide formation of a series of homologous bromocycloalkanes upon treatment with sodium benzenethiolate have been determined to ascertain the effect of ring size on reactivity. The 'rate profile', *i.e.*, reaction rate *vs.* ring size, for these nucleophilic substitutions (S_N2) was determined. A linear free-energy relationship could be derived from computed hydride affinities of cycloalkanes and rates of typical S_N1 reactions, whereas rates of S_N2 reactions exhibited a strong discrepancy from the seven- up to the twelve-membered rings. This discrepancy was rationalized by a careful examination of the geometry of the intermediates and transition states involved in these reactions.

1. Introduction. – In the early fifties, *Brown et al.* [1–3] recognized characteristic effects of ring size on the reactivity of a series of model substrates. They suggested to use plots of rates *vs.* ring size, so called 'rate profiles', as tools to diagnose mechanistic details, in particular the geometry of key intermediates or transition states. According to this concept, first- and second-order substitution reactions (S_N1 and S_N2, resp.) should exhibit like ring dependences. As both processes involve a planarized C-atom as a high-energy species, the principal reactivity-controlling factor should be the extra strain ('internal strain' or 'I-strain') caused by the change of a tetragonal to a trigonal C-center.

This simplified view raised objections by *Sicher* [4]. When comparing the rate profiles of two archetypical S_N1 reactions (*Fig. 1a*, *b*) [3][5] with intramolecular (*Fig. 1*,*c*) [6] and intermolecular (*Fig. 1*,*d*) [5] S_N2 displacements, he spotted significant discrepancies in the C_8-C_{15} range.

This comparison was flawed by two experimental shortcomings, however. On one hand, the kinetic work monitored only the consumption of the substrate, but did not rigorously quantify the products formed. Thus, important side reactions may have remained undetected. On the other hand, the juxtaposition was not continued into the area of the smallest rings, cyclobutyl and cyclopropyl derivatives. Such an extension should be especially meaningful if one considers the coincidence of five-, six-, and seven-membered-ring reactivities (*Fig. 1*). We, thus, set out to bridge these gaps and to propose a detailed and comprehensive justification of the measured rate constants.

2. Results. – The benzenethiolate (PhS^-) anion ranks among the most-powerful nucleophiles in protic solvents [7]. Moreover, the reactivity of PhS^- towards bromo- or

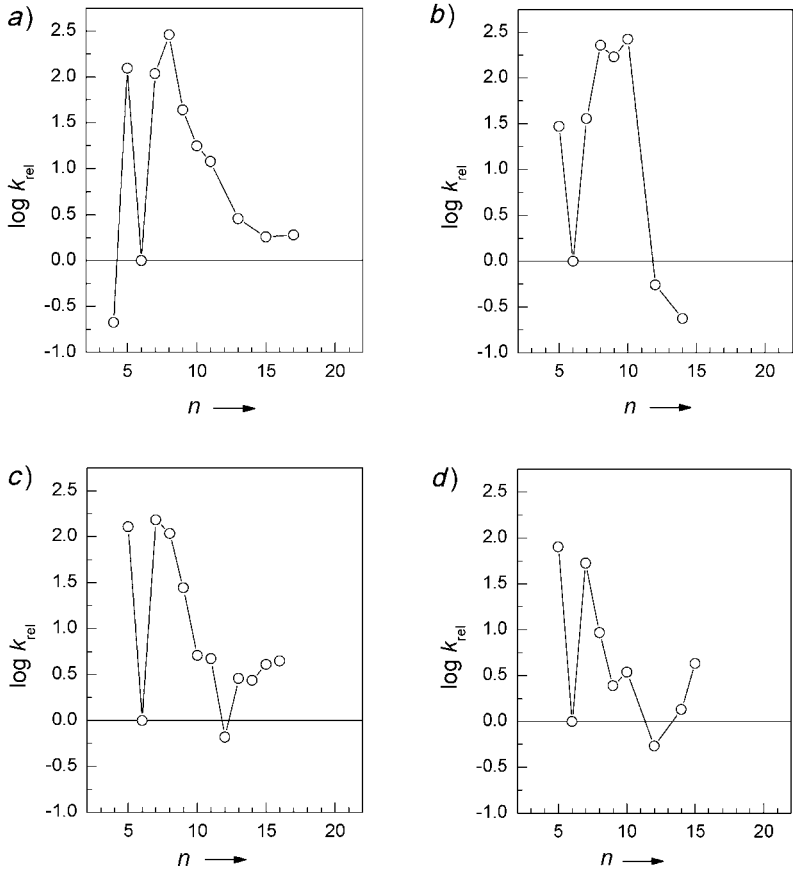


Fig. 1. *Effect of ring size on rates of* a) *solvolysis of 1-chloro-1-methylcycloalkanes in 80% EtOH at 25°,* b) *solvolysis of bromocycloalkanes in 40.9% aqueous 1,4-dioxane at 45°,* c) *base-catalyzed cyclization of* cis-N-*(2-mercaptocycloalkyl)benzamides in 80% EtOH at 30°,* d) *reaction of bromocycloalkanes with KI in acetone at 60°*. All rate profiles are normalized to the six-membered ring (log $k_{rel} = 0.0$).

iodoalkanes is increased by factors ranging from 10^2 to 10^4 when replacing MeOH by polar aprotic solvents like DMF [8]. To perform substitution reactions on cyclopropyl and cyclobutyl substrates in a homogeneous medium, PhSNa was allowed to react in DMF at 0° with the bromocycloalkanes **1b**–**h** and 3-bromopentane (**1i**), the open-chain reference, to the corresponding cycloalkyl phenyl sulfides **2b**–**i** (*Table 1*). As the sole exception, bromocyclopropane (**1a**) required higher temperatures. Absolute rate constants of 5.0×10^{-5}, 1.3×10^{-4}, and 7.7×10^{-4} l mol^{-1} s^{-1} were determined at 95°, 110°, and 142°, respectively. Subsequent rate extrapolation to 0° according to the *Arrhenius* equation gave a rate constant of 1.1×10^{-8} l mol^{-1} s^{-1}. The evolution of the reactions was followed by gas chromatography (GC), which allowed us to determine both the substrate and product concentrations. In this way, bromocyclohexane and -dodecane were found to give rise not only to the corresponding substitution products **2d** and **2h**, but also to cyclohexene due to elimination, and to cyclododecane and

phenyldisulfide formed probably by a single-electron-transfer side reaction. The correspondingly corrected S_N2 rates are numerically compiled in *Table 1*, and graphically presented in *Fig. 2*.

