Quantitative Evaluation of Steric Effects in S_N2 Ring Closure Reactions

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Abstract: Rates of cyclization vary markedly with ring size; five-membered rings and six-membered rings close rapidly while formation of four-membered rings and of seven-membered rings is very much slower and is in competition with polymerization. The presence of alkyl substituents usually causes a large enhancement of the rate of cyclization; this is the "*gem*-dialkyl" effect. It is generally agreed that these rates are controlled by steric effects, but quantitative treatments have not been successful. The plausible idea of relating rates to free energies of formal ring closure of alkanes fails for rings having four to seven members: product rings are not always suitable models of the transition states for these rings. In the present study we have used a different theoretical approach to predict rates of S_N2 ring closure of bromoalkylamines, $Br(CH_2)_{n-1}NH_2$. We have treated the unsubstituted series with $n = 4$–7 and the variously dialkylated derivatives for $n = 5$. Experimentally the rates cover a range of nearly 10^9, and our calculated rate constants agree with those observed within a factor of 2. These results are surprisingly good, but there are close parallels in the successes of similar theoretical treatments of steric effects in other reaction series. We estimate enthalpies of activation by molecular mechanics; the model of the S_N2 transition state is a trigonal bypyramid whose somewhat distorted geometry is defined in individual detail by the force field. For a given bromoalkylamine the entropy of activation of ring closure has been assumed to be equal to the entropy of formal ring closure of the analogous alkane. The validity of the entropy assignments is greatly enhanced by the regularities we have found through a detailed analysis of the entropies of formation of alkanes, of cycloalkanes, and of their mono- and dimethyl derivatives. There is no simple way to summarize the idiosyncratic contributions of individual structures to the enthalpies and entropies of activation in the S_N2 ring closures. It is possible to state, however, that most earlier postulates have greatly overestimated the importance of entropic effects. As between intermolecular reactions and closure of a four-membered ring the entropic effect $T\Delta\Delta S^{\ddagger}$ amounts to about 7 kcal/mol, a highly significant factor. But the difference in $T\Delta\Delta S^{\ddagger}$ between closing a four-membered ring and closing a five-membered ring is only 0.9 kcal/mol, a rate factor of 4 in favor of the smaller ring, while the $\Delta\Delta H^{\ddagger}$ difference is 10.6 kcal/mol in the opposite direction. The striking *gem*-dialkyl effects treated in the present study span a range of rates of 10^6, and they are almost entirely enthalpic in origin. We present a modern update of the popular Ruzicka hypothesis of ring closure for simple rings having from 4 to 15 atoms.

Ring closure to form five-membered rings and six-membered rings is highly favored over competing intermolecular reactions such as polymerization and is usually favored over formation of rings of other sizes. The classical explanation due to Ruzicka views this situation as the resultant of two competing factors: an unfavorable strain energy that hinders formation of small rings, which strain becomes negligible for five- and six-membered rings, while the probability of ends meeting is most favorable for closing three-membered rings and progressively diminishes throughout the homologous series as the ring size becomes larger.[1,2] A number of reviews summarize the available experimental data and the attempted theoretical interpretations.[3–7]

Other structural factors lead to further enhancements of rates of cyclization. A well-known example is alkyl substitution; the result rate acceleration is called the "*gem*-dialkyl effect" or the Thorpe–Ingold effect.[2c–g] With appropriate molecular design acceleration can attain spectacular levels as in the Koshland examples of bicyclic lactones[8] or in the Cohen examples of alkylated *o*-hydroxyhydrocinnamic acids.[9]

Organic chemists tend to think in terms of reaction paths using such phraseology as "approach to the less hindered side" or "probability of ends meeting". There is a temptation to invent new terms such as "orbital steering"[8] or "stereopopulation control"[9] which are based on the idea of especially constrained reaction paths, an entropic effect. For quantitative treatment it is obviously sufficient to evaluate free energies of just two states, the reactant state and the proposed model of the transition state. In fact it is more precise to use the Eyring transition state model than the reaction path model even for qualitative discussion.

Quantitative theoretical treatments of cyclization reactions are in a preliminary stage. The Koshland bicyclic lactone formation has been treated in terms of hydrocarbon surrogates for the hydroxy acid, for the lactone, and for the tetrahedral intermediate.[10] Molecular-mechanics computations gave the relative enthalpies, and it was shown that most of the "orbital steering" effect is due to steric crowding in the ground state, an enthalpic effect. This study can profitably be extended using more realistic models, though other work has shown that the rather crude hydrocarbon models are capable of reliable predictions.[11a] Wilcox reports molecular-mechanics evaluation of strain in an example of the Cohen series and again has shown that "stereopopulation control" is primarily an enthalpic effect operating through strain in the hydroxy acid.[12] This study also deserves extension since the calculations are based on an ad hoc force field applied to only two hydroxy acids.

Attempts to place the Ruzicka hypothesis[1] on a quantitative basis have up to the present used product rings as models of the transition states.[3,4,7] Relative free energies can be calculated for formal reactions such as cyclization of *n*-butane to cyclobutane (eq 4) or of *n*-butene to cyclobutane.

This formal modeling was applied many years ago by Allinger and Zalkow in a theoretical attempt to calculate the *gem*-dialkyl effect in the cyclohexane series.[13] Alkyl substitution lowers the free energy of ring closure, but there are no experimental data for comparison.

Formal cyclization of unsubstituted alkanes leads to the following relative $\Delta\Delta G$ values (see Table IV):[7] for closure of three-membered rings, 20 kcal/mol; four-, 19; five-, 0.1; six-, −3.1; seven-, 1.9; eight-, 6.2. These translate to the following theoretical relative rates; three-, 2×10^{-15}; four-, 1×10^{-14}; five-, 0.8; six-, 190; seven-, 4×10^{-2}; eight-, 3×10^{-5}. Experimental relative rates, however, are entirely different. The relative rate of S_N2 closure of five-membered rings is about 100–1000 times faster than closure of six-membered rings.[3,4,7] The prediction of 1/200 is therefore wrong by about 10^4 or more. Seven-membered rings and four-membered rings close at about the same rate, and the prediction is wrong by about 10^{12}. These results make it clear that product rings are not always suitable models of the transition states for S_N2 ring closure.

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Fortunately we no longer are required to choose known stable molecules as models of transition states. The molecular-mechanics procedure for extrapolating thermodynamic data can be used to evaluate enthalpic effects arising from steric factors for any desired model. As an example the Taft E_s values[14] for steric hindrance in ester hydrolysis are reproduced to within a factor of 2 using R_3CCOOH as the model for the ester and $R_3CC(OH)_3$ as the model for the transition state.[11b] The Taft values are reproduced to within a factor of 4 by the even much cruder models of $R_3CCH(CH_3)_2$ for ester and $R_3CC(CH_3)_3$ for transition state.[11a] Steric effects in certain S_N2 halide exchanges are now well understood.[15,16] The model transition state is a trigonal bipyramid; the detailed conformation, defined by the effect of the force field, is often considerably distorted.[16a]

Other examples of the use of molecular mechanics in the quantitative treatment of steric effects on equilibria or no rates include lactone formation,[17] the early work of Schleyer's group on prediction of rates of solvolysis of bridgehead halides and sulfonates,[18] attempts to calculate solvolysis of other systems,[19-21] oxidation of alcohols and reduction of ketones,[22] prediction of product distributions,[23] and prediction of conformer populations.[24]

The present study concerns the ring closure of bromoalkylamines, eq 1, and their alkylated derivatives, eq 2 and 3.

$$\underset{\mathbf{1}}{Br(CH_2)_{n-1}NH_2} \rightarrow \underset{\mathbf{2}}{\text{cyclic } (CH_2)_{n-1}NH_2^+\ Br^-} \quad (1)$$

$$\text{alkylated } \mathbf{1} \rightarrow \text{alkylated } \mathbf{2} \quad (2)$$

$$Br(CH_2)_{n-1}NMe_2 \rightarrow \text{cyclic } (CH_2)_{n-1}NMe_2^+\ Br^- \quad (3)$$

We have chosen these systems on account of their importance as general examples of S_N2 ring closure, and because the available experimental data cover a wide range of structures and of relative rates. Since S_N2 reactions show little sensitivity to polar effects,[16] these rates are governed primarily by steric factors.

