Reactivity of Strained Compounds: Is Ground State Destabilization the Major Cause for Rate Enhancement?[1]

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Abstract: Reaction and activation energies were computationally determined for the nucleophilic attacks of OH^- on 1-cyanobicyclobutane, 2-cyanobicyclobutane, and propionitrile using ab initio methods at the RHF/6-31+G* level. In the first reaction the central bond of the bicyclobutane moiety is cleaved. In the second reaction a side bond is fissioned, and in the third reaction an unstrained reference C−C bond is cleaved. The reaction energies are −38.3, −34, and −0.1 kcal, and the activation energies are 4.4, 30.6, and 41.6 kcal, respectively. Based on these data, traditional analysis suggests that the percent of strain relieved at the transition states of the first two reactions which have nearly the same thermodynamic driving force is 97% and 32%, respectively. These values, according to the linear free energy relationship approach point to an early transition state for the first reaction and a late transition state for the side bond cleavage. Examination of the computed geometrical parameters shows the opposite trends. Detailed analysis of these results suggests that the destabilization of the ground state cannot be considered as the major cause for the rate enhancement observed for strained substrates. Rather, an early transition state, which is usually accompanied by a low activation energy, results from a better capability of the frontier orbitals of the substrate to bond the entering nucleophile. Thus, the main chain of cause and effect in rate enhancement is molecular deformation → rehybridization → lower LUMO → better bonding capabilities. In bicyclobutane the lowest σ^* orbital is associated with the central bond which therefore is cleaved much faster than the side bond which in turn is more reactive than the C−C bond of propionitrile.

Introduction

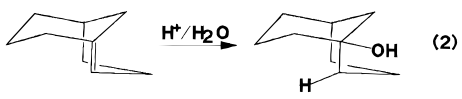
Strain is one of the fundamental concepts in organic chemistry and is considered a major factor in determining structure, energy and reactivity of many organic compounds.[2−4] In addition, strain energies have proven to be very valuable quantities for a synergistic interaction between experiment and theory.[5,6]

The effect of strain on a reaction center may be so pronounced that the strained molecule will exhibit chemistry which is practically nonexistent for the unstrained analog. A classical example is that of cyclopropane which undergoes C−C bond cleavage relatively easily, whereas extremely drastic conditions are probably required for the same process in propane.[6]

In general, the rate enhancement in "strain catalyzed reactions" is attributed to the destabilization of the ground state and partial release of strain energy at the transition state (TS). The degree of strain release at the transition state can be quantitatively defined (eq 1) as the difference in the activation energies of the strained (S) and the unstrained (US) compounds divided by the difference in their reaction energies.[7]

$$\text{deg of strain released at the TS} = \frac{E_a(\text{US}) - E_a(\text{S})}{\Delta E_0(\text{US}) - \Delta E_0(\text{S})} \quad (1)$$

Since, by definition, no strain is released in the reaction of the unstrained reference compound, the difference in the reaction energies is the strain energy released in the reaction of the strained compound. The difference in the activation energies corresponds to the strain energy which is released in the TS. The division of the two difference values in eq 1 gives the fraction of the strain energy which is released at the TS. This ratio, in combination with linear free energy relationship (LFER) methodology,[8−10] has been frequently used to locate the position of the TS along the reaction coordinate assuming a linear correlation between the position of the transition state and the degree of strain relief. For example in the hydration of bicyclo-[3.3.1]non-1-ene (eq 2), the degree of strain released at the TS was found to be 0.58. This value is slightly lower than the observed Bronsted α value 0.67, which is also an indicator for TS location.[11]



(2)

Another example is a high-level theoretical investigation of a

[⊗] Abstract published in *Advance ACS Abstracts,* December 15, 1995.

(1) This work was presented, in part, at the Italian−Israeli conference on Physical Organic Chemistry; Sassary 1994.

(2) Greenberg, A.; Liebman, J. F. *Strained Organic Molecules*; Academic Press: New York, 1978.

(3) Wiberg, K. B. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312.

(4) *Advances in Strain in Organic Chemistry*; Halton, B., Ed.; JAI Press, London, 1991; Vol. 1.

(5) See, for example: Wagner, H. U.; Szeimies, G.; Chandrasekhar, J.; Schleyer, P. v. R.; Pople, J. A.; Binkley, J. S. *J. Am. Chem. Soc.* **1978**, *100*, 1210. Dill, J. D.; Greenberg, A.; Liebman, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 6814. Horvat, D. A.; Borden, W. T. *J. Am. Chem. Soc.* **1988**, *110*, 4710.