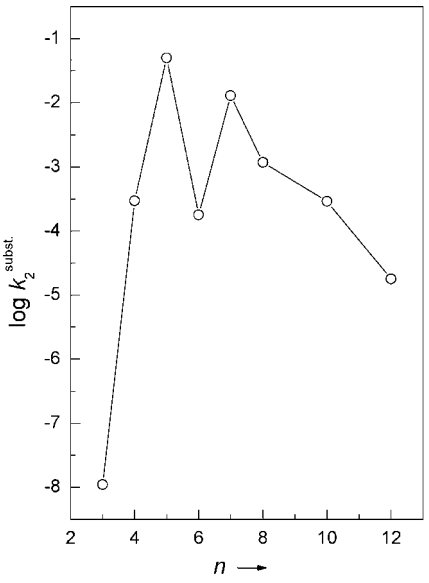
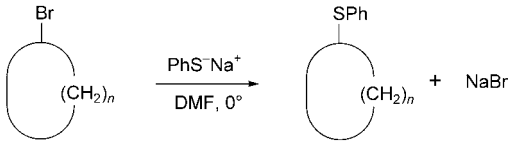


Fig. 2. *Rate profile for the substitution of bromocycloalkanes with PhSNa in DMF at 0°*

Table 1. *Pseudo-First-Order Rate Constants* [l mol^{-1} · s^{-1}] *for the Substitution of Bromocycloalkanes with PhSNa in DMF at 0°*



n [a])	Substrate	Product	$k_2^{subst.}$	log $k_2^{subst.}$
3	**1a**	**2a**	1.1 (± 0.1) · 10^{-8} [b])	– 8.0 (± 0.1)
4	**1b**	**2b**	2.97 (± 0.11) · 10^{-4}	– 3.53 (± 0.02)
5	**1c**	**2c**	4.99 (± 0.09) · 10^{-2}	– 1.30 (± 0.01)
6	**1d**	**2d**	1.76 (± 0.17) · 10^{-4} [c])	– 3.75 (± 0.02)
7	**1e**	**2e**	1.30 (± 0.04) · 10^{-2}	– 1.89 (± 0.01)
8	**1f**	**2f**	1.17 (± 0.04) · 10^{-3}	– 2.93 (± 0.01)
10	**1g**	**2g**	2.90 (± 0.07) · 10^{-4}	– 3.54 (± 0.01)
12	**1h**	**2h**	2.82 (± 0.08) · 10^{-5} [d])	– 4.55 (± 0.01)
∞ [e])	**1i**	**2i**	4.70 (± 0.16) · 10^{-2}	– 1.33 (± 0.02)

[a]) Ring size. [b]) Obtained by extrapolation to 0°. [c]) Cyclohexyl phenyl sulfide and cyclohexene were detected in a 53 : 47 ratio; $k_2^{subst.}$ was, thus, corrected by a factor of 0.53. [d]) Cyclododecyl phenyl sulfide and cyclododecane were detected in a 70 : 30 ratio. Phenyldisulfide was also present in 16% yield; $k_2^{subst.}$ was corrected by a factor of 0.70. [e]) 3-Bromopentane as open-chain reference compound.

3. Discussion. – 3.1. *General Considerations.* Before we can undertake an in-depth analysis of rate profiles, we have to return to the starting point. According to *Brown et al.* [1–3], the change in ring strain, when going from a tetragonal substrate to a trigonal intermediate or transition state, should be the dominant factor dictating the substitution rate of a cyclic compound in comparison with an acyclic analog. If this is true, S_N1 and S_N2 rate profiles should merely reflect the hydride affinities of cycloalkylcarbenium ions (*i.e.*, the $C^+ \cdots H^-$ heterolytic dissociation energies of cycloalkanes). Such thermodynamic quantities, though readily available for bicyclic structures [9][10], have never been established systematically for cycloalkanes [11][12]. This obligated us to calculate these hydride affinities using *ab initio* methods (see *Exper. Part*). The fundamental assumption that these data correlate linearly with the free activation energies (or simply log k_{rel}) of S_N1 solvolysis rates seemed plausible, but had never been validated. Our results confirm, except for the six-membered ring, the expectations. Contrarily, when one tries to correlate the S_N2 rate constants with the hydride affinities, from the five-membered ring on, no correlation can be observed (*Fig. 3*).

