Quantification of the Various Contributors to Rate Enhancement in Nucleophilic Strain Releasing Reactions

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Since cyclopropanes are much more reactive than cyclobutanes despite their nearly identical strain energy, it has become clear that rate enhancement in cyclopropanes is partly due to strain release but also partly due to an additional factor about whose nature there is no consensus. Activation and equilibrium energies for a series of nucleophilic reactions of MeO^-, MeS^-, $MeNH^-$, Me_2N^-, and $MePH^-$ with strained rings ranging from epoxide to aza-cubane were computed at the HF/6-31+G* level. Using the Marcus equation, in combination with the computed intrinsic barrier for the identity reactions of the same nucleophiles with the strain free reference compounds (e.g., MeO^- with Me−O−Me and Me_2N^- with Me_3N), enabled a quantitative determination of the individual contributions of the partial strain release and the additional factor to the overall lowering of the transition state energy. Analysis of the data reveals the following: (a) There is no contribution of the additional factor to rate enhancement in four membered rings for first row elements (O and N) and only a small contribution (∼2 kcal) for second row elements (S and P). This is to be compared with a contribution of 7−17 kcal for three membered rings. (b) A significant synergistic effect is observed. Thus, in housane, for example, the additional factor amounts to 12.7 kcal which is more (by nearly 5 kcal) than the sum of the individual contributions of the isolated three and four membered rings. (c) The magnitude of the additional factor was found to be Periodic Table row dependent.

As we have shown earlier,[1] rate enhancement in reactions where strain energy is released is not driven solely by partial strain release at the transition state. The classical demonstration that strain release is not the only contributing factor is obtained from a comparison of the reactivity of cyclobutane and cyclopropane. The two molecules have nearly the same strain energy (ca. 27 kcal) yet they differ vastly in their reactivity.[2] The most convincing evidence for the involvement of an additional contributor, besides partial strain release, to rate enhancement is the observation that in certain cases the transition state energy is lowered significantly more than the overall strain released in the reaction.[1a]

The nature of the additional factor is not clear. We have suggested that the excessive reactivity of some strained rings beyond the normal expectance is due to a change in hybridization at the site of attack. Thus, for example, structural deformation may lead to a lowering of the LUMO of the bond to be cleaved and as a result, in nucleophilic reactions, bonding to the nucleophile and energy gain commence earlier than in the corresponding unstrained substrates.[1a] Within the framework of the curve crossing model, the transition state is achieved earlier and at a lower energy.[3]

A different interpretation of the facile opening of three membered rings compared to four membered ones was offered by Houk et al.[4] Their suggestion is based on sigma aromaticity for the three membered rings and sigma antiaromaticity for the four membered rings at the corresponding transition states.

The major purpose of this work is to quantify, for the first time, the contribution of the two components, strain release and the additional factor, to the overall lowering of the activation barrier in the reactions of strained rings.

Methodology

The method we have adopted is based on the following reasoning. Relative to an isoergic reaction where reactants and products are at the same energy, the exothermicity in a reaction where strain energy is released will be partly reflected at the transition state by a lowering of its energy. For a "normal reaction" without any "special effects", the new activation energy can be calculated using the Marcus equation:[5]

$$Ea = Ea_{int} + \Delta E_0/2 + \Delta E_0^2/16Ea_{int}$$

The difference in activation energy between the intrinsic barrier (for the isoergic reaction) and the Marcus barrier is the strain contribution to the lowering of the activation energy. If the observed activation energy (ab initio computed) is lower than the one calculated by the Marcus equation, then the difference between the Marcus activation energy and the

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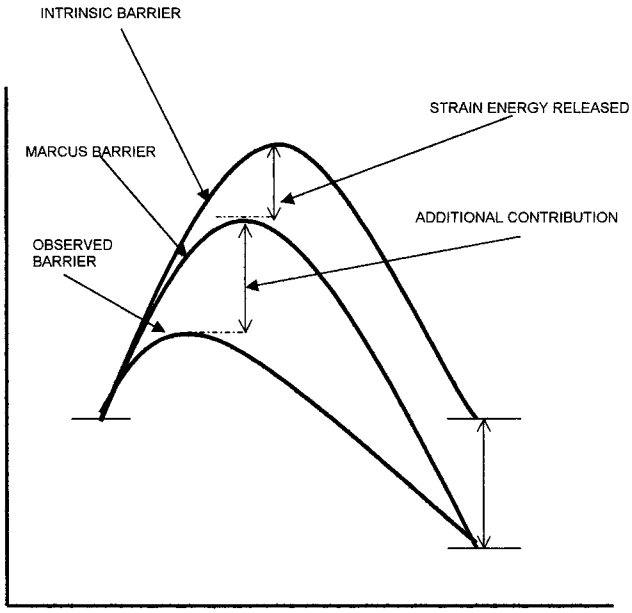

Figure 1. Reaction profiles for a reference identity reaction (intrinsic barrier), for the expected (Marcus) barrier based on partial strain release at the transition state, and for the observed (ab initio computed) barrier.

observed activation energy is the additional factor. Let us demonstrate the procedure by examining the reaction of methoxide with epoxide.

