

2016

## Ring Closures and the Hammond Postulate

Charles A. Kingsbury

*University of Nebraska-Lincoln*, [ckingsbu@gmail.com](mailto:ckingsbu@gmail.com)

Follow this and additional works at: <http://digitalcommons.unl.edu/chemfacpub>

 Part of the [Analytical Chemistry Commons](#), [Medicinal-Pharmaceutical Chemistry Commons](#), and the [Other Chemistry Commons](#)

---

Kingsbury, Charles A., "Ring Closures and the Hammond Postulate" (2016). *Faculty Publications -- Chemistry Department*. 100.  
<http://digitalcommons.unl.edu/chemfacpub/100>

This Article is brought to you for free and open access by the Published Research - Department of Chemistry at DigitalCommons@University of Nebraska - Lincoln. It has been accepted for inclusion in Faculty Publications -- Chemistry Department by an authorized administrator of DigitalCommons@University of Nebraska - Lincoln.

## Ring Closures and the Hammond Postulate

Charles A. Kingsbury

Department of Chemistry, University of Nebraska- Lincoln

Lincoln, NE 68588-0304

Email: [ckingsbu@gmail.com](mailto:ckingsbu@gmail.com), tel: (402)472-2706, FAX: (402)472-2750

### Abstract:

This work reports an investigation of ring closure processes in relation to the Hammond postulate. Calculations favor the importance of thermodynamics, not kinetics, as the basis for the Hammond postulate. A kinetically rapid, but thermodynamically unfavorable reaction is shown to resemble product. The ease of ring closure to three-membered rings, compared to four-membered rings, is thought to be associated with conformational mobility and perhaps vibrations coupled to the reaction coordinate motion in the case of four-membered rings.

Keywords: ease of ring closure, Hammond Postulate, Thorpe-Ingold effect, transition state theory

---

In 1953, J. E. Leffler proposed a relationship between kinetic free energy of activation in a chemical reaction with the thermodynamic free energy of the reaction.<sup>1</sup> Leffler stated that it could be useful in predicting whether the transition state resembled starting material or product. One line of evidence Leffler cited was the Bronsted catalysis law, which was later discredited when  $\alpha$  values of greater than unity were found.<sup>2-4</sup> In 1955, G. S. Hammond published a somewhat more detailed study, including some applications.<sup>5</sup> The principle became known either as the Hammond postulate, Hammond-Leffler, or, in Europe, the Polanyi-Hammond relationship.<sup>6,7</sup> Briefly, this postulate states that for atoms undergoing covalency change, the geometry of the transition state lies nearer starting material in molecular geometry (an "early" transition state) or product (a "late" transition state), whichever has the highest thermodynamic energy. The Hammond paper is among the top ten most cited in the Journal of the American Chemical Society. This relationship was extended to kinetics, in that a rapid reaction was said to resemble starting material, whereas a slow reaction resembles

products. Hammond was careful to point out that not every reaction will obey this idea.<sup>5</sup> The question remains whether thermodynamics is the dominate factor or if kinetics, itself, may be sufficient to establish earliness or lateness, In the present work, a kinetically rapid, but thermodynamically unfavorable reaction is shown to resemble product. .

In the ensuing years, a number of computational and theoretical studies have been reported.<sup>7-24</sup> Inconsistencies with the Hammond postulate have been reported.<sup>25-27</sup> Manz and Sholl have demonstrated the variability of the concept of earliness or lateness, and developed other metrics to describe the transition state.<sup>9</sup> However, bond distances in the transition state remain our focus of attention.

According to transition state theory, in a simple three-center transition state, such as X—Y—Z, the potential between X and Y is balanced by the potential between Y and Z.<sup>9</sup> The overall X—Y—Z vibration is termed “imaginary.” If a change is made in structure of the starting material, e.g. a change from Z = Cl as leaving group in a SN2 reaction, to Z = F, a more **endothermic** reaction will result. The C-F bond is more stable and the C-F vibration is of higher energy. In order to maintain the balance between X—Y and Y—Z forces, the Y—Z distance is increased, thus effectively reducing the attraction between Y—Z (the atoms are more highly stretched from a stable covalent distance). Conversely, the X—Y distance may be decreased to place the atoms closer to covalent bond distance, thus increasing the force of attraction between X—Y. Thus, a product-like or “late” transition state is said to exist. The question remains to the extent to which the X—Y—Z bond distances in the transition state are sensitive to factors destabilizing the molecule, but not intimately associated with X—Y—Z force constants *per se*. The incursion of external factors, e.g. bond bending, or quantum mechanical effects, may affect thermodynamic energy but do not directly concern X—Y—Z. Thus, force constants and overall energy may be related, but do not necessarily have a direct correspondence.

A second objective of this study concerns reasons for the ease of formation of three-membered rings despite the high strain and thermodynamic instability of the cyclopropane product.