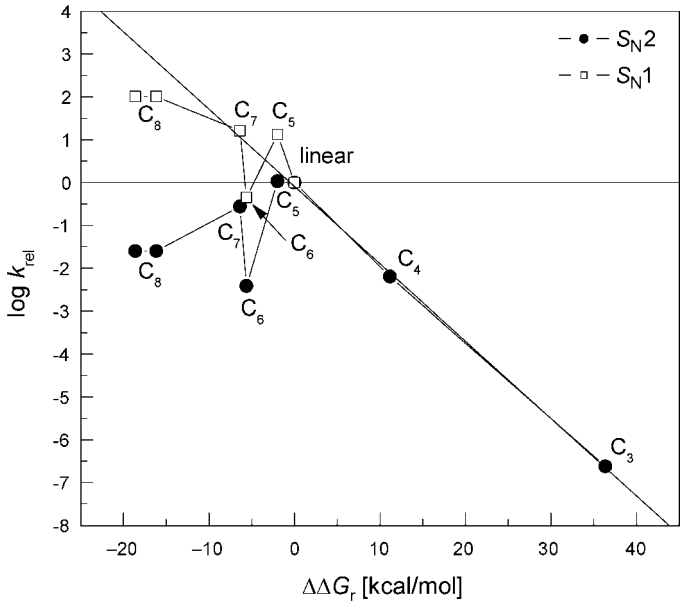


Fig. 3. *Relationship between* S_N1 *and* S_N2 *relative rate constants* (k_{rel}) *and hydride affinities* ($\Delta\Delta G_r$) *of the corresponding alkanes relative to the open-chain compound* (see text and *Table 3*).

In *Fig. 4*, a series of rate profiles are reproduced in which the ones previously shown (*Figs. 1,a–d* and *2*, now *Figs. 4a–e*, resp.) appear again. This time, however, they are all strictly normalized by choosing the open-chain analog as the reference ($k_{rel} = 1.0$). The newly supplemented 'rate profiles' feature the S_N1/S_N2 borderline solvolysis of cycloalkyl 4-methylbenzenesulfonates (*Fig. 4,f*) [2], the base-promoted dehydrobromination of bromocycloalkanes restricted to the formation of (*Z*)-cycloalkenes

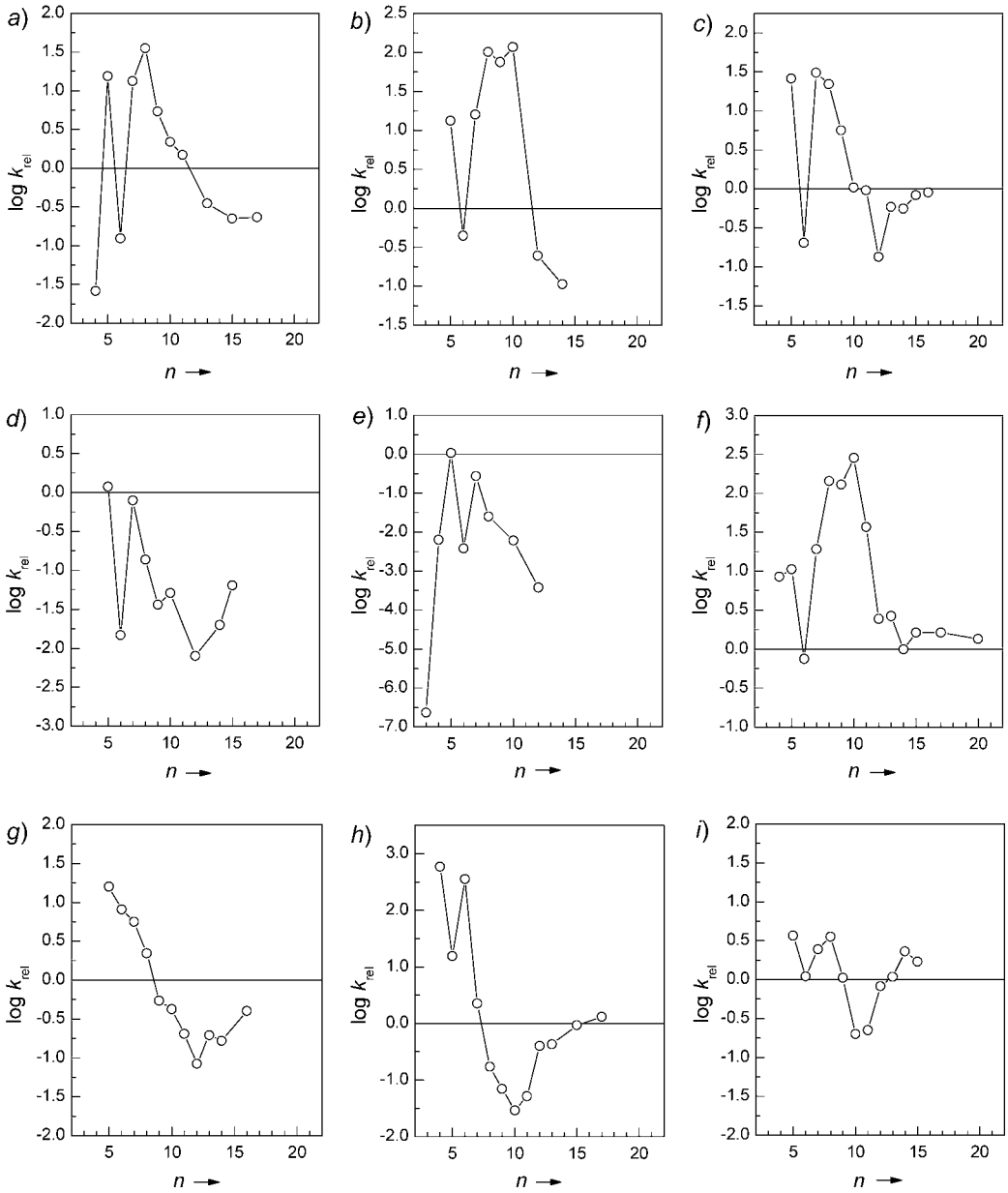


Fig. 4. *Effect of ring size on rates of* a) *solvolysis of 1-chloro-1-methylcycloalkanes in 80% EtOH at 25°*, b) *solvolysis of bromocycloalkanes in 40.9% aqueous 1,4-dioxane at 45°*, c) *base-catalyzed cyclization of* cis-N-*(2-mercaptocycloalkyl)benzamides in 80% EtOH at 30°*, d) *substitution of bromocycloalkanes with KI in acetone at 60°*, e) *substitution of bromocycloalkanes with PhSNa in DMF at 0°* (this work), f) *acetolysis of cycloalkyl 4-methylbenzenesulfonates at 70°*, g) *formation of (Z)-cycloalkenes with* ^{t}*BuOLi in DMF at 40°*, h) *reduction of cycloalkanones with* $NaBH_4$ *in i-PrOH at 0°, and* i) *quaternarization of* N-*methylazacycloalkanes with MeI in MeOH.* All rate profiles are normalized to the open-chain analog (log $k_{rel} = 0.0$).

