

Relative reactivity of three and four membered rings – the absence of charge effect †

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Radical (neutral) and electrophilic (cationic) ring opening reactions were studied computationally in order to probe the difference in reactivity between three and four membered rings. Using the Marcus equation we have shown that the activation energy for the four membered ring opening is close to the Marcus predicted barrier whereas three membered rings display much higher reactivity than that predicted by the Marcus equation. Thus, the reactivity of the three membered rings is enhanced, in addition to the strain release, by another factor which is not operative in the four membered rings. It is clear also that this factor is not charge dependent. The possible origin of this effect is discussed.

Introduction

Cyclopropane and cyclobutane have nearly the same strain energy (ca. 27 kcal mol⁻¹), yet they differ vastly in their reactivity – cyclopropane being much more reactive than cyclobutane.¹ Since these two rings are the building blocks of all other strained fused rings, it is imperative to determine whether cyclopropane displays an excessive reactivity or whether cyclobutane is to be considered an exceptionally unreactive molecule. The answer, needless to say, depends on the reference point; namely, the definition of “normal behavior”. In this context we will use the Marcus model² for the definition of normal behavior. *A reactivity pattern which obeys the Marcus equation (eqn. 1) will be defined as normal.*

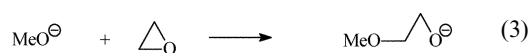
$$E_a = E_{a_{\text{int}}} + \Delta E_0/2 + \Delta E_0^2/16E_{a_{\text{int}}} \quad (1)$$

In order to demonstrate the method employed we will use the example of nucleophilic ring opening of oxirane and oxatane described in our previous work.³ In the first step we determine the intrinsic barrier ($E_{a_{\text{int}}}$ of the Marcus equation) by computing quantum mechanically the barrier for the identity S_N2 reaction shown in eqn. 2.



The corresponding reaction profile is schematically described as path ‘a’ in Fig. 1.

In the second step we compute quantum mechanically the reaction energy (E_0 for the analogous reaction with oxirane (eqn. 3).



Having ΔE_0 and the intrinsic barrier ($E_{a_{\text{int}}}$ previously determined), using the Marcus equation we can calculate the expected “normal” barrier (E_a – curve ‘b’ in Fig. 1). Finally, we compute quantum mechanically the energy barrier for the reaction of eqn. 3. If the barrier is identical to the one predicted by the Marcus equation, the system may be classified as “normal”. In the case of nucleophilic ring opening of an oxirane, the calculated barrier was found to be much lower (“c” Fig. 1), indicating an enhanced reactivity. In contrast, the quantum

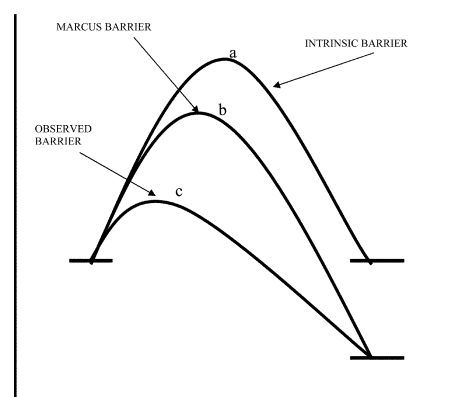


Fig. 1 Reaction profiles.

mechanically computed barrier for the four membered rings is very close to the Marcus (normal) barrier.