The molecules of this study (cf. Scheme 1) have a stabilized dicyanomethide carbanion X as nucleophile that attacks a carbon (Y) with a leaving group (Z) at the terminus of a hydrocarbon chain, thus closing a ring. The cyanide group was chosen as a carbanion stabilizing group as it is similar to the carbomethoxy group used in the experimental portion of this study, to be published separately.<sup>28</sup> The cyanide group is less demanding from a computational standpoint. Experimentally, the carbomethoxy group is preferred as the two cyanide groups frequently give rise to dark, intractable reaction mixtures.

Scheme 1 shows the X—Y and Y—Z bond distances in the transition states of ring closure to various ring sizes. The data are from the B3LYP/6-31G(d,p) method and basis set, unless otherwise specified.<sup>29,30</sup> Other methods and basis sets provide similar data. Trulahr, Garrett and Klippenstein have stated that DFT is unreliable to establish barrier heights.<sup>11</sup> Scheme 5 shows the geometry and energies of transition states at various levels of theory.

The calculated “activation energy” data are similar to experimental findings for the rates of ring closure reactions, namely that five and three-membered rings close the most readily, whereas the four-membered ring forms slowly (cf. Table I). Though stable, the six-membered ring closes more slowly than the five-membered ring.<sup>31</sup> For cyclopropane formation, the data are in accord with the Hammond principle in that formation of the highly strained three-ring product involves a late transition state (Scheme 1). However, a low barrier is predicted, and the process should be kinetically rapid, as is frequently observed.<sup>28,31</sup> In general there is no obvious relationship between the kinetic speed of reaction and the calculated position of the transition state for **1–6**.

Roughly linear geometry for X—Y—Z is found for **2–5**. However, for **1**, the X—Y and developing Y—Z bonds are not colinear. The X—Y bond seems splayed outward in the classical “bent bond” arrangement for cyclopropane.<sup>32</sup> This does not seem to impede rapidity of reaction. The dicyano methide center (X) is close to planarity in all cases. The reaction terminus (Y) also was close to planarity.

The conformation of the rings in the transition state resembles classical ideas, except for the seven-membered ring, **5**. The four-membered transition state, (cf. **2**), which was very difficult to locate, was not far from the “butterfly” (folded) conformation of cyclobutane.<sup>33</sup> The five-membered transition state (cf. **3**), which was easily located, occupies the “envelope” conformation, with the tip of the envelope at C3 (the developing bond being between C1 and C5).<sup>33</sup> The six-membered transition state (**4**) resembled the chair form of cyclohexane. A considerable number of attempts to locate a twist-boat transition state were unsuccessful. For the seven-membered ring (**5**) the transition state also was difficult to locate, and then had such a high energy, twisted conformation that it is hard to have confidence in it.<sup>34</sup> A more conventional transition state could not be located. The data for **5** are included only for rough comparison purposes only. The eight-membered transition state has not been located.

Since the computational data essentially represent gas phase reactions, whereas the experimental data are in solutions of much higher dielectric constant, the similarity between the calculated conformations of the transition state and experiment are somewhat surprising. The effect of varying dielectric constant in computations via the Onsager SCRF method, was not large.<sup>35,36</sup> Moving the dielectric constant in stages up to 24 (essentially the DK of ethanol), using RHF/6-31G(d,p) calculations, the C<sub>1</sub>—C<sub>3</sub>

transition state distance in **1** increased from 2.024 to 2.047Å, and the C<sub>1</sub>—Cl distance diminished from 2.39 to 2.36Å.

In Scheme 2, variations on the theme are shown. In **6**, the nucleophile X is stabilized by a single nitrile rather than two nitriles, thus making the nucleophilic carbon, X, much more reactive. Compared to the dinitrile **1**, the X—Y distance in **6** is longer and the Y—Z distance is shorter, indicative of an earlier transition state, in agreement with the Hammond postulate. The transition state for the structure lacking cyanides (X=CH<sub>2</sub><sup>-</sup>) (Z = Cl) was a strange twisted affair, although the transition state with fluoride (Z = F) as leaving group (**7**) was easily located, and quite conventional. The reason why Z = Cl is strange, but Z = F is perfectly usual is not understood at present. Observation of pictorial representations of the orbitals involved in the transition states of the two cases was not revealing, except that more X—Y crowding was seen for the twisted Z = Cl case..

In **8**, the X = (NC)<sub>2</sub>C<sup>-</sup> nucleophile is again present, but the leaving group Z is the less reactive fluoride group. The data for **8** are for MP2 and for RHF/6-31G(d,p) calculations, since B3LYP calculations did not identify a transition state. Generally speaking, the X—Y distance is shortened in **8** compared to **1** and the Y-Z distance is lengthened (compared to **7**) indicative of a later transition state, as the Hammond postulate predicts.