(*Fig. 4,g*) [13], the reduction of cycloalkanones with $NaBH_4$ (*Fig. 4,h*) [14], and the quaternarization of *N*-methylazacycloalkanes with MeI in MeOH (*Fig. 4,i*) [15].

The comparison of these transformations shows that each reaction type has its typical rate profile, which can be taken as a 'fingerprint' to determine the reaction mechanism. As noticed before, when one compares the rate profile of an S_N1 reaction (*Fig. 4,b*) with that of an S_N2 reaction (*Fig. 4,e*), the two profiles differ clearly, indicating that different effects have to be considered. For S_N1 as well as S_N2 reactions, the reaction center planarizes at the transition state, which widens the bond angles to roughly 120°. *Sicher* called this the '*coplanarity effect*' [4]. In addition, a second steric effect must be considered for S_N2 reactions, *i.e.*, that the entering and leaving groups tend to be collinear (the so-called '*collinearity effect*'), as depicted in *Fig. 5* [4]. An S_N2 reaction can, thus, be treated as an S_N1 reaction plus the collinearity effect.

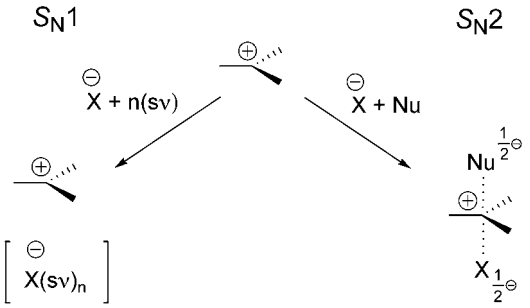


Fig. 5. *Coplanarity and collinearity – at the root of* S_N1 *and* S_N2 *mechanisms*

3.2. *Small Rings.* A very good correlation of the calculated hydride affinities and the S_N2 rates can be observed for the open-chain reference compound down to the four- and three-membered rings (see *Fig. 3*). As the hydride affinity concern only the stability of the alkane and its corresponding carbocation, the collinearity effect is assumed to have no influence on the reactivity of small rings. Although X-ray and gas-phase electron diffractions are useful tools to determine the geometry of cycloalkanes from cyclopropane to higher ring sizes [16][17], data concerning their respective carbocations remain unavailable. Therefore, the bond angles of cycloalkanes and of their corresponding carbocations were determined using *ab initio* methods (Table 2).

The important *Baeyer* strains of three- and four-membered rings imply a drastic increase in energy for the formation of the carbocationic intermediate compared to the open-chain reference, which rationalizes their low reactivity. These mechanisms can be related to the amine inversion of Me_3N as a reference, compared to those of methylaziridine and methylazetidine. The inversion of methylaziridine (17 kcal/mol) [18] and methylazetidine (10 kcal/mol) [18] is far slower than that of Me_3N (4.3 kcal/mol) [19], due to the higher activation energy for the planar transition state.

3.3. *Medium Rings.* For clarity, both S_N1 and S_N2 rate profiles, as well as the differences between them, are depicted in *Fig. 6*. The coplanarity effect (common to both mechanisms) can, thus, be separated from the collinearity effect (specific to S_N2 reactions). *Fig. 6* shows that the alignment of the nucleophile, the reaction center, and the leaving group, from the five- to the ten-membered rings, becomes more and more

Table 2. *Bond Angles* [°] *of Cycloalkanes and Their Corresponding Carbocationic Intermediates* (H–C$^+$–C angle)

n[a])	Alkane	Carbocation	Δ[b])
3	117.9	147.5	22
4	110.8/118.1[c])	132.3	6.7–14
5	109.3–112.9[d])	123.7	3.3–6.9
6	109.0/110.2[c])	118.4	0.7–1.9
∞ [e])	109.0	116.5	0.0

[a]) Ring size. [b]) Deformation [°] relative to the open-chain compound. [c]) The left value corresponds to an axial H-atom, the right one to an equatorial one. [d]) Depends on which H- and C-atoms are considered. [e]) Pentane as open-chain reference; the most-stable conformation of the pent-3-ylium cation mentioned here corresponds to a double W-shape.

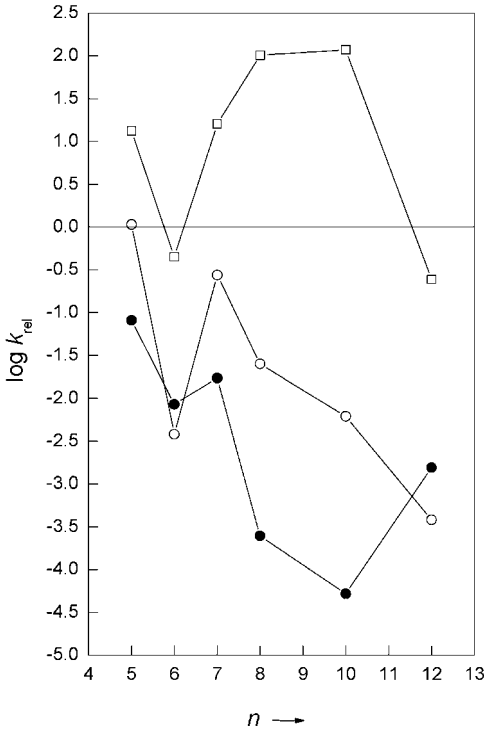


Fig. 6. *Solvolysis of bromocycloalkanes in 40.9% aqueous 1,4-dioxane following an* S_N1 *pathway* (□), *and substitution of bromocycloalkanes by PhSNa in DMF* (this work) *following an* S_N2 *pathway* (○). The collinearity effect is represented by filled circles (●).

difficult. Furthermore, from the seven-membered to the ten-membered ring derivatives on, the rate-enhancing influence of the coplanarity effect no longer dominates the situation, whereas the opposite collinearity effect operates strongly.