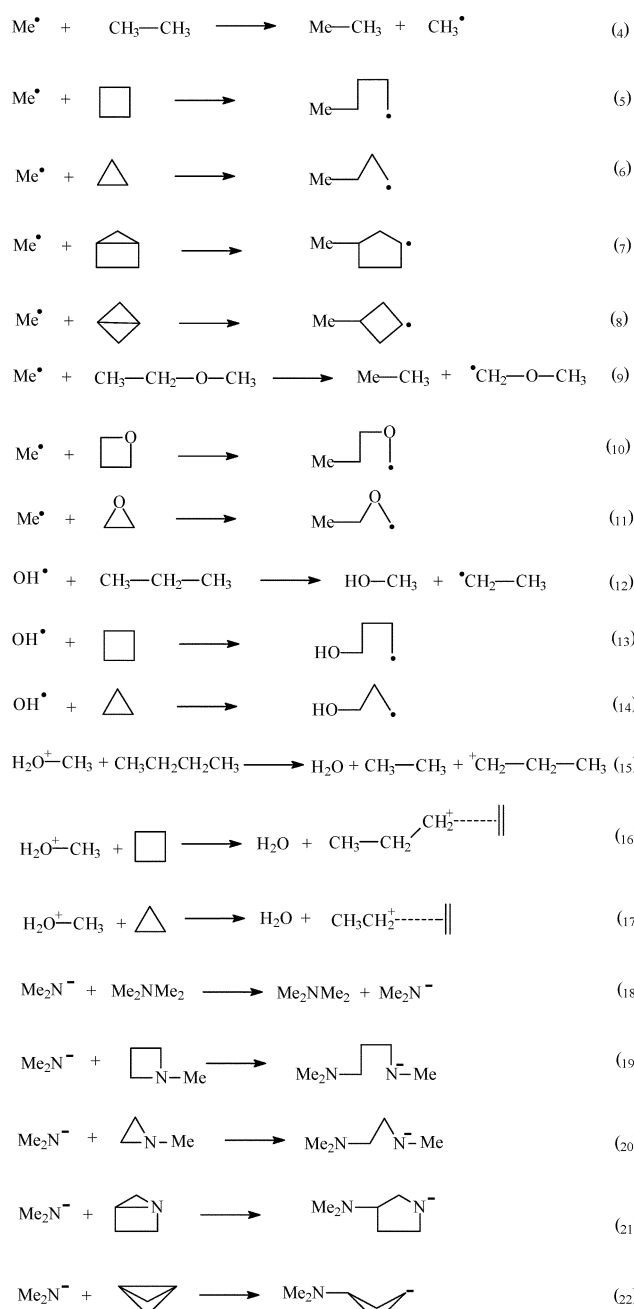
The origin of the excessive reactivity of three membered rings is not clear. Several explanations have been put forward. Houk suggested⁴ that the phenomenon stems from aromaticity of the transition state for the reactions of the three membered rings as opposed to the antiaromaticity of the transition state in the reactions of the four membered rings. We have pointed to the frontier orbitals, suggesting that for more deformed molecules, these will be more amenable to bonding.⁵ Recently, Banks proposed for the reactions of amines with the corresponding heterocycles, that rate enhancement in the case of three membered rings stems from electrostatic interactions.⁶

In the present work we show that the higher reactivity of three membered rings is not reaction type or charge dependent. This conclusion is based on an extension of our previous study on nucleophilic (anionic) reactions to radical reactions (neutral) and some electrophilic (positive charge) reactions.

Results

Two types of radical reactions were studied; one in which substrates were reacted with methyl radical (reactions 4–11, Scheme 1) and the other in which they were reacted with hydroxyl radical (reactions 12–14). The reactions were studied at the B3LYP/6-31G* level.⁷ In electrophilic reactions in which the electrophilic agent was the bare methyl cation, the reactions proceed spontaneously to the products with no energy barrier (at the HF/6-31G* level). Therefore we studied these reactions with water as methyl cation carrier (reactions 15–17). Upon

† Electronic supplementary information (ESI) available: Gaussian archive file. See <http://www.rsc.org/suppdata/ob/b3/b314869f/>



Scheme 1

encounter, the reactants form complexes. These complexes were taken as the ground states of the reactants. In certain cases colinearity was imposed upon the entering group/carbon/leaving group array, in the reactants and products but not in the transition structure. Each transition structure was characterized by frequency analysis. In addition, in certain cases, the IRC procedure was used to ascertain the connection between the transition state and the products. In all cases the expectation value $\langle S^2 \rangle$ was very close to the value of 0.75 for a pure doublet state. All computations were done using the Gaussian 94/98 programs.⁸

The energies of the ground state complexes, transition states and products are listed in Table 1.

Discussion

Table 2 lists the *ab initio* reaction energies and the corresponding activation energies followed by the Marcus calculated “normal” activation energies. Relating to the reactions with Me radical the values in the Table show that cyclobutane (eqn. 5) displays a normal behavior in the sense that the *ab initio*

computed activation energy falls within 0.5 kcal mol⁻¹ of the Marcus activation energy. Cyclopropane on the other hand, has an *ab initio* computed activation energy of 24.5 kcal mol⁻¹ which is lower by *ca.* 9 kcal mol⁻¹ than the expected activation energy based on the Marcus equation (last column in Table 2). This confirms our previous results³ obtained for nucleophilic reactions, where “normal” behavior was observed for four membered rings while three membered rings displayed a much higher reactivity (lower barrier) than expected.

Moving to housane and bicyclobutane (eqn. 7 and 8) one can see that additivity in the “excessive reactivity” is nearly fully observed. Thus, housane is composed of edge-fused three and four membered rings. The sum of the reductions in activation energy of these individual components is 8.6 (9.1–0.5) kcal mol⁻¹ and the observed reduction in activation energy, compared to the Marcus activation energy (Table 2) is 9.0 kcal mol⁻¹. The same holds for bicyclobutane where the reduction of activation energy on the basis of additivity should be $2 \times 9.1 = 18.2$ kcal mol⁻¹ and the observed value was found to be 20.1 kcal mol⁻¹.