Our procedure is to estimate enthalpies of activation by molecular mechanics[11,25-27] and entropies of activation by analogy with the entropies of formal ring closure reactions of alkanes.[7,28] The presentation is accordingly organized into three sections: we consider first the procedures for evaluation of entropies of activation, next we provide a description of the principles of and limitations of the use of molecular mechanics to estimate enthalpies of activation, and finally we present our theoretical derivation of the rates of the ring-closure reactions. We limit our theoretical treatment to the unsubstituted homologues of **1** with n = 4-7 and to the dialkyl-substituted derivatives for n = 5. In particular we have left out the closure to ethylenimine (n = 3) for two reasons: the force field does not at present include functions and constants suitable for three-membered rings, and the variable rates of closure of three-membered rings relative to closure of rings of other sizes strongly suggests that special bond hydridization factors may be important in controlling rates for three-membered rings.[6] By this we mean that there may be significant resonance effects involving all three atoms of the ring being formed, such special effects being absent in closure of larger rings because of isolation by the extra atoms in the ring.

Entropies of Ring Closure. There are at least three ways to calculate entropies of formation: (1) through a statistical-mechanical calculation using vibrational terms estimated by molecular mechanics; (2) through group additive methods based on generalized summaries of entropy factors;[3,4,28] (3) by direct extrapolation from analogous systems. This latter is potentially the most reliable providing that the analogy is sufficiently close.

Equation 4 is an example of a formal cyclization and eq 5 is the corresponding intermolecular combination reaction; ΔS_{int} is the intrinsic entropy of the reaction, that is, entropy corrected for the extraneous factors of symmetry number and presence or absence of *dl* pairs. Within the error limit (std dev) of 0.4 cal deg^{-1} mol^{-1} the differential entropy of ring closure, eq 6, can be expressed as a linear function of n, the number of carbon atoms, eq 7.[29]

$$CH_3(CH_2)_{n-2}CH_3 \rightarrow \text{cyclic } (CH_2)_n + H_2 \qquad \Delta S_{\text{int}}(\text{ring}) \quad (4)$$

$$CH_3(CH_2)_{l-2}CH_3 + CH_3(CH_2)_{m-2}CH_3 \rightarrow CH_3(CH_2)_{n-2}CH_3 + H_2 \quad (5)$$

$$n = l + m \qquad \Delta S_{\text{int}}(\text{inter})$$

$$CH_3(CH_2)_{i-2}CH_3 + CH_3(CH_2)_{l-2}CH_3 \rightarrow \text{cyclic } (CH_2)_i + CH_3(CH_2)_{j-2}CH_3 + CH_3(CH_2)_{k-2}CH_3 \quad (6)$$

$$l = j + k \qquad \Delta\Delta S_{\text{int}}(\text{closure})$$

$$\Delta\Delta S_{\text{int}}(\text{closure}) = \Delta S_{\text{int}}(\text{ring}) - \Delta S_{\text{int}}(\text{inter}) = 34.901 - 2.868n \ (s = 0.4) \quad (7)$$

Entropies are for the gas phase but are referenced to the hypothetical standard state of 1 M. The six-membered ring is exceptional because of the relative rigidity of the chair form. Equation 7 also applies with the same accuracy to the formal ring closure:

$$CH_2{=}CH(CH_2)_{n-3}CH_3 \rightarrow \text{cyclic } (CH_2)_n \quad (8)$$

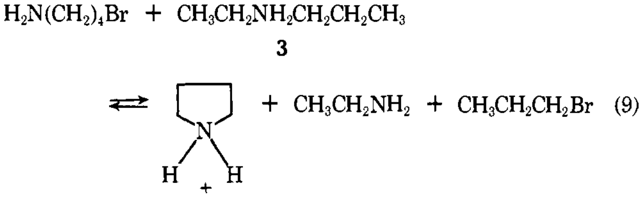
The entropy data are developed in the Calculations section. There are too few data to permit similar computations of ring closures for molecules incorporating heteroatoms, but entropies of the following two formal combination reactions are the same within respective error limits:

$$CH_3(CH_2)_{l-2}CH_3 + CH_2{=}CH(CH_2)_{m-3}CH_3 \rightarrow CH_3(CH_2)_{l+m-2}CH_3 \qquad \Delta\Delta S = -31.32$$

$$CH_3(CH_2)_{l-2}OH + CH_2{=}CH(CH_2)_{m-3}CH_3 \rightarrow CH_3(CH_2)_{l-2}OCH_2(CH_2)_{m-2}CH_3 \qquad \Delta\Delta S = -32.07$$

There are striking regularities in the entropies of formation of methyl-substituted alkanes and cycloalkanes. These are summarized in the Calculations section and in Table I. It is possible that some of these correlations gloss over small systematic trends in entropies of formation and of cyclization, but the smoothed values appear to be correct to within better than 1 cal deg^{-1} mol^{-1}, and they suffice for present needs.

We now consider the relationships between eq 6 and the formal S_N2 ring closure equilibrium, eq 9. The close structural similarities in these two formal reactions and the general pattern of regularities among entropies of formation strongly support the hypothesis that for similar ring sizes the entropies of eq 6 and 9 will be nearly the same; the 2.868 cal deg^{-1} mol^{-1} increment may be expected to hold for both formal reactions for n = 4, 5, 7, and the cyclohexane value for n = 6. It is our postulate that the entropy relationships also hold for the transition states and that the entropies of activation for ring closure may be equated to the experimental entropies of ring closure summarized in Table I.



$$H_2N(CH_2)_4Br + CH_3CH_2\overset{+}{N}H_2CH_2CH_2CH_3$$

3

Table I. Intrinsic Entropies of Ring Closure

ring size, open chain	substitution ring	$\Delta\Delta S_{\text{inl}}$(closure),[a,b] gibbs, M, 298 K	
3 unsubs		26.3	
4 unsubs		23.4	
5 unsubs		20.5	
6 unsubs		17.7[c]	12.1[d]
7 unsubs		14.8	
8 unsubs		11.9	
5 monoalkyl	monoalkyl	23.3	
6 monoalkyl	monoalkyl	20.5	
5 monoalkyl	dialkyl	21.2	
6 monoalkyl	dialkyl	18.4[c]	12.8[d]
5 dialkyl	dialkyl	23.3	
6 dialkyl	dialkyl	20.5[c]	14.9[d]

[a] For formation of cycloalkanes or cycloalkenes, corrected for symmetry and for *dl* pairs so as to apply to a single stereoisomer of reactant and of product having a symmetry number of one. These values compare closely with the values of $\Delta\Delta S_{\text{inl}}$ of Table III of ref 7 if symmetry numbers of 14 for cycloheptane and 16 for cyclooctane are used. [b] $\Delta\Delta S_{\text{int}}$ means that these values are relative to the corresponding intermolecular reactions, eq 6; 1 gas, 298 K. [c] Interpolated for fully flexible six-membered ring. All rings (except cyclopropane) are treated as flexible. [d] For "rigid" chair cyclohexane. It should be noted that all entropy data in this table are consistently derived smoothed values which summarize a large body of experimental data for alkanes, alkenes, and cycloalkanes.

The proposals concerning use of eq 7 in the computation of entropies of activation for cyclization have some recent experimental support. Entropies of activation data for cyclization of $Br(CH_2)_{n-2}COO^-$ in 99% dimethyl sulfoxide[1b,c] may somewhat arbitrarily be correlated by a straight line; $\Delta S^{\ddagger}(\text{calcd}) = 5.271\ (\pm 2.5) - 2.356\ (\pm 0.32) n_c$, $s = 2.5$, $r^2 = 0.90$ for $n_c = 3\text{–}5, 7\text{–}11$. This is not a great correlation, but it is well within the estimated uncertainties of the experimental $\Delta S^{\ddagger}$ values.[1b] Results are not much changed by breaking off at $n = 10$, 12, or 13, but the leveling of $\Delta S^{\ddagger}$ at still larger n ultimately leads to a much lower r^2 as values of $\Delta S^{\ddagger}$ for n up to 23 are included. The slope -2.4 is within acceptable agreement with the theoretical slope -2.868 value of eq 7. The rather large uncertainties in $\Delta S^{\ddagger}$ are due to the well-known strong correlation between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ and to the absolute statistical requirement that data be random (unbiased), a requirement that is seldom fulfilled in practice.