(6) Lawrence, C. D.; Tipper, C. F. H. *J. Chem. Soc.* **1955**, 713. Skell, P. S.; Starer, I. *J. Am. Chem. Soc.* **1960**, *82*, 2971. Wiberg, K. B.; Kass, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 1988.

(7) A referee pointed out that although this equation seems plausible, it contradicts the Hammond postulate (Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334). Namely, in a reaction where much strain energy is released, the Hammond postulate would predict an early TS. Yet, the earlier the TS, the less it will benefit from strain energy release. The latter will be more pronounced for a product like TS.

(8) Lefller, J. E.; Grunwald, E. *Rates and Equilibria of Organic Reactions*; Wiley: New York, 1963.

(9) *Correlation Analysis in Chemistry*; Chapman, N. B., Shorter, J., Eds.; Plenum: New York, 1978.

(10) See, however, criticism of this approach: Hoz, S.; Basch, H.; Goldberg, M. *J. Am. Chem. Soc.* **1992**, *114*, 4364. Hoz, S. *Acta Chem. Scand.* **1992**, *46*, 503. Hoz, S. *Acc. Chem. Res.* **1993**, *26*, 69.

(11) Chiang, Y.; Kresge, A. J.; Wiseman, J. R. *J. Am. Chem. Soc.* **1976**, *98*, 1564.

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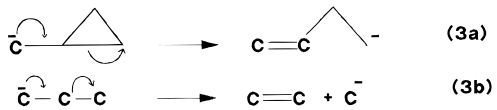
unimolecular carbanionic ring opening (eq 3a)



In this study the activation energy of the cyclopropyl derivative was ca. 20 kcal/mol lower than that for the unstrained analog (eq 3b), and the calculated degree of strain energy released at the TS was concluded to be 80%.[12]

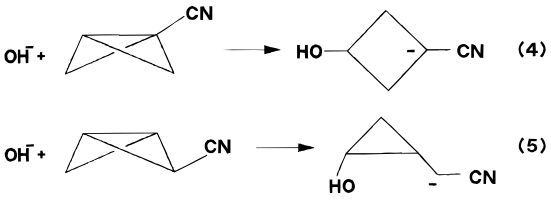
Thus the basis of the traditional analysis and understanding of strain effect on reactivity lies in the assumption that the observed rate enhancement stems from the destabilization of the ground state of the strained compound. In this paper it will be shown that ground state destabilization is only part of the reactivity story and may even have only a marginal effect on the increased reactivity.

Methodology and Computational Procedures

The *ab initio* RHF computations were performed with the Gaussian 92 package using the 6-31+G* basis set[13] on IBM RS/6000 workstations. The geometries of the reactants, products, and transition states were optimized by gradient methods and their stationary point character checked by frequency calculations. The conformation of the product was arrived at by using the IRC method from the appropriate transition state. The major structural parameters are given in Table 1.

Results and Discussion

The cleavage reactions of the central and the side bonds in the course of hydroxide attack on cyano substituted bicyclobutane were studied. For an attack directed toward cleavage of the central bond, the bicyclobutane was substituted by a cyano group at a bridgehead position. For side bond cleavage, the activating cyano group was positioned on C2, the methylene carbon (eqs 4 and 5 respectively).

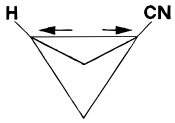
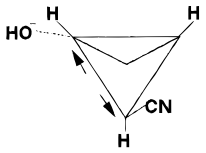
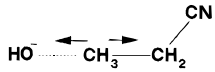
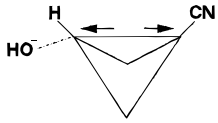
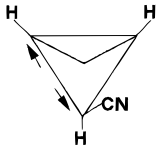


The cyano group on C2 can adopt either an exo or an endo position. Both cases were studied and found to give essentially the same results. Therefore only the results for exo substitution will be reported here.

In addition to the cleavage reactions of the central and the side bonds, a strain free reference reaction—the reaction of hydroxide with propionitrile (eq 6)—was studied. In this SN2 reaction, as in the reactions of the cyanobicyclobutane systems above, the leaving group is >C−CN.