For a S_N1 reaction, the rate profile can be explained by *Brown*'s *I*-strain effect. Ejection of bromide from medium-sized bromocycloalkanes leads to a decrease in overlapping of substituents or transannular interactions. Compared to the open-chain reference, this results in a higher reaction rate for solvolysis, and fits with the decrease

in hydride affinities (see *Fig. 3*). For macrocycles ($n > 12$), their structures tend to look like those of linear secondary bromoalkanes, having almost no ring strain, and the reaction rates are slow (see *Fig. 4,f*).

An important anomaly appears for the six-membered ring. The calculated hydride affinities predict that bromocyclohexane should react faster than the open-chain reference 3-bromopentane (see *Fig. 3*). Contrary, the experimentally obtained rate profiles reveal a clear rate minimum for the six-membered ring derivative for S_N1 solvolysis, as well as S_N2 substitution reactions (see *Figs. 4,a–f*). *Sicher* [4] rationalized this rate minimum with the energetically unfavorable formation of the carbocationic intermediate. Since cyclohexyl halides or cyclohexane are almost perfectly staggered and strain-free, ejection of halide or hydride would destabilize the carbocationic intermediate due to the ecliptic positions of the H-atoms around the reaction center (*Fig. 7*). This explanation and the experimental results for the six-membered ring are in contradiction with the calculated hydride affinities.

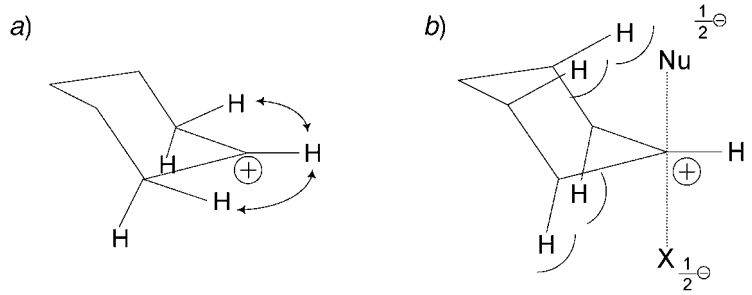


Fig. 7. *The cyclohexyl carbocation. a*) S_N1 Intermediate, *b*) S_N2 transition state.

cis-4-*tert*-Butyl-1-bromocyclohexane (Br-atom in an axial position) reacts with PhSNa 58-times faster than its thermodynamically more-stable *trans* isomer (Br-atom in equatorial position) [20]. However, as bromocyclohexane reacts only four times slower than *cis*-1-bromo-4-(*tert*-butyl)cyclohexane, the axial/equatorial equilibration in the former cannot justify the poor reactivity towards nucleophilic substitution compared to the open-chain analog. Until now, we have no rationale for the discrepancy between the calculated hydride affinities (if one does not consider a wrong computational prediction) and the rate constants of S_N1 and S_N2 reactions for cyclohexyl derivatives.

Due to the high number of possible reactive conformations of bromocyclooctane, it would be meaningless to compare experimental S_N1 rates with computed hydride affinities.

If one considers now S_N2 reactivities and the difference between S_N1 and S_N2 rate profiles, as illustrated in *Fig. 6*, the collinearity effect varies along the sequence $C_5 < C_6 \cong C_7 < C_{12} < C_8 < C_{10}$. The cyclopentyl carbocation has a reaction center that is not at all masked by the ring substituents. The incoming nucleophile, the reaction center, and the leaving Br^- can be easily aligned. On the other hand, the bromocyclohexane–PhS^- transition state does not allow such correct alignment, due to the axial H-atoms in positions 2, 3, 5, and 6 (see *Fig. 7*).

At first glance, increased ring size in the medium-sized rings would lead to a decreased steric hindrance at the reaction center. A more-careful analysis shows that the problem is more complex, and leads to the opposite conclusion. The attack of the nucleophile at bromocyclooctane is hindered by the H-atoms in positions 2, 3, 7, and 8 of the chair/chair and chair/boat structures, similarly to the six-membered ring. In addition, hindrance due to the H-atoms in positions 4 and 6 of the boat/chair conformer, and in position 5 of the boat/boat structure strongly affects the collinearity effect (*Fig. 8*). Such transannular interactions culminate at the ten-membered ring, and then start to vanish from the twelve-membered ring to the open-chain compound (see *Fig. 6*).

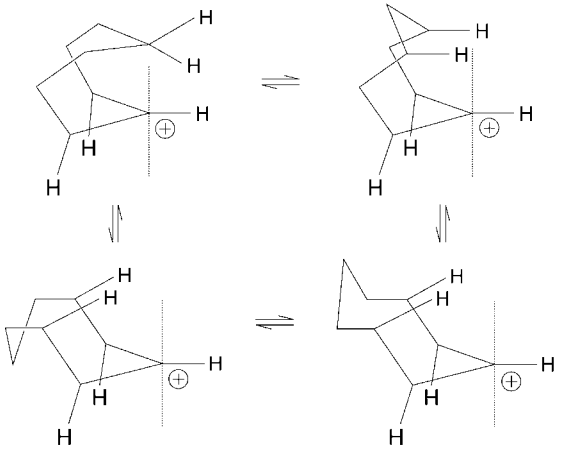


Fig. 8. *Conformers of the cyclooctyl carbocation*

Of course, changes in reactivity are a sum of various effects. But, in a simplified way, the S_N1 and S_N2 rate profiles can be rationalized by three effects: the angular distortion, which is peculiar to small rings, the decrease in overlapping and transannular effects between the ground state and the transition state of medium-sized rings, and the collinearity effect, important only for medium-sized rings.