Enthalpy Estimates via Molecular Mechanics. The enthalpy of formation of a given compound may be expressed as a summation of four terms:[11,16,25]

$$\Delta H_f = \text{base enthalpy} + \text{SM} + \text{SE} + \text{const} \qquad (10)$$

These are a base enthalpy, a statistical mechanical energy,[25,26] a steric energy, and a constant which represents enthalpy of solvation and possibly other quantities. The base value for an alkane may be represented as a sum of group terms, one for each of the CH_3, CH_2, CH, and C groups present. The steric energy (SE) is calculated by molecular mechanics for the conformation of lowest energy. The statistical-mechanical correction allows for population of multiple conformations having energies only slightly higher than the conformation of minimum energy.[27] Steric energy includes strain energy but is not equal to strain energy; the value of steric energy for a given molecule depends on the details of the force field. If we need to calculate ΔH_f, we must establish appropriate base enthalpy terms for each particular force field in use. The steric energy is therefore a composite quantity; it includes strain energy plus some arbitrary and usually small fraction of the base enthalpy. In most applications both the force field and the base enthalpies are parametrized to give gas-phase values. The constant term in eq 4 then would represent the enthalpy of solution.

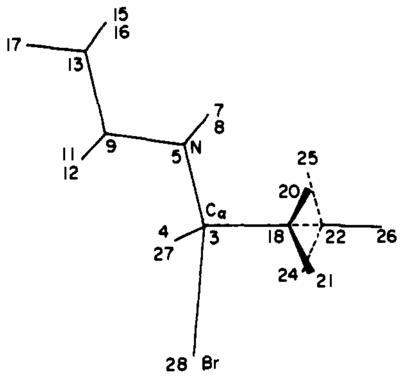


Figure 1. Transition-state model for reaction of $CH_3CH_2NH_2$ and $CH_3CH_2CH_2Br$. Four pairs of hydrogen atoms appear eclipsed in this view.

The enthalpy of activation is derived by the formalism of the equations

$$\Delta \text{SE}_1 = \text{SE(ts 1)} - \text{SE(gs 1)} \qquad (11)$$

$$\Delta H_1^{\ddagger} = \Delta \text{SE}_1 + \text{const}_1 + \Delta \text{SM}_1$$

$$\Delta \text{SE}_2 = \text{SE(ts 2)} - \text{SE(gs 2)} \qquad (12)$$

$$\Delta H_2^{\ddagger} = \Delta \text{SE}_2 + \text{const}_2 + \Delta \text{SM}_2$$

$$\Delta\Delta \text{SE}_{12} = \Delta \text{SE}_2 - \Delta \text{SE}_1 \qquad (13)$$

$$\Delta\Delta H_{12}^{\ddagger} = \Delta\Delta \text{SE}_{12} + \Delta\Delta \text{SM}_{12} + \text{const}_{12}$$

In eq 11 and 12 the differences in steric energies between transition state (ts) and ground state (gs) account for the strain-energy increase or decrease. The const_1 includes those base value terms that do not cancel at this stage; it also includes hybridization and other energy changes that occur in forming the transition state, and it includes solvation effects. $\Delta\Delta \text{SE}_{12}$ is a true strain energy difference.

For a properly selected reaction series all base value terms drop identically from the double difference $\Delta\Delta H_{12}^{\ddagger}$ and need not be separately evaluated. The constant term const_{12} represents residual differential effects of solvation and differential electronic effects.

Consideration of these principles shows that eq 13 is applicable to all members of the reaction series summarized in eq 1 and 3, each of which represents reaction of a primary bromide with a primary amine. For all these $\text{const}_{12} \cong 0$. However, reactions of primary amines may encounter different hybridization energies than do tertiary amines; thus we cannot expect const_{12} to be small if we attempt to compare members of the reaction series of eq 1 with members of the series of eq 3. The presence of an appreciable polar factor would, of course, show up in const_{12}, but S_N2 reactions are not sensitive to polar factors.[16] We can therefore expect that the sum of $\Delta\Delta \text{SE}_{12}$ and $\Delta\Delta \text{SM}_{12}$ values will be equal to, or proportional to, $\Delta\Delta H_{12}^{\ddagger}$.

Theoretical Calculation of Rates of Cyclization. Detailed structures of the transition states are not known, but the general structure is a distorted trigonal bipyramid, Figures 1–3. Since applicable force constants are also not known, we have examined several possibilities based on our earlier studies.[11,16] The force constants define the details of the models of the transition states. We report here on two such models that were applied to the complete data set. It is important to note that several previous evaluations of steric effects on relative rates have shown that a reasonable model of the transition state together with reasonable estimates of force constants, consistently applied, will give useful quantitative accounts of steric hindrance and of steric acceleration.[10,11,18,22] The converse also holds: the fact that a model does prove successful is no guarantee that it is correct in detail.

Table II. Steric Energies and Relative Rates of Ring Closure for ω-Bromoalkylamines[a]

reactants	SE reactants	SM[b]	SE (TS)	$\Delta\Delta H_{rel}^{\ddagger}$ [c]	$\Delta\Delta S_{rel}$ [d]	$\Delta\Delta G_{rel}^{\ddagger}$ [c]	log k[e] obsd	log k[f] calcd	log k obsd − calcd
1 $EtNH_2$ + *n*-PrBr	3.20	0	22.28	0	0	0		−4.44	
2 $EtNH_2$ + $(CH_3)_3CCH_2Br$	5.40	0	30.80	6.32	0	3.98		−7.36	
3 $H_2N(CH_2)_3Br$	2.13	0.27	30.15	11.67[g]	23.4	0.34	−5.08	−4.69	−0.39
4 $H_2N(CH_2)_4Br$	2.67	0.39	23.17	1.03	20.5	−5.46	−0.06[h]	−0.43	0.37
5 $H_2N(CH_2)_5Br$	3.11	0.63	23.90	1.08	12.1	−2.93	−2.08	−2.29	0.21
6 $H_2N(CH_2)_6Br$	3.70	0.86	31.36	7.72	14.8	0.45	−4.60	−4.77	0.17
7 $H_2NCMe_2CH_2CH_2CH_2Br$	4.60	0.12	24.29	0.49	23.3	−6.64	0.24	0.43	−0.19
8 $H_2NCH_2CMe_2CH_2CH_2Br$	7.22	0.12	23.11	−3.31	23.3	−9.03	2.09	2.18	0.09
9 $H_2NCH_2CH_2CMe_2CH_2Br$	6.26	0.12	27.35	1.89	23.3	−5.75	−0.84	−0.22	−0.62
10 $N_2NCH_2CEt_2CH_2CH_2Br$	12.78	0	27.41	−4.45	23.3	−9.75	2.67	2.71	−0.04
11 H_2NCH_2-*i*-$Pr_2CH_2CH_2Br$	24.00	0	36.54	−6.54	23.3	−11.06	3.85	3.68	0.18

[a] Units kcal, mol, s, 298 K. [b] Statistical-mechanical correction taken from alkane values: ref 11, 27. [c] Relative to reaction 1; cf. eq 9. Values are based on the "tight" model of the transition state. $\Delta\Delta G_{rel}^{\ddagger}$ from eq 15 with $b = 0.63$. [d] From Table I. [e] Values for reactions 3, 5, and 6 from Freundlich as summarized in ref 7; others from data of ref 32 as derived in Calculations. [f] Log $k = (-6.0499 - \Delta\Delta G^{\ddagger})/1.3634$. Standard deviation 0.34, $r^2 = 0.987$; reaction 3 not used in evaluating the intercept (−6.0499) and the factor 0.63. [g] Increased by 3 kcal to correct systematic underestimate of SE for four-membered rings. [h] Freundlich value is −0.30 and was estimated from chloroalkylamine values.

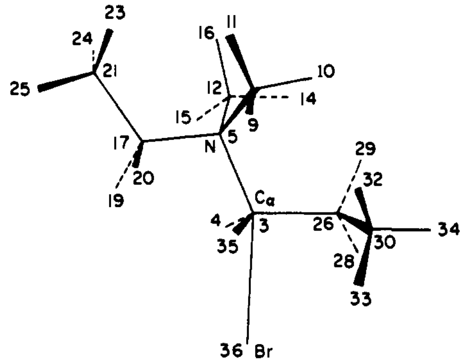


Figure 2. Transition-state model for reaction of $CH_3CH_2N(CH_3)_2$ and $CH_3CH_2CH_2Br$.