The reactions of methyl radical with oxirane and oxatane as well as the reactions of hydroxyl radical with cyclopropane and cyclobutane (entries 9–14 in Table 2) were also studied. Unlike the cases of the previous reactions, the strain-free reactions used here as standards were not isoergic (eqn. 9 and 12 respectively). Therefore, the intrinsic barrier was derived using the Marcus equation and the quantum mechanically computed values of E_a and ΔE_0 for these reactions. The intrinsic barrier was found to be 50.8 kcal mol⁻¹ for the reactions of methyl radical with the oxirane and oxatane, and 39.7 kcal mol⁻¹ for the reactions of hydroxyl radical with cyclopropane and cyclobutane.

The data for all the radical reactions discussed above show that the activation energies for the four membered ring opening reactions are close to the values predicted by the Marcus equation, while those for the three membered rings are significantly smaller than expected. Evidently in radical reactions also, three membered rings show higher reactivity than anticipated on the basis of the Marcus equation. Thus, *the validity of the statement “three membered rings show enhanced reactivity whereas four membered rings display normal reactivity” is not charge or reaction type dependent.*

The reactions with the oxo derivatives (entries 9–11 in Table 2) pose an interesting question regarding a basic assumption embedded in the LFER and to some extent also in Marcus theory. It is believed that factors which affect the energies of the reactants and products are partially operative also at the transition state. Namely, these principles apply only to a single segment of a reaction path passing through a saddle point and connecting adjacent minima (in the direction of the path). However, in the present case we identified one conformational factor which appears only at the product stage. In the product, the carbon carrying the radical center rotates in such a way that the singly occupied orbital overlaps with the p- π lone pair on the neighboring oxygen atom. However, at the transition state, the two orbital systems are (nearly) orthogonal. Thus, the stationary point at the end of the reaction path segment to which the Marcus equation is applied is itself a conformational transition structure.

Calculations on a model radical – methoxymethylene (**1**) show that the conformation which allows orbital overlap (**1a**) is more stable than the perpendicular one (**1b**) by 5.8 kcal mol⁻¹.

Thus, since this factor stabilizes only the products, we ‘destabilized the products’ by adding 5.8 kcal mol⁻¹ to their energies. Doing this caused only marginal changes. The intrinsic barrier was reduced from 50.8 to 48.0 kcal mol⁻¹ and the expected Marcus barriers for oxatane and the oxirane were reduced by only 0.2–0.3 kcal mol⁻¹.

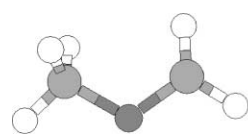
It is interesting to compare the radical reactions (eqn. 4–8) with the nucleophilic reactions of dimethylamide and the

Table 1 *Ab initio* calculated energies for the reactions of Scheme 1. Energies are given in a.u.

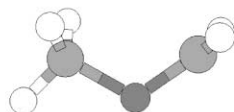
Eqn. No.	Substrate	Reactant	TS	Product
Reactions of Me radical				
4	CH ₃ -CH ₃	-119.668863	-119.591801	-119.668863
5	c-butane	-197.05162	-196.995452	-197.098625
6	c-propane	-157.733685	-157.6947	-157.785155
7	Housane	-235.118623	-235.094856	-235.210261
8	Bicyclobutane	-195.786294	-195.774485	-195.861919
9	CH ₃ CH ₂ OCH ₃	-234.182806	-234.106639	-234.192615
10	Oxatane	-232.943804	-232.889915	-232.993618
11	Oxirane	-193.6249	-193.583133	-193.681196
Reactions of OH radical				
12	CH ₃ -CH ₂ -CH ₃	-194.869577	-194.808051	-194.872938
13	c-butane	-232.939143	-232.900541	-232.98872
14	c-propane	-193.623519	-193.598409	-193.674807
Reactions of H ₂ O-CH ₃ cation				
15	BuH	-272.542837	-272.471216	-272.500127
16	c-butane	-232.318801	-232.289044	-232.329183
17	c-propane	-271.339502	-271.282121	-271.346603

Table 2 Reaction, activation and Marcus activation energies for the reactions of Me and OH radicals, H₂O-Me⁺ and Me₂N⁻. Energies are given in kcal mol⁻¹