4. Conclusions. – The present study was didactically motivated. The influence of a given ring size on chemical reactivity was observed more than 40 years ago, when data on reactivity of ring compounds began to accumulate. We intended to draw attention to the so-called 'rate profile' approach as one of the rare tools to probe the geometry of transition states. Therefore, various rate profiles were presented as 'fingerprints' for different reaction mechanisms. Our experimental data are meant to bridge the present gaps dealing with the rate profiles for the important class of S_N2 displacements and substitutions to small rings. High-level *ab initio* calculations provided hydride affinities for three- to eight-membered cycloalkanes. These correlate well, except for the cyclohexyl carbocation, with the experimentally determined S_N1 solvolysis rates. While the three- to seven-membered rings exhibit common behavior in both S_N1 and S_N2 profiles, measuring rate constants of eight- to twelve-membered cycloalkyl derivatives, and comparing them with an open-chain-analog rate, is a crucial and flexible test to

locate a given reaction in the S_N1-S_N2 continuum, halogen substitution by PhS^- being considered an extreme S_N2-type process.

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Experimental Part

General. For laboratory routine and abbreviations, see recent publications from this laboratory [21–23]. Compounds **1a–f** and **1i** are commercially available. Cycloalkyl phenyl sulfides **2a–f** and **2i** have been reported in the literature, but were insufficiently characterized. Compounds **2g** and **2h** have never been described. Therefore, complete and optimized working procedures, as well as ample evidence for identity and purity, are presented below for compounds **2a–i**.

Bromocyclodecane (**1g**). A slow stream of HBr was passed for 2 h through a soln. of (*Z*)-cyclodecene (14 g, 0.10 mol) in CH_2Cl_2 (0.20 l) at 25°. A 1.0M aq. soln. (0.20 l) of NaOH was added, and the product was extracted with pentane (5 × 0.20 l). The org. layers were dried (Na_2SO_4) and evaporated, and the residue was distilled to afford a colorless oil (12 g, 55%). B.p. 84–85°/4 Torr (lit. b.p. 128°/14 Torr [24]). $n_D^{20} = 1.5132$ (lit. $n_D^{20} = 1.5134$ [5]. $d_D^{20} = 1.212$. ^{1}H-NMR: 4.26 (sym. *m*, 1 H); 2.0 (*m*, 4 H); 1.4 (br. *m*, 15 H).

Bromocyclododecane (**1h**). During 1 h, PBr_3 (54 g, 0.20 mol) was added dropwise to molten cyclododecanol (74 g, 0.40 mol) at 100°, maintaining the temperature below 130°. The reaction mixture was poured onto crushed ice (0.20 kg) and extracted with Et_2O (4 × 0.30 l). The combined org. layers were washed with a sat. aq. soln. of $NaHCO_3$ (0.20 l), and dried (Na_2SO_4). After evaporation of the solvents, distillation afforded a colorless oil (34 g, 34%). B.p. 108–109°/3 Torr (lit. b.p. 111–112°/3 Torr [25]). $n_D^{20} = 1.5094$ (lit. $n_D^{20} = 1.5097$ [25]). $d_D^{20} = 1.164$. ^{1}H-NMR: 4.26 (sym. *m*, 1 H); 2.1 (*m*, 2 H); 1.9 (*m*, 2 H); 1.4 (br. *m*, 15 H).

Cyclopropyl Phenyl Sulfide (**2a**). PhSNa (20 g, 0.15 mol) and **1a** (6.0 g, 50 mmol) were heated for 20 h at 100° in DMF (50 ml). Then, H_2O (0.20 l) was added, and the mixture was extracted with pentane (4 × 0.20 l). The combined org. layers were washed with H_2O (0.20 l), dried (Na_2SO_4), and evaporated. Distillation afforded a colorless oil (4.8 g, 64%). B.p. 70–72°/3 Torr (lit. b.p. 62–63°/1 Torr [26]. $n_D^{20} = 1.5817$ (lit. $n_D^{20} = 1.5801$ [26]). d_D^{20} 1.052. ^{1}H-NMR: 7.37 (*d*, *J* = 7.3, 2 H); 7.28 (*tm*, *J* = 7.6, 2 H); 7.13 (*t*, *J* = 7.5, 1 H); 2.19 (sym. *m*, 1 H); 1.1 (*m*, 2 H); 0.7 (*m*, 2 H). Anal. calc. for $C_9H_{10}S$ (150.24): C 71.95, H 6.71; found: C 72.19, H 6.87.

Cyclobutyl Phenyl Sulfide (**2b**). Analogously from bromocyclobutane (**1b**; 6.8 g, 50 mmol) for 2 h at 25°: 5.2 g (63%). Colorless oil. B.p. 82–84°/3 Torr (lit. b.p. 67.5–68°/1 Torr [27]. $n_D^{20} = 1.5787$. $d_4^{20} = 1.039$. ^{1}H-NMR: 7.3 (*m*, 4 H); 7.2 (*m*, 1 H); 3.89 (*qt*, *J* = 7.8, 1 H); 2.5 (*m*, 2 H); 2.0 (*m*, 4 H). Anal. calc. for $C_{10}H_{12}S$ (164.27): C 73.11, H 7.36; found: C 72.93, H 7.25.