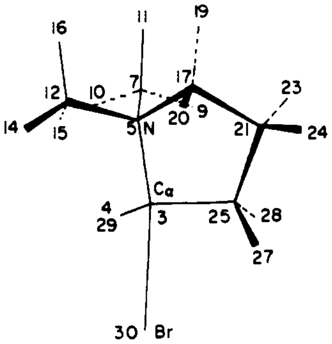


Figure 3. Transition-state model for cyclization of $(CH_3)_2NCH_2CH_2CH_2CH_2Br$.

Since steric energies are calculated for the conformation of minimum energy we must include a suitable estimate of the statistical-mechanical term, eq 11-13. For open-chain molecules the value for the analogous alkanes[11,26,27] should be adequate; cyclic compounds or transition states will have a negligible SM correction because all available low-energy conformations are of nearly the same energy.

Entropy values in Tables II and III are from Table I. The experimental rates of ring closure, log k(obsd), are taken from the literature;[7,30-32] further details are given in the Calculations.

Combination of estimates of $\Delta\Delta H^{\ddagger}$ and of $\Delta\Delta S^{\ddagger}$ gives a series of theoretically calculated $\Delta\Delta G^{\ddagger}$ values to be used in a linear free energy (LFR) expression to predict log k(cyclization). The conventional LFR treatment requires that the slope and the intercept must both be adjusted for each reaction series. This is so because we have no way at present to calculate absolute rate constants (intercept) nor can we predict the sensitivity (slope) of a given reaction series to the varying structural parameters. This situation holds for steric effects as well as for polar effects.[16b] Thus the Taft E_s values correlate steric effects in acid-catalyzed esterification and hydrolysis of ethyl esters with unit slope (by definition), but the required slope differs for other esters and for alkaline catalysis.[16b]

The conventional LFR approach would be to obtain slope and intercept for the equation

$$\log k = a' + b'\Delta\Delta G^{\ddagger} \qquad (14)$$

but we prefer to adopt a somewhat unconventional LFR treatment that is more appropriate to our assumption that $\Delta\Delta S^{\ddagger}$ values of Table I and $\Delta\Delta\mathrm{SM}^{\ddagger}$ values are to be used without adjustment; this requires the equation

$$\begin{aligned} -RT \log k_{\mathrm{ring}} &= a + b\Delta\Delta\mathrm{SE}^{\ddagger} + \Delta\Delta\mathrm{SM}^{\ddagger} - T\Delta\Delta S^{\ddagger} \\ &= a + \Delta\Delta G^{\ddagger} \qquad (15) \end{aligned}$$

The intercept a is the predicted $-RT \log k_{\mathrm{intermolecular}}$ and the slope b is a fraction that adjusts the span of the strain-energy part of $\Delta\Delta H^{\ddagger}$.

Steric energies presented in Tables II and III were calculated by the force field described below; these define a "tight" model of the transition state having a nearly normal N···C bond. Although this choice apparently leads to too much crowding, the relative $\Delta\Delta\mathrm{SE}_i^{\ddagger}$ values give an excellent quantitative prediction of relative rates if all are reduced by 37%, that is, scaled by the factor $b = 0.63$, eq 15; see footnote *c*, Table II. A "loose" model based on the opposite extreme with a long N···C bond also gave somewhat too great a range of $\Delta\Delta\mathrm{SE}_i^{\ddagger}$; the scaling factor here is 0.81. Agreement between observed and calculated log k values is about equally good for either model.

A least-squares computation of a and b of eq 15 for a linear free energy relationship is a generalization of the double difference formalism of eq 13. The correlation coefficient provides the best available objective measure of goodness of fit,[33] and our value of $r^2 = 0.987$ (6 df, $s = 0.34$) shows that direct computation of steric effects from molecular structure is now capable of giving steric correlations comparable to the best of the empirical linear free energy treatments;[38] the latter are not generally capable of treating steric effects.

There are regrettably too few data to carry out an adequate evaluation of the ring closure of the dimethylamino derivatives. The available results are summarized in Table III. We did not attempt to obtain a scaling factor for the these $\Delta H^{\ddagger}$ values since work in progress will permit a more definitive evaluation in the near future.

Table III. Steric Energies and Relative Rates of Ring Closure for ω-Bromoalkyldimethylamines[a]

reactants	SE reactants	SM[b]	SE (TS)	$\Delta\Delta H_{rel}{}^{\ddagger}$[c]	$\Delta\Delta S_{rel}{}^{\ddagger}$[c,d]	$\Delta\Delta G_{rel}{}^{\ddagger}$	log k[e] obsd	log k[f] calcd
1 $Me_3N + EtBr$	3.39	0	27.65	−4.73	0	−4.73		−4.55
2 $EtNMe_2 + n\text{-}PrBr$	4.58	0	33.57	0	0	0		−7.27
3 $Me_2N(CH_2)_3Br$	4.54	0.27	33.54	−0.26	24.1	−7.44	−4.28	−2.98[f]
4 $Me_2N(CH_2)_4Br$	5.15	0.56	27.93	−6.77	21.2	−13.09		0.28
5 $Me_2N(CH_2)_5Br$	5.79	0.76	30.12	−5.42	12.8	−9.23	−1.95	−1.95
6 $Me_2N(CH_2)_6Br$	6.27	0.90	36.44	0.28	15.5	−4.34	−4.77	−4.77

[a] Units kcal, mol, s, 298 K. [b] Statistical-mechanical correction taken from alkane values: ref 11, 19. [c] Relative to reaction 2. [d] From Table I. [e] From ref 7. [f] $\log k = -7.2728 - 0.5767\Delta\Delta G$, exact fit to reactions 5 and 6. [f] Increased by 3 kcal since force field underestimates strain of four-membered rings.

Table IV. Differential Enthalpies, Differential Intrinsic Entropies, and Differential Free Energies of Ring Closure

n	$\Delta\Delta H$		$\Delta\Delta S$		$\Delta\Delta G$		$\Delta\Delta G^{\ddagger}$
3	27.49[a]		25.22[c]	(26.30)[d]	19.97[e]		
4	26.45		23.49	(23.43)	19.45		0.34[g]
5	6.47	(6.51)[b]	21.23	(20.56)	0.14	(0.38)[f]	−5.46
6	0.46	(0.51)	12.06	(12.10)	−3.13	(−3.10)	−2.93
7	6.29	(6.57)	14.84	(14.83)	1.87	(2.15)	0.45
8	9.69	(10.65)	11.77	(11.96)	6.18	(7.09)	
9		(14.09)		(9.09)		(11.38)	
10		(14.83)		(6.22)		(12.98)	
11		(13.63)		(3.35)		(12.57)	
12		(9.94)		(0.49)		(9.79)	
15		~2.0		(−8.12)		(~4.4)	

[a] ΔH_f(cycloalkane) − ΔH_f(alkane) − 10.07; the − 10.07 is ΔH for eq 5. Entries are $\Delta\Delta H$ (eq 6) = ΔH (eq 4) − ΔH (eq 5); based on observed values from ref 41. Units kcal mol^{-1}. [b] ΔH_f(cycloalkane) − $4.976n$; based on calculated ΔH_f for cycloalkanes reported in ref 25. [c] S_f(cycloalkane) − S_f(alkane) + 31.21 − 1.987 ln (24.47) + 1.987 ln ($2n/18$) + 5.19 + 1.987 ln 18; latter two terms are for eq 5; the standard reference state is gas phase, 1 M. Units cal deg^{-1} mol^{-1}. [d] From Table I, and, except for $n = 6$, from eq 7. [e] From *a* and *c*; units kcal mol^{-1}. [f] From *b* and *d*. [g] From Table II (eq 15).

Discussion

We consider four major aspects of the computational results: (1) the origins of the failure of the Ruzicka hypothesis in predicting rates of S_N2 ring closure of rings for $n = 4$, 5, 6, and 7; (2) the quality of the experimental data; (3) the *gem*-dialkyl effects; (4) the modern status of the Ruzicka hypothesis.

The differences in predictions of relative rates of S_N2 ring closure based on product rings as models for the transition states (original Ruzicka hypothesis) and relative rates based on the trigonal-bipyramid model of the transition states arise entirely in the enthalpy terms; the two models use identical entropy estimates. There is a 26 kcal/mol difference in $\Delta\Delta H$ for eq 6 between cyclobutane and cyclohexane (Table IV), while the difference in $\Delta\Delta H^{\ddagger}$ for the transition state for eq 9 is 10.6 kcal/mol. The two models therefore differ by a factor of 2×10^{11} in predicted relative rates for four-membered rings vs. six-membered rings due to differences in enthalpy predictions.