In the first step we compute (ab initio) the intrinsic barrier (Ea_{int}) of the strain free identity reaction − methoxide + dimethyl ether (eq 1). Then we compute (ab initio) the reaction energy (ΔE_0) of the reaction of methoxide with epoxide (eq 2). Using the intrinsic barrier and ΔE_0, we apply the Marcus equation to calculate the expected (Marcus) activation energy for the latter reaction (see Figure 1). The difference between the intrinsic barrier (eq 1) and the Marcus activation energy for the reaction of epoxide (eq 2) is the strain contribution to the lowering of the activation energy.

In the next step, we compute (ab initio) the activation energy (Ea) for the reaction of methoxide with epoxide (eq 2).

The difference between the Marcus activation energy and the observed (ab initio computed) activation energy for the reaction of methoxide with epoxide is the contribution of the additional factor to the lowering of the transition state energy (Figure 1).

Energy and structure computations were done at the HF/6-31+G* level using the Gaussian 94/98 programs.[6] To ensure the validity of the results, several computations were carried out also at the B3LYP/6-31+G* and the MP2/6-31+G*//6-31+G* levels. Since these corroborated the HF/6-31+G* results we quote here only results of the latter method with which many more series of reactions were computed.

The ion−dipole complexes of the nucleophiles and the substrates were taken as the ground states of the reactants. In certain cases, collinearity (of X−C−X where X is the attacking atom in the nucleophile and the atom whose bond to the attacked carbon in the ring is cleaved) was imposed in these complexes. Each transition state was characterized by a frequency analysis. In addition, in certain cases, the IRC procedure was used to ascertain the connection between the transition state and the products.

Results and Discussion

The reactions are grouped in sets according to the identity of the nucleophilic atom.

The reactions studied are shown in Chart 1; the ground state, transition state, and products energies are given in Table 1. The activation energies and their components, the equilibrium energies, and the relevant geometrical data are given in Table 2.

Activation Energies. It is clear that the more deformed the carbon atom which undergoes nucleophilic attack, the lower the kinetic barrier. Examination of the Me_2N series clearly demonstrates this. The lowest activation energy is obtained for the bicyclobutane system in which the bridgehead carbon is known to have an inverted geometry.[7] The highest barrier among the ring opening reactions is that of the least deformed carbon belonging to the cyclobutane system. Analysis of the data shows that there is no correlation between the kinetics and the thermodynamics of the various reactions even within a set. This clearly hints to the intervention of an additional factor besides simple strain release. The absence of correlation between the kinetics and the thermodynamics becomes obvious from a comparison of the data for the three and the four membered rings in each set. The exothermicity of the four membered ring opening is roughly identical to that of the three membered ring (containing the same elements). The average difference between the two in the various sets is ca. 2 kcal. However, the activation energies differ immensely. This is more pronounced for the second row elements (S and P) where the activation energies for the reactions of the four membered rings are twice as high as those for the three membered rings. We have no explanation for this difference between the behavior of the first and second row elements.

Interestingly, for the same ring size, the activation energies are controlled by the valence of the nucleophilic atom within a row. Namely, Ea(N) > Ea(O) and Ea (P) > Ea(S). Moreover, the activation energies for the four membered rings obey very closely the observation reported earlier that, in identity S_N2 reactions, the activation energies are dictated by the position of the element in the Periodic Table and closely follow the rule Ea = (valence)(11 kcal/mol)[8] (found at the G2+ level of calculation for the identity reactions).

The Additional Factor. By subtracting the ab initio computed activation energy from the Marcus activation energy, we obtain the additional factor to the lowering of the reaction barrier. Values of the additional factors