In all three reactions, the most stable ion−dipole complex of the reactants was calculated to have the OH^- bound to a proximate hydrogen atom rather than to the carbon which undergoes the attack. For the bicyclobutanes the preferred attachment was to the hydrogen atom on the bridgehead carbon, whereas on the propionitrile it was to the hydrogen α to the CN group. In order to simplify the reaction coordinate, the position of the hydroxide in the reactant ion−dipole complex was restricted to the direction of approach toward the appropriate carbon at the corresponding transition states. The major results are given in Table 2.

Table 1. Major Geometrical Parameters[a] of Species Calculated at the RHF/6-31+G* Level

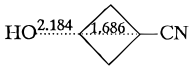
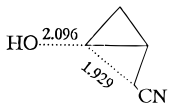
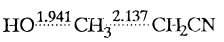
	C*−O, Å	C*−C(CN), Å	O−C*−C(CN), angle	C*−C−(CN), angle	interflap[b] angle
			Reactions		
					
S[c]		1.478		130.52	122.06
R[d]	2.679	1.501	163.37	133.14	122.19
TS	2.184	1.686	163.37	123.73	132.42
P[e]	1.415	2.138	137.51	139.52	170.47
					
S[c]		1.495		117.54	118.98
R[d]	2.897	1.497	151.41	118.9	120.27
TS	2.096	1.929	151.41	114.27	107.35
P[e]	1.402	2.589	140.14	111.12	107.11
					
S[c]		1.532		112.19	
R[d]	2.871	1.538	175.39	114.41	
TS	1.941	2.137	175.39	111.06	
P[e]	1.42	3.983	175.39	66.99	
					
A[f]		1.678		120.44	129.16
B[g]	1.52	1.678	163.37	175.62	137.98
C[h]	2.184	1.678	163.37	124.23	132.11
					
A[f]		1.695		117.15	116.94
B[g]	2.792	1.695	151.41	117.6	117.18
C[h]	2.184	1.695	151.41	116.32	111.42
					
A[f]		1.732		109.89	
B[g]	2.789	1.732	175.39	112.53	
C[h]	2.184	1.732	175.39	113.29	

[a] Angles are given in deg. [b] Defined as $C_3-C^*-C_1-C_4$ dihedral angle. [c] Isolated substrate. [d] Reactant complex. [e] Products in the conformation obtained by the IRC method. [f] Stretch 0.2 Å of the C−C bond from equilibrium. [g] Stretch 0.2 Å of the C−C bond from equilibrium. Optimization in the presence of OH^- restricted to the TS direction of attack. [h] Stretch 0.2 Å of the C−C bond from equilibrium. Optimization in the presence of OH^- restricted to the TS direction of attack with an O−C distance of 2.184 Å.

(12) Tonachini, G.; Bernardi, F.; Schlegel, H. B.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2*, **1988**, 705.

(13) Gaussian 92, Revision C, Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; and Pople, J. A.; Gassian, Inc.: Pittsburgh, PA, 1992.

Table 2. Reaction Parameters for OH^- Attack on the Three Substrates[a,b]

TS	E_a	reaction energy	total strain relief	amount of strain relieved at TS	% of strain relieved at TS
	4.4 (4.4)	−38.3 (−35.8)	38.2 (34.9)	37.2 (36.3)	97 (104)
	30.6 (30.0)	−34.0 (−32.1)	33.9 (31.2)	11.0 (9.3)	32 (30)
	41.6 (40.7)	−0.1 (−0.9)	0	0	0

[a] Energies in kcal/mol; bond length in Å. [b] Data corrected for RHF ZPEs (scaled by a factor of 0.89) are given in parentheses.

As can be seen from Table 2, the reaction energies for the cleavage of the two C−C bonds in bicyclobutane are nearly the same (within 5 kcal from each other). This is in accord with expectations based on the fact that the substituted cyclopropane and cyclobutane products have nearly the same strain energies.[2,14] However, in spite of the nearly similar thermodynamic driving force for the two reactions, the side bond cleavage has a significantly larger difference (26 kcal) activation energy. According to conventional interpretation the activation energy is smaller for the central bond cleavage because a larger amount of the strain energy has already been released at its transition state. More specifically, this transition state should be relatively product-like and therefore most of the strain energy (97%, Table 2) has been released; leading to a significantly low activation energy. On the other hand, the TS for the side bond cleavage would be interpreted as having to be more reactant-like with only a relatively small portion of the strain energy released at the TS (32%, Table 2). The activation energy is therefore rather large. However, examination of the relevant reaction geometrical parameters in Table 2 leads, in agreement with the Hammond postulate (see reference in footnote 7), to the opposite conclusion. In terms of the C−C bond distances, the TS is achieved much earlier for the attack on the central than on the side bond of bicyclobutane (C−C distances of 1.686 and 1.929 Å, respectively). Therefore it is not reasonable to suggest that a differential release of strain energy is responsible for the observed large difference in BCB activation energies.[15]