Although the steric energies of a molecule are the resultant sum of many factors, it is possible here to identify the major factor: introducing the roughly 90° angles of the trigonal bipyramid (Figures 1-3) introduces a large steric strain for all S_N2 reactions. This strain is particularly unfavorable for intermolecular reactions, and for closure of all rings from $n = 5$ on up. But the strain in the transition state for $n = 4$ is not greatly larger than the strain in product cyclobutane. In other words, the product rings do not adequately represent the leveling effect of the strains in the several transition states, the four-membered ring being way out of line. The $\Delta\Delta H$, $\Delta\Delta G$, and $\Delta\Delta G^{\ddagger}$ values are shown in Figure 4.

The contrast between the five- and six-membered rings is more subtle. Cyclopentane is strained with respect to cyclohexane by about 6 kcal/mol,[26] but the two transition states have almost the same $\Delta\Delta H^{\ddagger}$. The equal $\Delta\Delta H^{\ddagger}$ circumstance arises from a combination of many relatively small terms; for example, the symmetrical staggering of hydrogen atoms in cyclohexane is spoiled in part for the transition state, so that there is more angle strain, and nonbonded interactions between hydrogens are enhanced; on the other hand, the transition state for the pyrrolidinium ion still has considerably more torsional strain than does the transition state for the piperidinium ion.

Turning next to the experimental data in Table II, there are certain limitations of accuracy. For example, the Freundlich values are reported only to one significant figure. Also the reported pyrrolidine ring closure rate was not directly observed but was instead interpolated from rates of reaction of the chloroalkylamines.[7,30,31] The Brown and van Gulick study was evidently a preliminary report,[32] and it presents single observed rate values for most of the compounds. Furthermore, we had to convert these observed values to absolute rate constants at 25 °C, and, while our arithmetic does not alter relative rates in either the Freundlich or the Brown and van Gulick series, it does leave some uncertainty as to overall compatibility between the two series. The residual errors of the correlation then are hardly greater than the experimental uncertainties of the data. To put matters in perspective, it is unlikely that any of the reported rate constants are in error by much more than a factor of 2; we would expect that errors in relative rates within each series will generally be less than 20%. There were differences in the solvents in the Freundlich series and in the Brown and van Gulick series, but both were predominantly aqueous. The range of experimental data is insufficient to warrant any extensive examination of force fields.

The *gem*-dialkyl acceleration on progressing from dimethyl to diethyl to diisopropyl substitution, entries 8, 10, and 11 of Table II, arises from differential crowding in the ground-state molecules. The 100-fold difference between 1,1-dimethyl-4-bromobutylamine, entry 7, and 2,2-dimethyl-4-bromobutylamine, entry 8, arises primarily from less crowding in the ground state, due to fewer gauche interactions (entry 7) and to a small additional extent from added crowding in the tran-

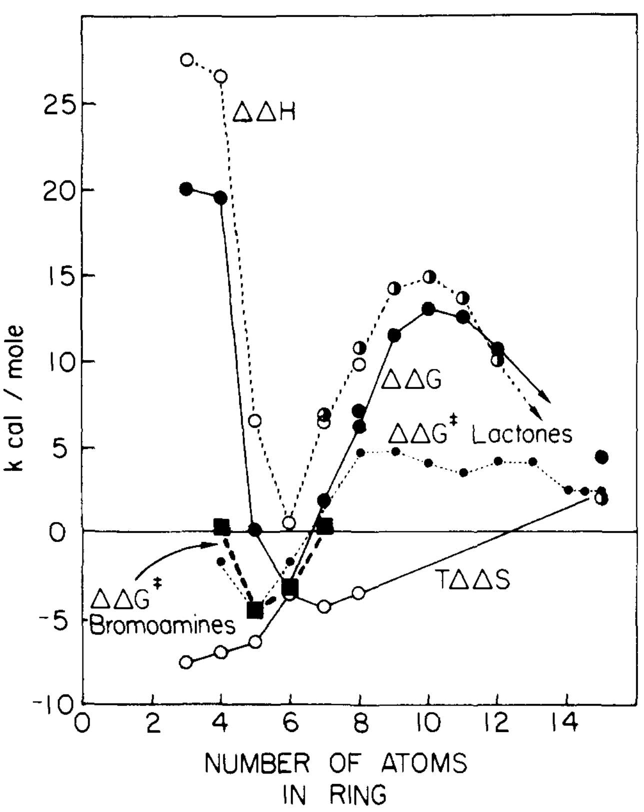


Figure 4. Thermodynamics of ring closure of cycloalkanes (eq 6) (●○◑); $\Delta\Delta G^{\ddagger}$ for closure of $Br(CH_2)_{n-1}NH_2$ (experimental and theoretical values coincide for n = 4–7 and for n = 15) (■); and experimental $\Delta\Delta G^{\ddagger}$ for closure of $Br(CH_2)_{n-2}COO^-$ (●). The lactone data are taken from ref 1c. $\Delta\Delta G^{\ddagger}$(lactone) = $-1.58(\log k + 0.66)$ and the 0.66 value comes from ref 46 as an appropriate average value for $-\log k$ for the intermolecular reaction. See Table IV.

sition state (entry 8). It is clear that prediction of relative rates must consider both ground states and transition states and that qualitative predictions will be valid if both effects operate in the same direction or if one is dominant.

Entry 9 of Table II is a neopentyl system; the neopentyl effect is rate retarding while the concomitant *gem*-dimethyl substitution is accelerating. Perhaps the best comparison is between entries 8 and 9. The calculated retarding effect here is 2.4 while the observed is 2.9 (log k units). For the open chain, entries 1 and 2, the calculated neopentyl retardation is 2.9. Such numbers are further subject to various secondary effects due to ground-state repulsions between Br and CH_3 groups and the calculated retardation would vary somewhat in larger molecules having the neopentyl moiety.

In halide exchange reactions the Ingold data show an average value of 40 000 for $k(n\text{-PrX})/k(neo\text{-PeX})$ for six reaction series, an average of 4.6 in log k[16a,42] Calculated ΔΔSE values are pretty much the same: 6.3 (Table II) for $R'NH_2$ + RBr and 7.0 for Br^- + RBr.[16a] The calculated difference in $\Delta\Delta H^{\ddagger}$ for the two types of nucleophile arises primarily from the b = 0.63 factor in eq 15.

It appears that there are relatively large medium influences on steric effects which will require sorting out. For example, ρ_s = 1.000 by definition for acid-catalyzed hydrolysis of RCOOEt.[14] Yet Milstien and Fife report ρ_s = 0.47 for "spontaneous" hydrolysis of $RCOOC_6H_4NO_2$-p[43a] while the Harfenist and Baltzly data require ρ_2 = 1.9 for acid-catalyzed alcoholysis of RCOO-β-naphthyl in i-PrOH.[43b] For a relatively small ΔE_s of 2, Δ log k would be either 1 or 8 depending on the reaction system, a very large difference.

Models of the transition states for three reactions are shown in Figures 1–3. There is appreciable distortion away from the conventional symmetrical trigonal bipyramid. The departure of the N-C_α-Br angle from linearity constitutes a general mechanism for diminishing interference with the β substituents of RCH_2Br.[15,16] The nonplanarity of the C-C_α-$(H)_2$ grouping in the present study arises from the adoption of a relatively short N-C_α distance. The structure is therefore "product-like." Figure 2 shows the relatively high degree of crowding in the reaction of n-propyl bromide with ethyldimethylamine, while Figure 1 shows the situation with the less hindered ethylamine. Figure 3 shows a typical ring closure. The unsymmetrical appearance in Figure 3 is one evidence of crowding. Cartesian coordinates for these three transition states are presented in the supplementary material. Summaries of the geometries for the C_α region for all transition states are presented in supplementary Table S.I.[39] Crowding has the greatest effect on the N-C_α-Br angle, which may be as small as 150°. There is also a considerable effect on the C-C_α-N angle. Other angles remain within a 10° range for all examples. The detailed partitioning of the steric energies is presented in Table S.II.[39]

The Ruzicka Hypothesis 50 Years Later. The Ruzicka hypothesis was a significant step in developing a theory of ring closure. It correctly recognized that both probability factors (entropy) and energy factors (strain, enthalpy) must be considered. It is clear from the discussion that the authors were aware of loose ends: the hypothesis does not really account for the then known facts that large rings can be made while attempts to make intermediate-sized rings (n = 9–11) encountered difficulties of vanishingly low yields. The relative importance of entropic and enthalpic factors was in fact completely misjudged. The modern statement of the Ruzicka hypothesis in terms of thermodynamics of alkane to cycloalkane ring closure (eq 6) is summarized in Table IV and in Figure 4. The standard state is taken as 1 M gas phase at 25 °C and the cyclization reactions are referenced to the corresponding intermolecular reaction. The $\Delta\Delta H$ values are based on experimental data through cyclooctane[41] and are based on the Schleyer values for larger cycloalkanes (for consistency with the calculations summarized in Tables II and III). The calculated $\Delta\Delta H$ values for n = 8–12 reflect the effects of hydrogen crowding in the intermediate-sized rings. We have estimated that $\Delta\Delta H$ will be 2 kcal/mol for n = 15; quantitative data are lacking.