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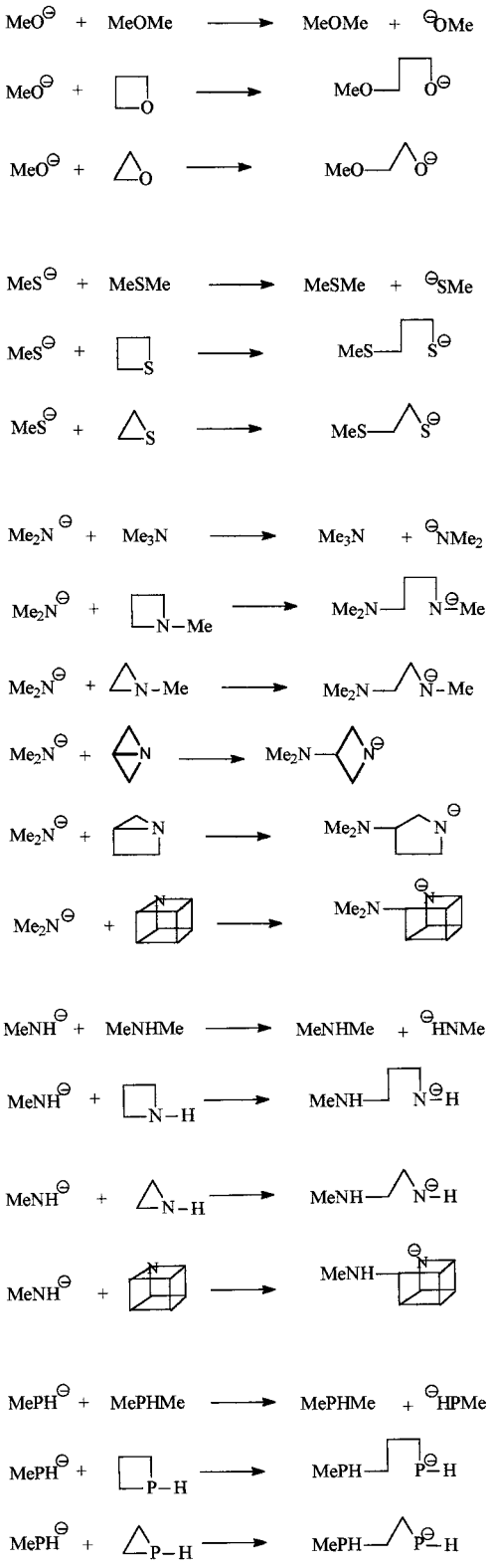
Chart 1



(in kcal) to the lowering of the activation energy are given in Table 2.[9]

It is most convenient to compare the additional factor of the three with that of the four membered rings within each set. Such a comparison draws attention to two phenomena. The first is that, within a set, the strain driven barrier is nearly identical for the three and the four membered rings. Namely, the Marcus activation energy as well as the strain contribution are, in general,

Table 1. Ground State, Transition State, and Product Energy in AU

	R	TS	P
MeO^- + Me−O−Me	-268.49121	-268.439909	
MeO^- +	-306.340201	-306.30587	-306.377636
MeO^- +	-267.298972	-267.276088	-267.34027
MeS^- + Me−S−Me	-913.8698824	-913.8189615	
MeS^- +	-951.719702	-951.686643	-951.74845
MeS^- +	-912.6873551	-912.6711332	-912.7164622
Me_2N^- +	-306.859306	-306.789379	
Me_2N^- +	-344.704198	-344.6501899	-344.739112
Me_2N^- +	-305.661648	-305.621665	-305.697902
Me_2N^- +	-304.455747	-304.43825	-304.502495
Me_2N^- +	-343.502141	-343.482288	-343.570203
Me_2N^- +	-456.976768	-456.942001	-457.048286
$MeNH^-$ + Me−N(H)−Me	-228.79091	-228.720264	
$MeNH^-$ +	-266.633718	-266.583666	-266.673531
$MeNH^-$ +	-227.594364	-227.558273	-227.639178
$MeNH^-$ +	-417.941044	-417.909038	-418.021396
$MePH^-$ + Me−P(H)−Me	-801.40973	-801.336576	
$MePH^-$ +	-839.251609	-839.20052568	-839.2837732
$MePH^-$ +	-800.213672	-800.1867377	-800.2525683

within 1 kcal of each other for the three and four membered rings. *Therefore, the excessive reactivity of the three membered rings should clearly be attributed to the additional factor which is much larger in the three membered rings than in the four membered rings.* The difference between the two reaches as high as 13 kcal.

It is extremely surprising to see that the near absence of the additional factor in four membered rings is so overwhelming that it manifests itself even in the cubane system—the most strained molecule in this study. Thus, in the reaction of azacubane, the exothermicity of the reaction is ca. 50 kcal and the additional factor is only 2.6 kcal. This is to be compared with 1.3 kcal for azacyclobutane and 8.2 kcal for aziridine—both reactions with an exothermicity of ca. 22 kcal. This manifests more than ever the difference between the three and the four membered rings. That is, regardless of the molecular structure and the total strain imposed on the four membered ring, it will not display any excessive reactivity.

