

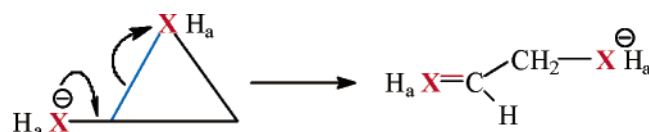
Strain Energy Release and Intrinsic Barriers in Internal Nucleophilic Reactions

Joel L. Wolk, Esther Rozental, Harold Basch, and Shmaryahu Hoz*

Department of Chemistry, Bar-Ilan University, Ramat-Gan, Israel 52900

shoz@mail.biu.ac.il

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X = O, S, N, P and C.

This paper reports computational data for the energetics of internal attacks, both in ring-opening reactions (eq 3) where strain energy is released and in model, strain-free systems (eq 4). A comparison is drawn with the corresponding bimolecular processes. The exothermicity of three-membered ring-opening reactions is significantly larger than that of the four-membered ring systems. However, using the Marcus equation, it is shown that the higher reactivity of the three-membered rings is intrinsic to the system and does not stem only from a higher thermodynamic driving force. The intrinsic barriers for the strain-free reactions are shown to be dominated by the position of the nucleophilic and nucleofugic atoms in the periodic table, as in the bimolecular S_N2 reactions, although a π rather than a σ bond is formed in these reactions.

Introduction

In this paper, we attempt to shed light on two issues: the relationship between ring-opening reactions and ring strain energy on one hand and the intrinsic barriers in internal nucleophilic reactions on the other hand, using the same data set.

Strain. Despite having nearly the same strain energies, three- and four-membered rings differ vastly in their reactivity, the three-membered ring being much more reactive.¹ Several explanations were advanced for this phenomenon. Houk suggested² that the difference in reactivity stems from aromaticity of the transition state for the reactions of the three-membered rings, as opposed to the antiaromaticity of the transition state in the reactions of the four-membered rings. For the reactions of amines with the corresponding heterocycles, Banks recently proposed that rate enhancement in the case of three-membered rings stems from electrostatic interactions.³ We have suggested

that, the more distorted the bond, the more the frontier orbitals will be amenable to bonding.^{4,5} In addition, we have pointed out that simple mechanical considerations must lead to a higher reactivity of the three-membered rings. Namely, cleaving a bond in cyclopropane annihilates two out of the three strain centers, whereas in four-membered rings, two strain centers out of four are destroyed. Moreover, in a three-membered ring, the angle of the remaining strained corner is widened as a result of the stretching of the opposite bond at the transition state. This widening is distributed between *two* angles in the four-membered ring, thus attenuating the strain energy in the latter to a lesser degree.⁶

A necessary step in the process of a proper analysis is to determine the expected (normal) reactivity for these reactions and measure the observed reactivity against the one expected. For bimolecular reactions, this was done by calculating the intrinsic barrier from the strain-free reaction shown in eq 1 for the reaction of methoxide as a nucleophile and then calculating the expected barrier for the reaction in eq 2 using the Marcus equation⁷ and the reaction energy.

(1) (a) Greenberg, A.; Liebman, J. F. In *Strained Organic Molecules*; Academic Press: New York, 1978. Wiberg, K. B. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312. (b) 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.

(2) (a) Sawicka, D.; Houk, K. N. *J. Mol. Model.* **2000**, *6*, 158. (b) Sawicka, D.; Li, Y.; Houk, K. N. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2349. (c) Sawicka, D.; Wilsey, S. Houk, K. N. *J. Am. Chem. Soc.* **1999**, *121*, 864.

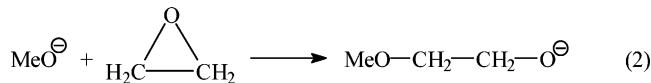
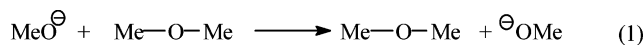
(3) Banks, H. D. *J. Org. Chem.* **2003**, *68*, 2639.