The entropic progress ($T\Delta\Delta S$) (Table I, Figure 4) is linear up through about C_{12} (except for cyclohexane) but the curve should begin to level somewhat as n becomes still larger since the large rings will have increasing freedom of libration.

In Table IV and in Figure 4 are also shown $\Delta\Delta G^{\ddagger}$ for ring closure of $Br(CH_2)_{n-1}NH_2$ to cyclic immonium ions. The experimental values and the theoretical values effectively coincide. Except for n = 4 and n = 5, which fail spectacularly, there should be quite good quantitative agreement between $\Delta\Delta G$ and $\Delta\Delta G^{\ddagger}$; cycloalkanes are good analogues for cyclic iminium ions, and the special transition state geometry becomes a progressively smaller perturbation as n increases. The data for testing these predictions are limited. Salomon[44] reports rates of cyclization of large bromo amines in 30 mol % isopropyl alcohol at 73.3 °C: for n = 7 (k = 330 × 10^{-4} min^{-1} in ref 44c or 1500 × 10^{-4} min^{-1} from the temperature data in alcohols in ref 44b), for n = 14 (8.5 × 10^{-4}, or 3 × 10^{-4} to be consistent with yields in ref 43d), for n = 15 (7 × 10^{-4}, or 14 × 10^{-4} based on yields), for n = 17 (19 × 10^{-4}, which is consistent with yields). The rates of the intermolecular reactions are reported to be from 0.01 to 0.2 M^{-1} min^{-1}, but these are only moderately consistent with yields. The imprecise experimental $\Delta\Delta G^{\ddagger}$ values for these rings therefore range from 2 to 4 kcal/mol for n = 14–17 and are consistent with the guesses of $\Delta H^{\ddagger}$ for large rings. It appears that cyclic products are not formed from rings of intermediate size[44d] and this is also consistent with predictions.

It is clear that ring closures of other systems cannot all be predicted by any single curve. Various structural types such as cyclic peptides or lactones will follow different curves. We illustrate these considerations with two examples. The theoretical calculations of Allinger[45] on cyclic ketones show a lesser crowding for intermediate cyclic ketones than for cycloalkanes by several kilocalories per mole. The $\Delta\Delta H^{\ddagger}$ and the $\Delta\Delta G^{\ddagger}$ curves for the cycloalkanones will therefore have a lower "bump" in the $n = 8$–12 region. The bump should be still lower for lactones since replacing a CH_2 group by an oxygen atom will reduce across-ring hydrogen repulsions. Theoretical calculations have not yet been made, but the experimental data of the Illuminati group[1c] on lactone formation from $Br(CH_2)_{n-2}COO-$ show such a trend. The lactone points are shown in Figure 4.

It is also obvious that no simple curve can suffice to show the numerous possibilities due to alkyl substitution nor to the even more complex polycyclic systems. In principle steric effects for nearly all possibilities can now be quantitatively predicted by the procedures used in the present study.

Calculations

The Force Field. Details of the force field are summarized in Table V. This is an extension of the force fields we have used in previous studies.[11,16,26,40] Based on experience in other studies, the relative results are not expected to be sensitive to modest variations in the constants. We rely primarily on the fact that the hydrocarbon portion of the force field is based on values developed by Schleyer's group and has been shown to give generally reliable results from hydrocarbons.[11,25,26] To this we have added values for nitrogen and for bromine which have given useful values in earlier studies. For the transition state we assume that the N-C bond is fairly close in length to the bond in the product. The other assumptions are similar to those we used in our study of the bromide exchange.[16] Calculations were also made with other N-C bond distances derived from weaker N-C_α force constants.

Entropies. All data were taken from ref 41. For n-alkanes from propane through octane the intrinsic entropy of formation, using $\sigma = 18$ (symmetry number), is given for 1 M gas phase, 298 K, by $S_{\text{int}} = 42.144 + 9.402n$ where n is the number of carbon atoms; $s = 0.1$. For cycloalkanes with $n = 3$–$5, 7, 8$, $S_{\text{int}} = 41.255 + 6.534n$, $s = 0.54$. Chair cyclohexane is omitted in calculating the slope and intercept since the relatively rigid structure has an exceptionally low entropy.

The assignment of symmetry numbers to restricted rotors such as methyl groups and to rings which are not pseudorotators is at best an approximation. We have used $\sigma = 2n$ for all rings except for cyclohexane, for which we use Benson's value of 6.[28] In fact the linear equation is also an approximation since the correct form should have a ln n term; however, the curvature is small over the range $n = 4$–15, and the linear approximation introduces negligible error. The entropy values in Table I may have systematic errors, but they have been consistently derived from the experimental alkane data with no adjustments.[47]

For alkylated C_6–C_9 $S_{\text{int}} = 42.144 + 9.402n - 1.394$ (for first alkyl side chain) $- 2.031$ (for second alkyl side chain). The standard deviation is 0.4 for 21 compounds. The positions of the alkyl groups are immaterial. Intrinsic entropy was based on structural symmetry corrections as follows: for R_3C-X (C_3, $\sigma_s = 3$), and for $(CH_3)_2CH(CH_2)_{n-6}CH(CH_3)_2$ ($\sigma_s = 1.5$ average). All other structural factors used $\sigma_s = 1$; in each case, $\sigma_{\text{Me}} = 3^k$ where k is the number of methyl groups; $\sigma = \sigma_s\sigma_{\text{Me}}$. For the five dimethylcyclopentanes $S_{\text{int}} = 91.92 \pm 0.2$ and for the seven dimethylcyclohexanes $S_{\text{int}} = 93.1 \pm 0.9$, irrespective of position of substituents. The reported entropies are not all independent.

The intrinsic entropy of eq 4, $\Delta S_{\text{int}}(\text{ring}) = 23.968 - 2.868n = \Delta S_{\text{f;int}}(\text{cycloalkane}) - \Delta S_{\text{f;int}}(\text{alkane}) + \Delta S_{\text{f}}(H_2)(= 31.21) - R \ln 24.47$. The intrinsic entropy of eq 5, $\Delta S_{\text{int}}(\text{inter}) = 10.93 = -42.144 + 31.21$. Cyclization reactions such as 3-methylpentane to methylcyclopentane, 2,2-dimethylpentane to dimethylcyclopentane, and the corresponding two cyclohexane closure all have $\Delta S_{\text{int}}(\text{closure}) = 2.81 \pm 0.15$ gibbs + $\Delta S_{\text{int}}(\text{unsubstituted})$. Closures of 2-methylhexane to 1,1-dimethylcyclopentane or 2-methylheptane to 2,2-dimethylcyclohexane (flexible) have $\Delta S_{\text{int}}(\text{closure}) = 0.72 \pm 0.2 + \Delta S_{\text{int}}(\text{unsubstituted})$.