If the selectivity in reaction paths cannot be attributed to differential strain release, what then is the factor which causes the observed difference? Within the framework of phenomenological models, a common practice is to dissect the examined quantity into its contributing factors. One way by which the differences among activation energies of various systems can be analyzed is to compare the individual contributions of the nucleophile, the substrate, and the interaction between them to the overall activation energy among the different reactions. For this purpose the energies of the individual fragments have to be computed. Clearly, since the separated entities can be computationally analyzed using their TS geometries but not necessarily the precise electronic structure that they acquire at the TS, only a semiquantitative picture can be obtained from such an analysis. The energies of the hydroxide anion, the bicyclobutanes, and these reference units at their corresponding TSs geometries were thus computed. As expected, the variations in the OH^- energy due to geometry (i.e., O−H distance) changes upon going from the free hydroxide ion to the TS geometries are rather small (<0.1 kcal) for all three reactions and do not contribute much to the difference in the activation energies. On the other hand, the difference in the distortion energies of the BCB substrates to reach the respective TS geometries are rather large. Stretching the bicyclobutane side bond by more than 0.4 Å (the TS distance) raises its energy by ca. 30 kcal more than stretching the central bond by ca. 0.17 Å (its TS distance) (Table 3). Thus, the distortion of the substrates to their corresponding TS geometries seems to be the major contributor to the differences in activation energies among the three reactions. These results imply that the bonding energy, namely, the interaction energy between the nucleophile and the distorted substrate (of the TS geometry) is nearly identical in the corresponding TSs.

Table 3. Energy (E) Changes Due to Substrates Distortion to TS Geometries

reaction	E,[a] kcal
central	10.96
side	39.54
reference	59.15

[a] Relative to the fully optimized structure.

Table 4. Energy (E) Changes upon C−C Bond Stretch from Equilibrium

bond stretch, Å	relative E, kcal		
	central	side	reference
0.0	0.0	0.0	0.0
0.1	2.5	2.8	2.8
0.2	8.3	9.5	9.5
0.3	16.2	18.2	18.3
	GVB		
0.0	0.0	0.0	
0.2	2.3	5.4	
0.3	5.7	11.7	

The question to be asked at this point is why do the different reactions achieve the TS at such different locations along the reaction coordinate. In other words, why has the side bond to be stretched as much as 0.4 Å to achieve the proper amount of bonding so that the transition state could be attained, whereas the central bond can be stretched to a much smaller extent. In order to clarify this point the central and the side bonds of bicyclobutane were separately stretched to the same extent (at each point the rest of the molecule was fully optimized), and the rise in energy for the two was compared. Since it is expected that the central bond with its partial π bond character needs to be more correlated than the side bond, the comparison should be made with correlated bonds. Therefore, the same calculations were repeated at the GVB level (Table 4 and Figure 1. The GVB calculations used one pair of electrons and two orbitals—bonding and anti-bonding of the bond to be cleaved). The data clearly show that the stretching of the central and the side bonds as well as that of the C−C bond in the reference molecule results in nearly the same rise in energy also at the GVB level (the differences are rather small compared to the differences in the activation energies). *Thus, it is unlikely that in the cleavage of the central bond more strain energy is released earlier along the reaction coordinate than in the later TS of the side bond cleavage. The key to the differences seems to lie in* the *preferential proclivity of the bridgehead carbon to*

(14) Schleyer, P. v. R.; Williams, J. E.; Blanchard, K. R. *J. Am. Chem. Soc.* **1970**, *92*, 2377.

(15) MP2 calculations on the RHF/6-31+G* geometries were performed. The results suggest a barrierless ($E_a = -0.7$ kcal) reaction for the central bond cleavage. Substituting the MP2 values into eq 1, the amount of strain released at the TS is found to be 103%. This of course supports our conclusion even further. The results of these single point calculations are documented in the supporting information.