(4) Sella, A.; Basch, H.; Hoz, S. *J. Am. Chem. Soc.* **1996**, *118*, 416.

(5) Sella, A.; Basch, H.; Hoz, S. *Tetrahedron Lett.* **1996**, *31*, 5573.

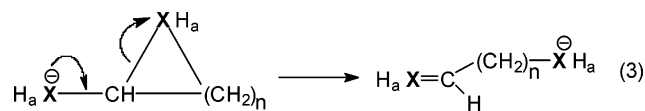
(6) Wolk, J. L.; Sprecher, M.; Basch, H.; Hoz, S. *J. Org. Biomol. Chem.* **2004**, *2*, 1065.

(7) Marcus, R. A. *Annu. Rev. Phys. Chem.* **1964**, *15*, 155.



Comparison of the Marcus barrier, the barrier calculated on the basis of the reaction energies and the intrinsic barriers using the Marcus equation, with the one calculated for the actual three- and four-membered ring reactions will point at the structure exhibiting behavior that deviates from the normal, be it excessive reactivity of the one or inertness of the other.

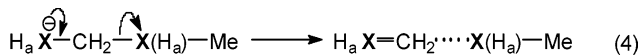
We have used this procedure for bimolecular nucleophilic,⁸ electrophilic, and radical⁶ ring-opening reactions. In this paper, we complete the study by assessing internal, unimolecular ring-opening reactions (eq 3) in the same way.



X = O, S, N, P and C.

n = 1, 2; a = 0, 1, 2

The reference, strain-free “calibrating” reaction in this case is shown in eq 4.



X = O, S, N, P and C.

Our preliminary results indicated that the reactions of eq 3 differ from the bimolecular ones by the three-membered ring-opening reactions being significantly more exothermic than the four-membered ones. Thus, in addition to the other aspects, the internal reactions differ from the bimolecular reactions by the three-membered rings having an appreciably higher thermodynamic driving force than the four-membered rings.

Intrinsic Barriers and the Periodic Table. Examination of the activation energies of the series of the reference reactions such as that of eq 1 leads us to the observation that the intrinsic barriers in S_N2 reactions are governed by the position of the nucleophilic atom in the periodic table⁹ (the study of the intrinsic barrier was extended to cationic nucleophilic reactions by Uggerud and co-workers¹⁰). The height of the barrier is given with relatively high accuracy (SD = 0.11) by eq 5.

$$E_{\text{int}}^{\ddagger} \approx 10 \times \text{valence (kcal/mol)} \quad (5)$$

Thus, for example, the intrinsic barrier in the identity reaction of F[−] with Me−F, Cl[−] with Me−Cl, as well as for the other halogens was around 10 kcal/mol. Similarly, for the oxygen group, e.g., MeS[−] with Me−S−Me, it was ca. 20 kcal/mol, etc. This was later extended also to nucleophilic attacks on nitrogen as the central atom.¹¹

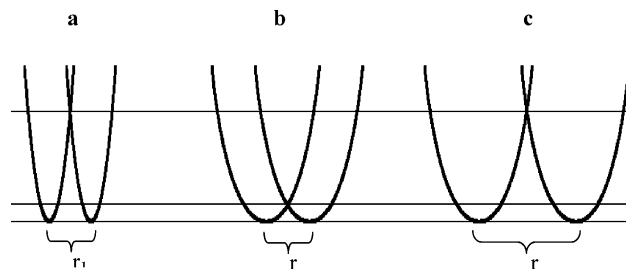


FIGURE 1. Schematic presentation of potential surface crossing points for: (a) first row elements; (b) second and higher rows elements with bond lengths as in a; (c) lower rows elements with bond lengths adjusted to size.

An attractive explanation for this phenomenon was suggested by Arnaut and co-workers.¹² In a descriptive way, the essence of their explanation is as follows: the height of a barrier is roughly determined by the crossing point of the potential surfaces of the reactants and products (Figure 1).