Eqn. No.	Substrate	ΔE_0	E_a	Marcus E_a	E_a relative to Marcus
Reactions of Me radical					
4	CH ₃ -CH ₃	0	48.4		
5	c-butane	-29.5	35.2	34.8	0.5
6	c-propane	-32.3	24.5	33.6	-9.1
7	Housane	-57.5	14.9	23.9	-9.0
8	Bicyclobutane	-47.5	7.4	27.5	-20.1
9	CH ₃ CH ₂ OCH ₃	-6.2	47.8		
	Intrinsic barrier		50.8		
10	Oxatane	-28.1	35.9	37.7	-1.8
11	Oxirane	-35.3	26.2	34.7	-8.5
Reactions of OH radical					
12	CH ₃ -CH ₂ -CH ₃	-2.1	38.6		
	Intrinsic barrier		39.7		
13	c-butane	-31.1	24.2	25.6	-1.4
14	c-propane	-32.2	15.8	25.2	-9.4
Reactions of H ₂ O-CH ₃ cation					
15	BuH	26.8	44.9		
	Intrinsic barrier		30.0		
16	c-butane	-4.5	36.0	27.9	8.2
17	c-propane	-6.5	18.7	26.9	-8.2
Reactions of Me ₂ N ⁻ ^a					
18	Me ₃ N	0.0	43.9		
19	<i>N</i> -Me- <i>c</i> -azabutane	-21.9	33.9	33.6	-0.3
20	<i>N</i> -Me-aziridine	-22.7	25.1	33.2	8.2
21	Azahousane	-42.7	12.5	25.1	12.7
22	Azabicyclobutane	-29.3	11.0	30.4	19.5

^a Data taken from reference 3a.**1a**

-154.3618223 a.u.

**1b**

-154.3525604 a.u.

corresponding cyclic aza derivatives (eqn. 18–22).³ The data for the latter series of reactions is given at the end of Table 2. Since the basis set used in the present work is different from the one used for the generation of the data for the nucleophilic reactions, a quantitative comparison cannot be performed.

Nevertheless, similarity in trends, if they existed, would be easily discernable. Fig. 2 shows the correlation between the radical reactions and the nucleophilic reactions for (a) the reaction energies and (b) the activation energies. The good linear correlation obtained indicates that the phenomenon of excessive reactivity of compounds containing three membered rings is indeed common to anionic as well as to neutral reactions.

We also extended this study to positively charged electrophiles (eqn. 15–17 in Table 2). As we have mentioned above, methyl cation was too reactive for this purpose. Therefore, in these computations, performed at the HF/6-31G level, we used water as methyl cation carriers; namely H₂OCH₃⁺ (protonated MeOH). Since the strain free reference electrophilic reaction (eqn. 15) is not an identity reaction, the intrinsic barrier for these reactions was again calculated from the Marcus equation

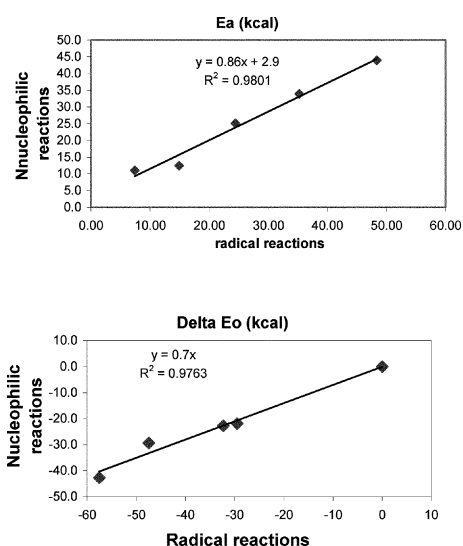
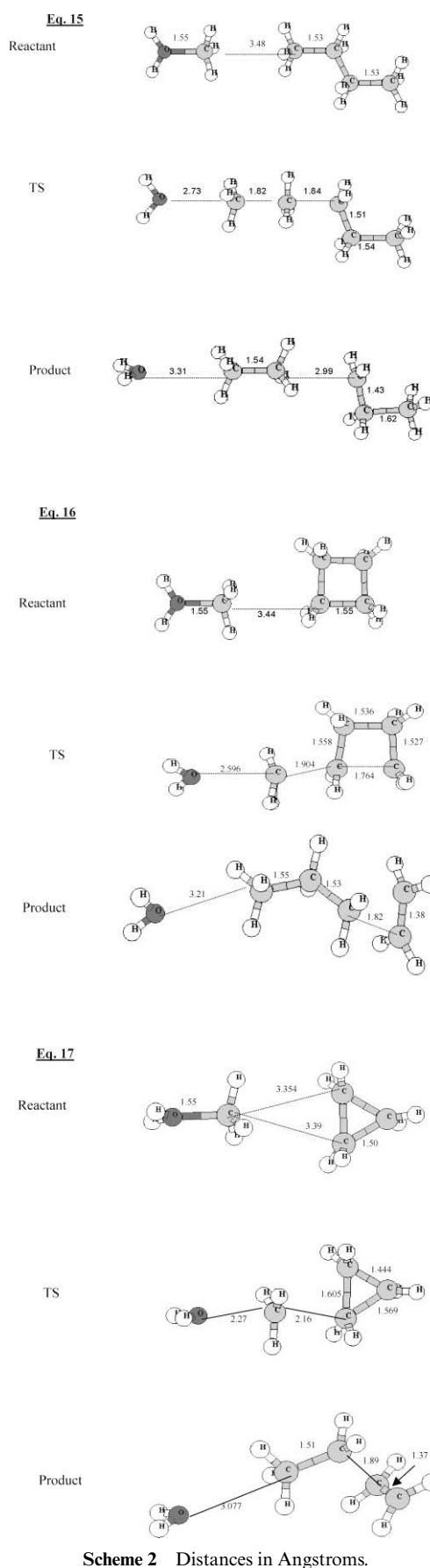