Cyclopentyl Phenyl Sulfide (**2c**). Analogously from bromocyclopentane (**1c**; 7.5 g, 50 mmol) for 2 h at 25°: 4.5 g (51%). Colorless oil. B.p. 89–91°/2 Torr (lit. b.p. 97–99°/2 Torr [26]). $n_D^{20} = 1.5740$ (lit. $n_D^{20} = 1.5734$ [28]). $d_4^{20} = 1.040$. ^{1}H-NMR: 7.36 (*dm*, *J* = 7.3, 2 H); 7.28 (*tm*, *J* = 7.5, 2 H); 7.18 (*tm*, *J* = 7.5, 1 H); 3.60 (*m*, 1 H); 2.1 (*m*, 2 H); 1.8 (*m*, 2 H); 1.6 (*m*, 4 H). Anal. calc. for $C_{11}H_{14}S$ (178.30): C 74.10, H 7.91; found: C 73.96, H 7.85.

Cyclohexyl Phenyl Sulfide (**2d**). Analogously from bromocyclohexane (**1d**; 8.2 g, 50 mmol) for 2 h at 100°: 5.5 g (57%). Colorless oil. B.p. 97–99°/2 Torr (lit. b.p. 160–165°/17 Torr [29]). M.p. −7 to −4°. $n_D^{20} = 1.5718$ (lit. $n_D^{20} = 1.5683$ [28]). $d_4^{20} = 1.037$. ^{1}H-NMR: 7.40 (*dm*, *J* = 7.3, 2 H); 7.28 (*tm*, *J* = 7.3, 2 H); 7.21 (*tm*, *J* = 7.3, 1 H); 3.1 (*m*, 1 H); 2.0 (*m*, 2 H); 1.8 (*m*, 2 H); 1.6 (*m*, 1 H); 1.3 (*m*, 5 H). Anal. calc. for $C_{12}H_{16}S$ (192.32): C 74.94, H 8.38; found: C 74.73, H 7.97.

Cycloheptyl Phenyl Sulfide (**2e**). Analogously from bromocycloheptane (**1e**; 8.9 g, 50 mmol) for 2 h at 25°: 5.8 g (56%). Colorless oil. B.p. 125–128°/4 Torr (lit. b.p. 179–181°/17 Torr [29]). $n_D^{20} = 1.5705$. $d_4^{20} = 1.037$. ^{1}H-NMR: 7.37 (*dm*, *J* = 7.5, 2 H); 7.28 (*tm*, *J* = 7.3, 2 H); 7.19 (*tm*, *J* = 7.3, 1 H); 3.3 (*m*, 1 H); 2.0 (*m*, 2 H); 1.7 (*m*, 2 H); 1.6 (*m*, 6 H); 1.5 (*m*, 2 H). Anal. calc. for $C_{13}H_{18}S$ (206.35): C 75.67, H 8.79; found: C 75.50, H 8.71.

Cyclooctyl Phenyl Sulfide (**2f**). Analogously from bromocyclooctane (**1f**; 9.6 g, 50 mmol) for 2 h at 100°: 6.9 g (63%). Colorless oil. B.p. 132–135°/4 Torr (lit. b.p. 185°/13 Torr [30]). $n_D^{20} = 1.5736$ (lit. $n_D^{20} = 1.5846$). $d_4^{20} = 1.038$. ^{1}H-NMR: 7.38 (*dm*, *J* = 7.3, 2 H); 7.28 (*tm*, *J* = 7.3, 2 H); 7.20 (*tm*, *J* = 7.3, 1 H); 3.4 (*m*, 1 H); 2.0 (*m*, 2 H); 1.6 (br. *m*, 12 H). Anal. calc. for $C_{14}H_{20}S$ (220.38): C 76.30, H 9.15; found: C 76.22, H 8.84.

Cyclodecyl Phenyl Sulfide (**2g**). Analogously from bromocyclodecane (**1g**; 5.5 g, 25 mmol) for 2 h at 100°: 5.0 g (81%). Colorless oil. B.p. 148–151°/4 Torr. $n_D^{20} = 1.5652$. $d_4^{20} = 1.020$. ^{1}H-NMR: 7.39 (*d*, *J* = 8.1, 2 H); 7.28 (*tm*, *J* = 7.5, 2 H); 7.20 (*tm*, *J* = 7.5, 1 H); 3.47 (*qt*, *J* = 6.2, 1 H); 1.6 (br. *m*, 18 H). ^{13}C-NMR: 136.1; 131.4 (2 C);

128.8 (2 C); 126.4 (2 C); 46.3; 30.8; 25.3; 25.1; 24.6 (2 C); 23.6 (2 C). Anal. calc. for $C_{16}H_{24}S$ (248.43): C 77.35, H 9.74; found: C 77.27, H 9.69.

Cyclododecyl Phenyl Sulfide (**2h**). Under an inert gas atmosphere and in the dark, PhSNa (9.9 g, 75 mmol) was dissolved in DMF (50 ml) at 100°. 18-Crown-6 (20 g, 75 mmol) and **1h** (6.2 g, 25 mmol) were added. After 1 h, the mixture was allowed to cool down, and H_2O (0.20 l) was added. The product was extracted with pentane (4×0.20 l), the combined org. layers were washed with H_2O (0.20 l), dried (Na_2SO_4), and evaporated. To destroy traces of phenyldisulfide, the residue was dissolved in EtOH (50 ml) and treated with $NaBH_4$ (0.95 g, 25 mmol). After 1 h, the mixture was poured into H_2O (0.20 l), and extracted with pentane (4×0.20 l). The combined org. layers were dried (Na_2SO_4) and evaporated. The product was obtained upon crystallization from hexane/AcOEt 1:1. Colorless needles. M.p. 38–39°. ^{1}H-NMR: 7.35 (*d*, *J* = 7.0, 2 H); 7.29 (*tm*, *J* = 7.5, 2 H); 7.22 (*t*, *J* = 7.5, 1 H); 3.3 (*m*, 1 H); 1.6 (br. *m*, 22 H). ^{13}C-NMR: 136.0; 131.2; 128.7 (2 C); 126.3 (2 C); 44.7; 29.9; 24.1 (2 C); 23.7 (2 C); 23.4 (2 C); 23.3 (2 C); 22.1 (2 C). Anal. calc. for $C_{18}H_{28}S$ (276.19): C 78.20, H 10.21; found: C 78.28, H 10.08.