Table V. The Force Field

	ref[a]	force constant[b]	cubic
		Bonds	
C-C[c]	1.52	4.4	
C-H[c]	1.10	4.6	
C-N	1.46	4.6	
C-Br	1.94	2.6	
Cα-N	1.47	2.8	
Cα-Br	1.94	0.066	
		Angles	
H-C-H(P)	109.2	1.005×10^{-4}	-9.65×10^{-7}
H-C-H(S)	109.1	1.005×10^{-4}	-9.65×10^{-7}
H-C-C(P)	109.5	1.218×10^{-4}	-1.170×10^{-6}
H-C-C(S)	109.0	1.218×10^{-4}	$-1.170 \times ^{-6}$
H-C-C(T)	109.2	1.218×10^{-4}	-1.170×10^{-6}
C-C-C(S)	110.4	1.736×10^{-4}	$-1.667 \times ^{-6}$
C-C-C(T)	110.1	1.736×10^{-4}	-1.667×10^{-6}
C-C-C(Q)	109.5	1.736×10^{-4}	$-1.667 \times ^{-6}$
H-N-H	106	9×10^{-5}	
H-N-C	112	1.2×10^{-4}	
C-N-C	109	$1.7 \times ^{-4}$	
H-C-N	109	1.2×10^{-4}	
C-C-N	110	1.7×10^{-4}	
C-C-Br	110	1.25×10^{-4}	
H-C-Br	110	1.15×10^{-4}	
H-Cα-H	109.5	6.7×10^{-5}	
H-Cα-C	109.5	8.2×10^{-5}	
H-Cα-N	105	6×10^{-5}	
H-Cα-Br	105	6×10^{-5}	
C-Cα-N	105	6×10^{-5}	
C-Cα-Br	105	6×10^{-5}	
N-Cα-Br	180	3×10^{-5}	
		Torsions	
H-C-C-H barrier		1.617×10^{-3}	
H-C-C-C barrier		1.617×10^{-3}	
C-C-C-C barrier		1.037×10^{-3}	
		Nonbonded	
H···H	45.246	−3.75	−0.597
H···C	33.853	−3.582	−0.5880
C···C	107.402	−3.1169	−4.2981
H···Br	44.490	−2.62	−10.55
C···Br	99.47	−2.82	−7.74
H···N	33.853	−3.582	−0.5880
C···N	107.402	−3.1169	−4.2981

[a] Distance in ångstroms, angles in degrees. [b] Units are mdyn Å r^{-2}, mdyn Å deg^{-2}, mdyn Å barrier, mdyn Å deg^{-3}. The terms are used as follows: $V = (4.4/2)(r - 1.52)^2$, $V = (1.218/2) \times 10^{-4}(A - 109.5)^2 - 1.170 \times 10^{-6}(A - 109.5)^3$. The barriers are ⅑ the total and are applied to each separate torsional interaction. The Buckingham nonbonded functions are defined as follows: $V_{\text{HH}} = 45.246 \exp(-3.75r) - 0.597r^{-6}$. 1 mdyn·Å/molecule = 143.7 kcal/mol. [c] Also used for Cα-C and for Cα-H. Cα is the carbon atom at which substitution is occurring. For alkylated C_6–$C_9 S_{\text{int}} = 42.144 + 9.402n - 1.394$.

Estimation of Rates of Cyclization. Brown and van Gulick[32] report "observed" rate constants for ring closure in acetate buffers. We have converted these observed values to absolute rate constants by estimates of the pH of the buffers and the $pK_{RNH_3^+}$ of the amines. We based the pH estimates on Boyd's nomograph using the pH of the 1:1 buffer of appropriate total ionic strength and corrected for the buffer ratio by adding or subtracting 0.30 or 0.60.[49] The heat of ionization of carboxylic acids is nearly zero, and of $RCH_2NH_3^+$ is 13.7 kcal/mol.[50] We took the $pK_{RNH_3^+}$ values for several amines from the handbook.[51] We used 1.5×10^{-11} as the average, which when corrected to 30 °C was 2.17×10^{-11}. The overall expression is $\log K = \log K_{obsd} - pH + 10.66$. Although 4-bromo-2,2-dimethylbutylamine is represented by eight reported values, the other compounds are represented by one or two measurements. The reported k_{obsd} value for 4-bromo-2,2-diisopropylbutylamine is apparently in error by a factor of 100 as judged by the entries in the k_{ref} column of the table in ref 32. We corrected the rate constants from 30 to 25 °C using $E_{act} = 15.000$. The Freundlich values[7,31] were converted from units of min^{-1} to s^{-1}.

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Supplementary Material Available: Geometries of transition states (Table S.1), partitioning of steric energies (Table S.11), and Cartesian coordinates for transition states (10 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) L. Ruzicka, W. Brugger, M. Pfeiffer, H. Schinz, and M. Stoll, *Helv. Chim. Acta*, **9**, 499 (1926). (b) Modern data are summarized: L. Mandolini, *J. Am. Chem. Soc.*, **100**, 550 (1978). (c) C. Galli, G. Illuminati, L. Mandolini, and P. Tamborra, *ibid.*, **99**, 2591 (1977).

(2) Quoted in texts: (a) R. T. Morrison and R. N. Boyd, "Organic Chemistry", 3rd ed., Allyn and Bacon, Boston, 1973, p 292; (b) N. Allinger, M. P. Cava, D. C. De Jongh, C. R. Johnson, N. A. Lebel, and C. L. Stevens, "Organic Chemistry", 2nd ed., Worth Publishers, New York, 1976, p 869; (c) E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, 1962, p 168. (d) Other examples of *gem*-dialkyl effects: T. C. Bruice and W. C. Bradbury, *J. Am. Chem. Soc.*, **87**, 4846 (1965). (e) L. Eberson and H. Welinder, *ibid.*, **93**, 5821 (1971). (f) G. Galli, G. Giovannelli, G. Illuminati, and L. Mandolini, *J. Org. Chem.*, **44**, 1258 (1979). (g) I. B. Blagoeva, B. J. Kurtev, and I. G. Pojarlieff, *J. Chem. Soc., Perkin Trans. 2*, 1115 (1979).

(3) B. Capon and S. P;. Mc Manus, "Neighboring Group Participation", Vol. 1, Plenum Press, New York, 1976.

(4) M. I. Page, *Chem.Soc. Rev.*, **2**, 295 (1973).

(5) B. Capon, *Q. Rev., Chem. Soc.*, **18**, 45 (1964).

(6) C. J. M. Stirling, *J. Chem. Educ.*, **50**, 844 (1973).

(7) D. F. DeTar and W. Brooks, *J. Org. Chem.*, **43**, 2245 (1978).

(8) D. R. Storm and D. E. Koshland, Jr., *J. Am. Chem. Soc.*, **94**, 5805 (1972).

(9) S. Milstien and L. A. Cohen, *J. Am. Chem. Soc.*, **94**, 9158 (1972).

(10) D. F. DeTar, *J. Am. Chem. Soc.*, **96**, 1255 (1974).

(11) (a) D. F. DeTar and C. J. Tenpas, *J. Am. Chem.Soc.*, **98**, 4867 (1976); (b) *ibid.*, **98**, 7903 (1976).

(12) C. F. Wilcox, *J. Am. Chem. Soc.*, **98**, 4281 (1976).

(13) N. L. Allinger and V. Zalkow, *J. Org. Chem.*, **25**, 701 (1960).

(14) R. W. Taft, Jr., "Steric Effects in Organic Chemistry", M. Newman, Ed., Wiley, New York, 1956.

(15) P. B. D. de la Mare, L. Fowden, E. D. Hughes, C. K. Ingold, and J. D. H. Mackie, *J. Chem. Soc.*, 3200 (1955).

(16) (a) D. F. DeTar, D. F. McMullen, and N. P. Luthra, *J. Am. Chem. Soc.*, **100**, 2484 (1978); (b) D. F. DeTar, *J. Org. Chem.*, in press.

(17) M. H. P. Guy, G. A. Sim, and D. N. J. White, *J. Chem. Soc., Perkin Trans. 2*, 1917 (1976).

(18) G. J. Gleicher and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **89**, 582 (1967); R. C. Bingham and P. v. R. Schleyer, *ibid.*, **93**, 3189 (1971); J. L. Fry, E. M. Engler, and P. v. R. Schleyer, *ibid.*, **94**, 4628 (1972); S. A. Sherrod, R. G. Bergman, G. J. Gleicher, and D. G. Morris, *ibid.*, **94**, 4615 (1972); W. Parker, R. L. Tranter, C. I. F. Watt, L. W. K. Chang, and P. v. R. Schleyer, *ibid.*, **96**, 7121 (1974).

(19) J. S. Lomas, P. K. Luong, and J-E. Dubois, *J. Am. Chem. Soc.*, **99**, 5478 (1977); *J. Org. Chem.*, **44**, 1647 (1979).