For the lighter row elements, the bonds are strong; therefore, these potential surfaces are steeply inclined and their crossing point and consequently the barrier will be relatively high. For the heavier rows, with relatively shallow potential surface minima, the transition state will be much lower. However, because the heavier row elements are larger, the separation between the parabolae will be larger and, consequentially, the crossing point will be higher, resulting in a higher activation energy (Figure 1). Thus, in the cases studied, the mutual cancellation effect leads to a nearly constant intrinsic barrier down a column.

The calibrating reactions of the type shown in eq 4 provide the opportunity to examine the validity of the aforementioned model in a case where one of the reaction parties is already within a σ bond distance from the reaction center. Namely, the symmetry of the transition state prevailing in the identity S_N2 reactions is not retained, and the question posed is will the same pattern hold for these asymmetric reactions as well?

Methodology

To enable a comparison with previous data, the computations were performed at the HF/6-31+G* level with no correction for ZPE. We have shown in the past that higher-level computations (B3LYP/6-31+G* and MP2/6-31+G*) faithfully corroborate the results of the Hartree–Fock level calculations. Thus, because we were interested in trends rather than in the absolute values, we retained the Hartree–Fock level in the present study. It should be pointed out that the B3LYP methodology tends to underestimate the barriers in S_N2 reactions,¹³ and indeed, we were unsuccessful in repeating some of these calculations using density functionals because the barriers, which are already low in the HF procedure, practically vanished.

In all cases, the energies and geometries of the reactants, products, and transition states were calculated using the Gaussian 98 and 03 sets of programs,¹⁴ and the transition-state geometries were confirmed by frequency calculations. In some cases, the product conformation was verified using the IRC procedure.

Results and Discussion

Strain Release in Internal Nucleophilic Displacements. The Marcus intrinsic barriers for the internal reactions of the various

(12) Arnaut, L. G.; Pais, A. A. C. C.; Formosinho, S. J. *J. Mol. Struct.* **2001**, 563–564, 1.

(13) Basch, H.; Hoz, S. *J. Phys. Chem.* **1997**, 101, 4416 and references therein.

(8) Yi, R.; Basch, H.; Hoz, S. *J. Org. Chem.* **2002**, 67, 5891.

(9) Hoz, S.; Basch, H.; Wolk, J. L.; Hoz, T.; Rozenal, E. *J. Am. Chem. Soc.* **1999**, 121, 7724.

(10) (a) Uggerud, E. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1459. (b) Laerdahl, J. K.; Uggerud, E. *Org. Biomol. Chem.* **2003**, 1, 2935. (c) Laerdahl, J. K.; Bache-Andreassen, L.; Uggerud, E. *Org. Biomol. Chem.* **2003**, 1, 2943.

(11) Wolk, J. L.; Hoz, T.; Basch, H.; Hoz, S. *J. Org. Chem.* **2001**, 66, 915.

TABLE 1. Equilibrium and Activation Energies and the Intrinsic Barriers for the Reactions of Eqs 6–10^a

X (eq no.)	ΔE_o	E_a	E_a^{int}
C (6)	21.9	32.6	20.2
N (7)	16.5	18.3	7.9
P (8)	31.0	33.1	12.9
O (9)	8.9	8.9	2.5
S (10)	19.7	19.8	5.5

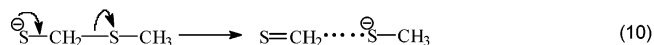
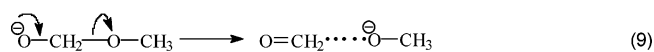
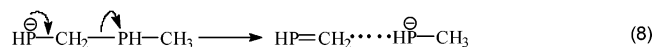
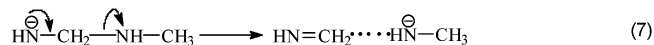
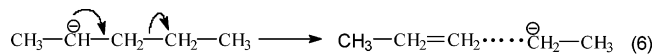
^a Values are in kcal/mol. The energies and the geometrical data of the various species are given in the Supporting Information section.