Fig. 2 Comparison of the energetics for nucleophilic and radical ring opening reactions.

using the computed ΔE_0 and E_a values for the strain free system and was found to be $30.0 \text{ kcal mol}^{-1}$. The reactions turned out to be more complex than simple substitution reactions where only one bond formation and one bond breaking take place. As shown in eqn. 16 and 17, the bond between the methyl group and the water molecule is cleaved, as is the carbon-carbon bond within the ring. The latter forms an ethylene π -complexed to the cationic terminus.⁹ Thus, the system finds refuge from the instability of a primary carbocation, at the price of cleaving a σ -bond and forming a π -bond in the formation of this π -complex. It should be noted that the activation energy for the reaction of cyclopropane is well below that of the Marcus predicted barrier whereas that for the four membered ring is *much higher* than the Marcus predicted barrier. The latter result is in contradistinction to all previous cases where the four membered ring displayed an activation barrier of magnitude very close to that of the Marcus barrier. A close examination of the two transition state structures (Scheme 2) explains this difference.

In the transition structure of the reaction of cyclopropane the distance between the two carbon atoms forming the ethylene unit has already decreased while the other two bonds are stretched. Thus, the factors which stabilize the product are also operative at the transition state. On the other hand, in the four membered ring, no such difference between bond lengths is observed. Therefore, the transition state does not benefit from said complexation and reflects a barrier higher than that predicted (Marcus) on the basis of the stabilized product.

As was mentioned above there are several suggested explanations for the excessive reactivity of the three membered rings compared to the four membered ones. It is possible to offer an explanation which is based on simple mechanical considerations. Clearly, ring strain originates from various sources. The Baeyer¹⁰ (angular) strain is the sum total of many effects that progress, not necessarily linearly, as the angle distortion increases. However, it is logical to assume that *Baeyer strain may have an energetic significance only when the deformed angle is confined between two "normal" bonds*. At the transition state of a bimolecular ring cleaving reaction, one of the ring's bonds is largely broken. Therefore, the strain associated with the two angles flanking the broken bond is essentially lost. Thus, formally, *in three membered rings this will imply "losing" 2/3 of the strain energy whereas in four membered rings only 1/2 of the strain energy will be lost at the transition state*. In addition, 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. Since according to Hooke's law the energy change is proportional to the square of the



change in the angle, it is clear that for a similar change in bond length, much more strain energy will be released in three membered ring than in the four membered one. Consequently, strain energy will be lost more rapidly as the three membered ring is cleaved than when a four membered ring is opened, and

the transition state in the former case will be achieved earlier and at a lower energy than that of the latter. It should be pointed out that this may not be the case in the unimolecular cleavage of a bond in a cyclic system *e.g.* homolytic cleavage, because for a given distance, in the absence of a concomitant bond formation to an external agent, the electron density may still be largely retained 'within' the bond in spite of the increasing interatomic distance.

Conclusion

We have previously shown that in nucleophilic ring opening reactions (negative charge), activation energies for the opening of the three membered rings are significantly lower than those for the four membered rings. In the present work we have shown that the same holds for neutral radical as well as for electrophilic reactions (positive charge). Thus, the phenomenon is not charge dependent, although in particular cases charge may contribute to the effect. We propose a simple explanation based on mechanical principles showing that strain energy is lost faster (earlier) in the ring opening of three than of four membered rings.

Acknowledgements

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