(20) D. Farcasiu, *J. Org. Chem.*, **43**, 3878 (1978).

(21) M. R. Smith and J. M. Harris, *J. Org. Chem.*, **43**, 3588 (1978).

(22) P. Müller and J-C. Perlberger, *J. Am. Chem. Soc.*, **97**, 6862 (1975); **98**, 8407 (1976); J-C. Perlberger and P. Müller, *ibid.*, **99**, 6316 (1977).

(23) E. Osawa, K. Aigami, and Y. Inamoto, *J. Chem. Soc., Perkin Trans. 2*, 172, 181 (1979); E. Osawa, H. Shirahama, and T. Matsumoto, *J. Am. Chem. Soc.*, **101**, 4824 (1979).

(24) S. G. Baxter, H. Fritz, G. Hellmann, B. Kitschke, H. J. Lindner, K. Mislow, C. Ruchardt, and S. Weiner, *J. Am. Chem. Soc.*, **101**, 4493 (1979).

(25) E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **95**, 8005 (1973).

(26) D. F. DeTar and C. J. Tenpas, *J. Org. Chem.*, **41**, 2009 (1976).

(27) D. F. DeTar, *Comput. Chem.*, 1, 35 (1976).

(28) S. W. Benson, "Thermochemical Kinetics", 2nd ed., Wiley, New York, 1976.

(29) There are various alternative and equivalent ways of formally defining entropies of combination and of ring closure. Based on six examples, $S_{inl} = 65.877 + (n - 3)9.402$ for $CH_3(CH_2)_{n-3}CH{=}CH_2$, $s = 0.13$; based on six examples, $S_{inl} = 40.918 + 9.402n$ for $CH_3(CH_2)_{l-1}O(CH_2)_{m-2}CH_3$ with $n = l + m$, $s = 0.29$; based on four examples, $S_{inl} = 41.669 + 9.402n$ for $CH_3(CH_2)_{n-2}OH$, $s = 0.36$. For the formal reaction $CH_3(CH_2)_{n-3}CH{=}CH_2 \rightarrow$ cyclic $(CH_2)_n$, $\Delta S_{inl} = 3.583 - 2.868n$, with the increment per CH_2 (or per bond) the same as for eq 7.

(30) (a) H. Freundlich and A. Kroepelin, *Z. Phys. Chem.*, (*Leipzig*), **122**, 39 (1926); (b) H. Freundlich and A. Krestnikoff, *ibid.*, **76**, 29 (1911).

(31) H. Freundlich and G. Salomon, *Ber.*, **66**, 355 (1933).

(32) R. F. Brown and N. M. van Gulick, *J. Org. Chem.*, **21**, 1046 (1956).

(33) The chemical literature includes a variety of proposals for defining goodness of fit.[34-38] Still other proposals not cited here are statistically incorrect. A generally recognized statistical quantity is r^2, the square of the correlation coefficient, also called the coefficient of determination. If we deinfe $\Psi^2 = [n/(n - n_p)][\sum(y - \hat{y})^2/\sum(y - \bar{y})^2]$ as suggested by Wold and Sjoström,[34] then we have $\psi^2 = 1 - r^2$; y is the observed value of the dependent variable, $\bar{y}$ is the average value, $\hat{y}$ is the calculated value, and n is the multiple correlation coefficient. This definition holds for any functional definition of y and any number of dependent variables. The following statistics are sufficient to summarize the results of an adjustment of parameters: the number of points n, the number of adjusted parameters n_p, the resultant standard deviations of the parameters. From these statistics it is possible to compute whatever confidence limits may be of interest.[35] It is confusing and nonproductive to clutter reports of statistical computations in terms of derived units such as 95% confidence limits. The Hamilton R[36] is used by crystallographers and has been recommended for use in lanthanide shift studies.[37] It is defined as $R^2 = \sum (y - \hat{y})^2/\sum y^2$; R is a less desirable quantity for general use since its value depends on how much $\bar{y}$ departs from 0 as well as on the range of the y.

(34) S. Wold and M. Sjoström in "Correlation Analysis in Chemistry", N. B. Chapman and J. Shorter, Eds., Plenum Press, New York, 1978, p 37.

(35) C. A. Bennett and N. L. Franklin, "Statistical Analysis in Chemistry and the Chemical Industry", Wiley, New York, 1954.

(36) W. C. Hamilton, "Statistics in Physical Science", Ronald Press, New York, 1964.

(37) B. H. S. Lienhard and A. J. Thomson, *J. Chem. Soc., Perkin Trans. 2*, 1390 (1977).

(38) S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, *Prog. Phys. Org. Chem.*, **10**, 1 (1973). The f value recommended in this review is actually identical with the Hamilton R,[36] and R is always less than ψ:[34] S. Ehrenson, *J. Org. Chem.*, **44**, 1793 (1979). In LFER studies as treated by Ehrenson et al., $y = \log (k/k_H)$, and hence $\bar{y}$ is often nearly 0, so that $R \simeq \psi$ for these studies treated by this particular convention.

(39) See paragraph at end of paper regarding supplementary material.

(40) D. F. DeTar and N. P. Luthra, *J. Am. Chem. Soc.*, **99**, 1232 (1977).

(41) D. R. Stull, E. F. Westrum, Jr., and G. C. Sinke, "The Chemical Thermodynamics of Organic Compounds", Wiley, New York, 1969.

(42) There are, however, as yet unexplained differences between the Ingold data those of P. D. Buarlett and L. J. Rosen, *J. Am. Chem. Soc.*, **64**, 543 (1942), who report a $k_{n\text{-BuBr}}/k_{neo\text{-PeBr}}$ of 470. The Ingold group does not cite this work: ref 15 and accompanying papers.

(43) (a) J. B. Milstien and T. H. Fife, *J. Am. Chem. Soc.*, **90**, 2164 (1968); (b) M. Harfenist and R. Baltzly, *ibid.*, **69**, 362 (1947).

(44) (a) G. Salomon, *Helv. Chim. Acta*, **17**, 851 (1934); (b) *ibid.*, **19**, 743 (1936); (c) *Trans. Faraday Soc.*, **32**, 153 (1936); L. Ruzicka, G. Salomon, and K. E. Meger, *Helv. Chim. Acta*, **20**, 109 (1937).

(45) N. L. Allinger, M. T. Tribble, and M. A. Miller, *Tetrahedron*, **28**, 1173 (1972).

(46) C. Galli and L. Mandolini, *J. Chem. Soc., Perkin Trans. 2*, 443 (1977).

(47) At the request of a referee we enlarge upon the basis for our choices of symmetry numbers for rings. Cyclobutane, cyclopentane, and cycloheptane have very low barriers to pseudorotation and the $R \ln (2n)$ approximation therefore is an appropriate correction to represent the entropy of the hypothetical single nonsymmetrical ring. The barrier to equalize 12 hydrogens of cyclohexane is nearly 11 kcal/mol and the cyclooctane equalization barrier is almost as high. The subject is summarized by Dale.[48] On this basis the appropriate symmetry corrections would be $R \ln 6$, as adopted and $R \ln 8$ (instead of the $R \ln 16$). Readjustment of our correlations to $R \ln 8$ for cyclooctane leads to no change in $\Delta\Delta S$ for C_6 and a change of less than 0.15 cal deg^{-1} mol^{-1} for C_4 and C_5, to 14.21 instead of 14.84 for C_7, and to 11.13 instead of 11.77 for C_8. This reduces log k(calcd) for the seven-membered ring by 0.14. The identification of entropies of activation with intrinsic entropies of formal ring closure is an approximation. We judge that the data in Table I are good to about 1 cal deg^{-1} mol^{-1} on the basis of the excellent overall successes of the several empirical equations which summarize the experimental entropies of formation of alkanes, cycloalkanes, and their methyl derivatives. An error of 1.4 in $\Delta\Delta S$ leads to an error of 0.3 in rate constant.

(48) J. Dale, *Top. Stereochem.*, **9**, 199 (1976).

(49) W. C. Boyd, *J. Am. Chem. Soc.*, **67**, 1035 (1945).

(50) R. P. Bell, "The Proton in Chemistry", Cornell University Press, Ithaca, N.Y., 1959, p 65.

(51) "Handbook of Chemistry and Physics", 51st ed., Chemical Rubber Publishing Co., Cleveland, 1970–1971.