TABLE 2. Equilibrium, Activation, and the Marcus Activation Energies for the Internal Reactions (Eq 3) and the Corresponding External Reactions (Eq 9)^a

X (ring size)	internal			bimolecular ^b		
	ΔE_o	E_a	E_a^{Marcus}	ΔE_o	E_a	E_a^{Marcus}
C (3)	-9.3	9.7	15.8	-29.4	36.2	48.6
C (4)	-4.6	15.2	18.0	-27.6	44.2	49.4
N (3)	-16.1	2.1	1.9	-22.8	25.1	33.2
N (4)	-9.8	5.9	3.8	-21.9	33.9	33.6
P (3)	-3.4	2.8	11.2	-24.4	16.9	34.5
P (4)	3.7	14.2	14.8	-20.2	32.1	36.4
O (3)	-16.9	0.0	1.2	-25.9	14.4	20.5
O (4)	-12.5	1.1	0.2	-23.5	21.5	21.5
S (3)	-4.8	0.0	3.3	-18.3	10.2	23.5
S (4)	-4.7	5.1	3.4	-18	20.7	23.6

^a Values are given in kcal/mol. ^b Data from ref 8.

X's were calculated using the strain-free reactions shown in eqs 6–10. Activation and equilibrium energies and the intrinsic



barriers for these are given in Table 1.

The equilibrium, activation, and the Marcus activation energies (calculated from the intrinsic barriers of Table 1 and the reaction energies) for the five reactions of eq 3 are given in Table 2.

It is instructive to compare the various energies associated with eq 3 with those of the previously calculated bimolecular processes (eq 11). The relevant data were added to Table 2.

(14) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision B.04; Gaussian, Inc., Pittsburgh, PA, 2003.

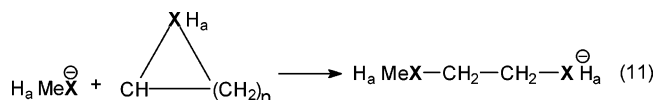


Table 2 displays several general features which we will briefly discuss. The two sets (uni- and bimolecular reactions) differ in their exothermicities. The exothermicity of the bimolecular reactions is 24 ± 4 kcal/mol, whereas that of the unimolecular systems is only 9 ± 7 kcal/mol. It should be noted that because the internal reactions were computed at the HF/6-31+G* level whereas the bimolecular reactions were treated at the G2+ level there could be some distortion in the comparison. However, because we are relating here to the ground-state energies, in light of the large difference between the exothermicities of the reactions, the above conclusion must be at least qualitatively correct. This difference in exothermicities could be attributed to the fact that in the internal reaction a π rather than a σ bond is formed.

As we have mentioned before, there are marked differences in the reaction exothermicity of the three- and four-membered rings within a set, compared correspondingly between the two sets. In the bimolecular reactions, the difference between the exothermicity of the three- and four-membered ring-opening reactions amounts to ca. 2 kcal/mol and is of the same magnitude as the difference between the strain energy of cyclopropane and cyclobutane. In the internal reactions, these differences are larger and amount to ca. 5 kcal/mol (except for X = S). We attribute this to the larger ability of the four-membered rings compared to the three-membered rings to disperse the negative charge.

In light of the above, the most striking feature is that a lower driving force in the internal reactions, for both three- and four-membered rings, corresponds to a higher reactivity. Namely, much lower activation energies are obtained for the intramolecular reactions despite their having lower exothermicities than those of the bimolecular ones.

We believe the reason for the low barrier in the internal π nucleophilic reactions¹⁵ is the following: In bimolecular reactions, one of the major origins for the reaction barrier is the interelectronic repulsion induced by the approach of the nucleophile to the substrate. However, in the case of π nucleophilicity, the nucleophile in its ground state is already within a σ bond distance from the electrophilic center and the interelectronic repulsion component is probably not much enhanced upon approaching the transition state. A similar argument was recently invoked for concerted γ elimination reactions.¹⁶

Finally, we would like to analyze and compare the reactivity in the internal reactions of three- and four-membered rings. In Table 2, besides the ab initio computed activation energies, the Marcus activation energies are also displayed. The low barriers and the spontaneous reactions in some cases do not permit a judicious analysis of the results. Namely, the higher reactivity of the internal reaction, in corroboration of the reactivity selectivity principle, attenuates the differences between the three-membered and the four-membered rings compared to external reactions. However, for X = P and C, it is clearly demonstrated that the four-membered rings display a barrier close to the normal (defined as the Marcus barrier) whereas the activation energy for the three-membered rings is much lower than expected.