(9) The results using the B3LYP/6-31+G* and the MP2/6-31+G*//6-31+G* methods gave for ΔE_0 values within 1 kcal of the HF/6-31+G* values. While calculated activation energies are significantly lower (e.g., 10 kcal for the intrinsic barrier), the strain and the additional contributions remain essentially the same. Thus, for example, the magnitude of the additional contribution for the reaction of oxatane was found to be −1.1 and 0.85 kcal at the B3LYP/6-31+G* and the MP2/6-31+G*//6-31+G* levels, respectively, compared to 0.0 kcal at the HF/6-31+G* level. For the reaction of epoxide, these were 4.0 and 5.9 kcal compared to 6.2 kcal using the HF/6-31+G* method. Similar results were obtained for the N-series validating the data obtained at the HF/6-31+G* method.

Table 2. Activation Energies and Their Components, Equilibrium Energies, and Geometrical Data Are Given in Table 2

			Ea	Strain	Additional	bond length at TS	
	ΔEo	Ea	Marcus	Cont.	Cont.	Nuc-C	C-Lg
MeO^- + Me-O-Me	0.0	32.2				1.897	1.897
MeO^- + 	-23.5	21.5	21.5	10.7	0.0	1.983	1.879
MeO^- + 	-25.9	14.4	20.5	11.7	6.2	2.059	1.781
MeS^- + Me-S-Me	0.0	32.0				2.447	2.447
MeS^- + 	-18.0	20.7	23.6	8.4	2.8	2.592	2.375
MeS^- + 	-18.3	10.2	23.5	8.5	13.3	2.651	2.219
$Me2N^-$ + 	0.0	43.9				1.973	1.973
$Me2N^-$ + 	-21.9	33.9	33.6	10.3	-0.3	2.276	1.825
$Me2N^-$ + 	-22.8	25.1	33.2	10.6	8.2	2.188	1.713
$Me2N^-$ + 	-29.3	11.0	30.4	13.4	19.5	2.128	1.851
$Me2N^-$ + 	-42.7	12.5	25.1	18.8	12.7	2.071	1.962
$Me2N^-$ + 	-44.9	21.8	24.3	19.6	2.5	2.154	1.924
$MeNH^-$ + 	0.0	44.3				1.989	2.819
$MeNH^-$ + 	-25.0	31.4	32.7	11.6	1.3	2.098	1.957
$MeNH^-$ + 	-28.1	22.7	31.4	12.9	8.7	2.180	1.871
$MeNH^-$ + 	-50.4	20.1	22.7	21.6	2.6	2.156	1.908
$MePH^-$ + 	0.0	45.9				2.549	2.547
$MePH^-$ + 	-20.2	32.1	36.4	9.5	4.3	2.662	2.452
$MePH^-$ + 	-24.4	16.9	34.5	11.4	17.6	2.787	2.297

For the second row elements P and S, the additional factor is boosted overall. Therefore, while for the elements O and N there is no additional factor in the four membered rings, for P and S there is a noticeable additional factor even for the four membered rings.

In most cases, there is an appreciable synergistic effect. Thus for example, in the nitrogen set, the contribution of the additional factor to the reaction of aziridine (8.2 kcal) is more than doubled (19.5 kcal) in the two edge-fused three membered rings of aza-bicyclobutane. Likewise, in housane, the additional factor (12.7 kcal) is more than the sum of its components (7.9 kcal).

Summary and Conclusions

We have found that, in general, the more deformed the system, the smaller the activation energy. This is so regardless of the total strain of the molecule. Thus, the strain energy of cubane is ca. 160 kcal/mol,[10] whereas the strain energy of bicyclobutane is about one-third of that[11] (data relates to the all-carbon systems). Yet, the activation energy in the reaction of the latter with Me_2N^- is only 11 kcal, whereas that of the former (in the aza series) is twice as much. In the case of the aza-bicyclobutane, the reduction in the barrier height (32.9 kcal) is more than the total strain energy released in the reaction indicating once more the presence of an additional contributor to rate enhancement besides strain release.

The contribution of the additional factor to the rate enhancement in the reactions of strained ring compounds has been quantitatively determined here. Several interesting features of this factor were revealed: (a) It is practically the sole contributor to the difference in reactivity between the three and the four membered rings. For the latter it is practically absent (except for the second row elements, where it is relatively small), and it is much larger for the three membered ring. (b) A significant synergistic effect was observed. Thus, despite the near absence of this component in the reactions of the four membered rings, when fused to a three membered ring as in housane, the additional factor amounts to 12.7 kcal, which is more (by nearly 5 kcal) than the sum of the contributions of the isolated three and four membered rings. (c) While, in general, activation energies were found to be valence dependent (Periodic Table column dependency), the magnitude of the additional factor was also found to be Periodic Table row dependent.

We hope that the quantification of the additional factor will in the future provide an unambiguous key to the origin of the phenomenon.

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Supporting Information Available: A listing of archive files for the optimized reactant complexes, transition states, and products. This information is available free of charge via the Internet at http://pubs.acs.org.

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