1-Ethylpropyl Phenyl Sulfide (**2i**). Analogously, as described for **2c**, from 3-bromopentane (**1i**; 7.6 g, 50 mmol). Colorless oil. B.p. 80–81°/3 Torr (lit. b.p. 125–128°/15 Torr [31]). $n_D^{20} = 1.5386$ (lit. $n_D^{20} = 1.5385$ [32]). ^{1}H-NMR: 7.39 (*dm*, *J* = 7.0, 2 H); 7.27 (*tm*, *J* = 7.3, 2 H); 7.20 (*tm*, *J* = 7.3, 1 H); 2.99 (*qt*, *J* = 6.2, 1 H); 1.6 (*m*, 4 H); 1.0 (*t*, *J* = 7.3, 6 H). Anal. calc. for $C_{11}H_{16}S$ (180.31): C 73.27, H 8.94; found: C 73.49, H 8.92.

General Kinetics Procedure. PhSNa (2.61 g, 19.7 mmol) was dissolved in DMF (100 ml). The soln. was cooled to 0° in an ice/H_2O (dist.) bath. Under vigorous stirring, a mixture of **1b**–**i** (1.00–1.12 mmol) and tridecane (approx. 0.10 g, serving as 'internal standard', *i.e.*, inert reference compound for quantification) were added. Samples (1.0 ml) were withdrawn in intervals, poured into a mixture of H_2O (15 ml) and pentane (3.0 ml). The org. layer was separated, dried (Na_2SO_4), and repeatedly injected into two GC columns of different polarity. The concentrations of substrate and product were determined by comparison of their peak areas with that of the internal standard, unequal detector sensitivities for the various compounds being corrected by calibration factors.

Evaluation of Rate Constants. The rate constants *k* of the reaction of bromocycloalkanes in the presence of a large excess of PhSNa were calculated according to pseudo-first-order reaction kinetics from the relationship $k = -1/(t \cdot [\mathrm{Nu}]) \cdot \ln([\mathrm{S}]/[\mathrm{S}]_0)$, where [Nu] is the concentration of the nucleophile (PhS^-), which can be considered as constant, and where [S] and $[S]_0$ are the concentrations of the substrates at times *t* and t_0, resp. The initial concentration $[S]_0$ was known by weighing in. The amounts of unconsumed substrate [S] were directly determined by GC using an internal standard for calibration. The absolute rate constants *k* were obtained by plotting $1/[\mathrm{Nu}] \cdot \ln([\mathrm{S}]/[\mathrm{S}]_0)$ *vs. t*, and by determining the slope of the best straight line through the measured points, as calculated by the method of least squares. As a control, it was also indirectly determined by subtraction

Table 3. *Total Energies* (MP2/6-311G), *Zero-Point Vibrational Energies* (ZPE), *Total Entropy Values* (*S*) *for Cycloalkanes and Cycloalkyl Carbocations* (most-stable conformers), *and Absolute* (ΔG_r) *and Relative* ($\Delta\Delta G_r$) *Hydride Affinities*

n	Alkane			Carbocation			ΔG_r[c])[e])	$\Delta\Delta G_r$[c])[f])
	6-311G[b])	ZPE[c])	*S*[d])	6-311G[b])	ZPE[c])	*S*[e])		
3	– 117.32	46.4	59.4	– 116.36	36.7	59.1	291.1	36.4
4	– 156.45	62.6	64.6	– 155.52	53.2	63.8	265.9	11.2
5	– 195.60	79.1	67.8	– 194.70	70.6	70.7	252.7	– 2.0
6[g])	– 234.74	95.5	74.6	– 233.84	88.1	76.3	249.1	– 5.6
7	– 273.85	111.9	81.0	– 272.96	104.5	79.9	248.3	– 6.4
8[h])	– 312.86	129.2	86.1	– 311.98	121.7	84.7	238.5	– 16.2
8[i])	– 312.97	127.5	80.9	– 312.09	120.8	79.4	236.1	– 18.6
∞[j])	– 196.78	90.3	81.5	– 195.88	83.0	79.5	254.7	0.0

[a]) Ring size. [b]) In hartrees. [c]) In kcal mol^{-1}. [d]) In cal mol^{-1} K^{-1}. [e]) The MP2/6-311G energy of the hydride anion is – 0.47616 hartree, and its entropy is 25.6 cal mol^{-1} K^{-1}. [f]) Relative to pentane and 3-pentyl carbocation. [g]) Chair conformation. [h]) Chair/chair conformation; values obtained with MP2/6-31G. [i]) Values obtained with MP2/6-311G; the most-stable structure for the carbocation is a μ-hydrido form according to this basis set. [j]) Pentane; the pent-3-ylium cation has a double W-shape.

of the amount of product, applying the relationship $[S]/[S]_0 = 1 - ([P]/[S]_0)$, where [P] is the concentration of cycloalkyl phenyl sulfide at time *t*. Two sets of measurements were performed for each substrate.

Computational Methods. Geometries of cycloalkanes and their corresponding carbocations were fully optimized at the *Møller–Plesset* level of theory [33–36] using the 6-311G basis set (*Table 3*). Computations were carried out with the program GAMESS [37]. The temperature was corrected to 273.15 K, and zero-point energies were multiplied by the empirical factor of 0.89 [38].

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