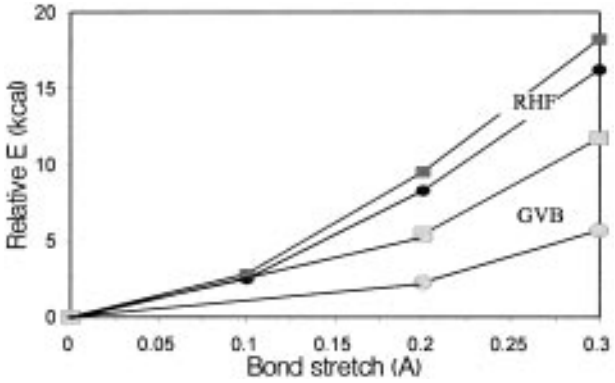


Figure 1. The energetic effects of a C−C bond stretch. The GVB data is shown in the inset.

Table 5. OH−Substrate "Bonding Component"

	central	side	reference
C−O distance (Å)[a]	1.52	2.792	2.789
bonding energy (kcal)	**−66.6**	**−20.6**	**−12.1**
bonding energy (kcal)[b]	**−19.9**	**−9.7**	**−1.6**

[a] C−C set to 0.2 Å and C−O optimized. [b] C−C set to 0.2 Å and C−O to 2.184 Å.

bond the approaching nucleophile in the two processes. The frontier MOs of bicyclobutane are associated with the central bond, and its LUMO is much lower than the σ^* of the side bond.[16] Since the gain in bonding energy is largely controlled by the HOMO (nucleophile)−LUMO (substrate) energy gap, more bonding is expected to be achieved earlier in the case of the central bond cleavage than in a side bond cleavage.

In order to test this hypothesis we have performed two sets of calculations on each of the three reactions. First the C−C bond to be cleaved was stretched by 0.2 Å, while the OH^- position along the path of attack as well as the other geometrical parameters were optimized. The energies of the separated hydroxide and the cyano bicyclobutane moiety each at their distorted geometries were also calculated. The difference between the energies of the separated species and of the combined complex can serve as a qualitative measure for the relative bonding capabilities of the substrates in the central, side and reference C−C bond cleavage reactions. The data in Table 5 clearly indicate that the bonding capability of the central bond is by far superior to that of the side bond, which in turn is larger than that of the model compound. The C−O distance in the case of the central bond converges to ca. 1.5 Å (bonding distance), whereas for the side bond and the model system it optimizes to ca. 2.8 Å, which is a loose complex distance. This, of course, by itself is indicative of the relative bonding tendencies of the various species involved. Nevertheless, the same procedure was repeated with the only difference being that the C−O distance was fixed at 2.184 Å for all three cases. The general picture described above repeated itself here as well, although the differences are not as spectacular as in the previous set of calculations.

The outcome of the earlier and more intensive bonding of a nucleophile to a substrate is twofold; the activation energy is lowered, and the TS is achieved earlier along the reaction coordinate. This is pictorially demonstrated in a traditional curve crossing diagram for the two reactions having (for the sake of simplicity) the same rising energy curve as a function of reaction coordinate while having different bonding curves. As can be seen from the diagram (Figure 2), the reaction for

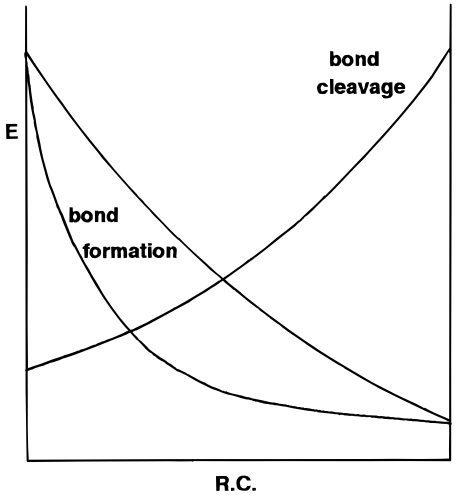


Figure 2. Curve crossing diagram for HO^- attack on the central and the side bonds of bicyclobutane and on the reference compound propionitrile.

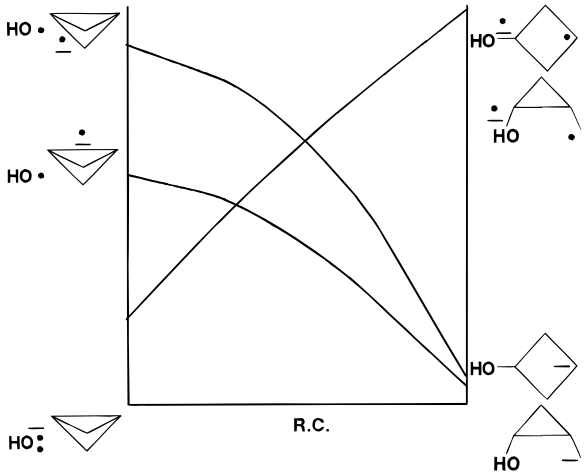


Figure 3. Shaik−Pross curve crossing diagram for the nucleophilic reaction of OH^- with bicyclobutane.

which the bonding is more enhanced at an earlier stage of the reaction has a lower barrier as well as an earlier TS.