(15) Hoz, S.; Gross, Z.; Cohen, D. *J. Org. Chem.* **1985**, *50*, 832.

(16) Habusha, U.; Rozental, E.; Hoz, S. *J. Am. Chem. Soc.* **2002**, *124*, 15006.

In other words, the excess reactivity relative to that expected for the three-membered rings (7.3 ± 1.2 kcal/mol) compared to the four-membered ring (1.7 ± 0.9 kcal/mol) is not a result of the larger driving force for the former because even after this is taken into account by the Marcus treatment the three-membered ring still displays excessive reactivity. Thus, the deviation from normal in these internal reactions as well should be attributed to the three-membered rings, whereas the four-membered rings exhibit normal behavior.

Internal Attacks and the Periodic Table. The reference reactions (eqs 6–10) used in the above study enable us to analyze some basic features in internal nucleophilic reactions. As we have shown in the introductory section, the intrinsic barrier in S_N2 reactions is dependent on the valence of the X central atom in the periodic table. Using the reference reactions above and the Marcus equation, we have determined the intrinsic barriers for the internal attacks (Table 1). We have struggled to extend the study to the other elements such as As and Se. However, these reactions were not amenable to simulation because the reaction products spontaneously reverted back to the reactants. Although the data set is relatively limited, one can see that the valence dependence applies to the internal reactions as well. The average activation energy for the divalent nucleophiles (O, S) is 4 ± 1.3 kcal/mol. For the trivalent nucleophiles (N, P), it is ca. 10.4 ± 2.5 kcal/mol, and for carbon, it is ca. 20 kcal/mol. A plot of the activation energy vs the valence gives a straight line (Supporting Information, Figure S1).

Although the data basis for our internal nucleophilic reaction is limited, it remarkably demonstrates the dependence of the intrinsic barriers, in these internal nucleophilic displacements, on the location of the X atom in the periodic table. This observation manifests the generality of the phenomenon. While making this statement, we would like to stress again that this study was not aimed at the determination of the absolute values for the activation energies but rather at revealing the trends within this system.

The application of the Marcus equation to the case at hand where a π bond is formed and not a σ bond as in S_N2 reactions

may be questioned. However, Shaik and co-workers¹⁷ have recently shown that the Marcus model is valid even though the cross sections of the potential surfaces do not have the classical parabolic shape. We believe that Arnaut's explanation¹² can be extended to this case as well, although the distance between the electrophilic and nucleophilic center at the transition state is even shorter than that of a σ bond. The reason is that the X–C bond length also increases as we go down the column, and some proportionality may be retained between the shallowness of the parabolae and the distance between their origins. Therefore, the compensation effect mentioned above is apparently operating in the internal reactions as well.

Summary and Conclusions

We have shown that in internal nucleophilic ring-opening reactions the exothermicity of the internal reactions is much reduced compared to the same ring opening induced by an external nucleophile. Yet, these systems, despite their lower driving force, are more reactive than the bimolecular ones. Using Marcus theory, it was shown that three-membered rings react faster than expected, whereas four-membered rings have a normal barrier.

The strain-free calibration reactions used to determine the intrinsic barrier for the above enabled us to determine the existence of the periodic table effect in internal (π) nucleophilic displacements. It was established that, indeed, the intrinsic barrier in these reactions depends on the location of the nucleophilic atom X in the periodic table.

Supporting Information Available: Figure S1, energies, and structural parameters for all the ground states and transition states discussed are given. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(17) Su, P.; Song, L.; Wu, W.; Hiberty, P. C.; Shaik, S. *J. Am. Chem. Soc.* **2004**, *126*, 13539.