A similar conclusion can be obtained also by using the Shaik−Pross curve crossing model[17] (Figure 3). On the reactant side the electron transfer excitation to the σ^* orbital of the central bicyclobutane bond will be easier than that of the side bond mainly because of the difference in the σ^* orbital energies. On the product side, excitation involves the LUMO of the C−O bond which, to a first approximation, requires the same amount of energy for the two processes. Thus, as can be seen from Figure 3, the Shaik−Pross approach also predicts a lower activation energy and an earlier TS for the central bond cleavage reaction.

Summary and Conclusion

The chemistry of bicyclobutane shows that the central bond is much more reactive than the side bond. In fact, the chemistry of the side bond is practically non-existent.[18] In accord with this observation the *ab initio* calculations reported here show that the barrier for the nucleophilic attack by OH^- on cyano activated bicyclobutanes is lower for central bond cleavage by

(16) Wiberg, K. B.; Peters, K. S.; Ellison, G. B.; Alberti, F. *J. Am. Chem. Soc*. **1977**, *99*, 3946.

(17) Pross, A.; Shaik, S. S. *Acc. Chem. Res*. **1983**, *16*, 363. Shaik, S. S. *Progr. Phys. Org. Chem*. **1985**, *15*, 197. Pross, A. *Adv. Phys. Org. Chem*. **1985**, *15*, 99. *Acc. Chem. Res*. **1985**, *18*, 212.

(18) Hoz, S. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987; Chapter 19.

ca. 25 kcal than for the side bond cleavage reaction. At room temperature this corresponds to a rate enhancement of ca. 18 orders of magnitude. The high selectivity is observed in spite of the similar thermodynamic driving force for the two processes.

The calculations also show that different degrees of strain release at the TS of the central/side bond cleavage reactions are not the cause for the difference in reactivity. In fact, individually stretching the two bonds to the same extent results in practically the some energy rise. Therefore, different degrees of strain release cannot be held responsible for the large difference in the activation energies. The results suggest that the different reactivity in the two processes stems primarily from the difference in the nucleophile−substrate bonding capabilities for the two reaction modes. The cleavage of the central bond is much more facile since, due to its low LUMO, the bonding interaction with the nucleophile's HOMO is much stronger than that of the side bond which has a higher σ^*. As a result bonding commences relatively early, and therefore the TS for the central bond cleavage is achieved early (see Figures 2 and 3). Thus, our conclusion is that in this case, and most probably in many other cases, it is mainly the bonding capability and not the strain induced ground state destabilizaton which is responsible for enhanced reactivity. The fact that strain and enhanced bonding capabilities go together is because the strain which emerges from deformation of bonding angles is oftentimes accompanied by significant rehybridization. This rehybridization results in lowering the antibonding and raising the bonding orbitals of the deformed bonds in the substrate which in turn become much more reactive than normal sp^3 bonds. Thus, overall, the deformation of the molecular framework results in (Figure 4) (a) ground state destabilization i.e. strain energy and (b) rehybridization → lower LUMO → better bonding capabilities. *In cases* (and probably many bimolecular reactions belong to this category) *where the TS is early, the major contribution to the rate enhancement would be that of enhanced bonding rather than strain release*.

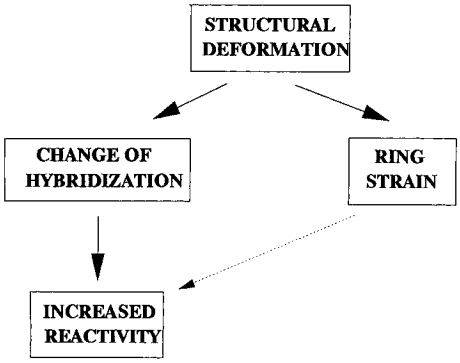


Figure 4. Causes and effects in what is called strain induced reactivity.

Supporting Information Available: Gaussian archive records for the geometry optimized molecules in Table 1, energies in hartrees for species given in Tables 1 and 3−5, MP2/6-31+G*//6-31+G* energies and RHF ZPEs for the structures of Table 2, and MP2/6-31+G*//6-31+G* energies for the endo attack (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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