The Thorpe-Ingold, or “gem-dialkyl” effect predicts that geminal substitution on the chain separating reacting centers facilitates ring closure.<sup>37-39</sup> Calculations indeed predicted a more facile ring closure with geminal dimethyl substitution at C2 to form a three-membered ring between C1 and C3 (cf.**9**). The data are shown in Table 1 and Scheme 3. The calculations also predict a more exothermic reaction for **9** compared to **1**, as well as a transition state that is closer to starting material. The low activation energy in **9** may be somewhat misleading, as calculations seem to indicate a rather high energy starting material. However, for the five-membered transition state (dimethyl substituted) as in **10**, little difference is evident compared to **3** in transition state bond distances.

The original reason given for the Thorpe-Ingold effect suggests that the bond angle between methyls is enlarged to reduce steric hindrance between methyls.<sup>37</sup> The C1-C2-C3 angle therefore must decrease. This places the reacting centers at C1 and C3 closer together, thus facilitating ring closure. In the starting material for ring closure **9**, termed **9sm**, the C1-C2-C3 angle is predicted to be 103°, considerably smaller than the 111° present in **1** (Scheme 4), in agreement with the old theory.<sup>39,40</sup> However, this rather extreme C1-C2-C3 angle in other calculations, e.g. MP2/6-31G(d,p), 105°; HF/6-31G(d,p), 105°, and molecular mechanics (110°). For the case where a single methyl is substituted at C2, the C1—C3 transition state distance (1.93Å) is intermediate

between the unsubstituted C2 case, **1** (1.89Å) and the dimethyl C2 substituted case, **9** (1.96Å).

For the potential five-membered ring, **10sm**, the chain C2-C3-C4 bond angle is 113° (Scheme 4). This is ca. 3° smaller than for the unsubstituted molecule, **3sm**. The calculations do not predict a rate enhancement for **10** vs **3**. The angle data are so highly dependent upon method and basis set that only very general conclusions seem justified.

In **11**, C2 is again disubstituted, but with an existing cyclopropane function, which would give a spiropentane upon second ring closure. In theory, the C1-C3 distance should spread, thus impeding reaction. As Scheme 4 shows, the bond angle between reacting groups, X and Y—Z, is 108° in **11sm** compared to 103° for **9sm**, but rather similar to **1sm**. The calculations predict that **11** has about a 4 kcal higher “activation energy” than **9**. One might have expected a higher value. For **11** the overall reaction energy, is about 8 kcal higher energy than in the case of **9**, but only 3 kcal higher than for **1**. The reaction is more endothermic and the transition state is substantially closer to product, compared to **1**.

The case where C2 is substituted with a methylene group (**12**) should produce an even more pronounced C1-C2-C3 angle spread. In **12sm**, the C1-C2-C3 angle (112°) is somewhat larger than for **1sm**, **9sm**, or **11sm**, although perhaps not as large as anticipated. The reaction is more endothermic and the transition state closer to product than for **1** and **9** (Scheme 3).

**Table 1: Ring Size vs. Activation “Energy” and Overall Reaction Energy (B3LYP/6-31G(d,p))**

cmpd	Size of Developing Ring	Activation “Energy” (kcal/mol)	Overall Reaction Energy (kcal/mol)
<b>1</b>	3 (geminal CN at C1)	10.8	+3.8
<b>2</b>	4 “	16.6	-0.5
<b>3</b>	5 “	9.2	-19.3
<b>4</b>	6 “	13.2	-22.3
<b>5</b>	7 “	(18.3)	(-14.8)
<b>6</b>	3: (single CN at C1)	0.4	-27.8
<b>7</b>	3: (no cyanides, F leaving group)	20.5	-13.6
<b>8</b>	3 (F leaving group)	52.8	(ring opens under F <sup>-</sup> attack)
<b>9</b>	3: (gem. dimethyls present on C2)	6.4(5.8)	-2.2(-2.2)
<b>10</b>	5: (gem. dimethyls present on C3)	9.3	-17.6

<b>11</b>	3: C2 substituted cyclopropane	10.1	+6.1
<b>13</b>	3: (NMe <sub>3</sub> leaving group)	0.1	-30.6

In **13**, the leaving group is  $Z = \text{N}(\text{CH}_3)_3$ . The leaving group, Z, is formally positively charged, whereas the dinitrile carbon C1, serving as nucleophile X, is formally negatively charged (cf. Scheme 2). The SN2 ring closure involves extinguishing two charges to create neutral products, which is highly favorable in a medium close to the gas phase.<sup>41</sup> The overall reaction energy is -30 kcal. In agreement with the high exothermicity, the transition state C1—C3 distance is extremely long, 2.16Å, compared to 1.89Å for **1** (chloride leaving group).

It is interesting to speculate on the reason(s) for the high reactivity of the ring closure to form the unstable three-membered ring (**1**). Three variations from a simple SN2 reaction are possible: (1) an electrostatically assisted SN1 process, (2), an internal electron transfer reaction, or (3) tunneling, perhaps associated with one of the previous two situations.

Regarding an anion electrostatically assisted SN1 reaction in the case of **1**, the irc scans indicate similar X—Y and Y—Z changes in bonding approaching the transition state.<sup>42-45</sup> There is no extreme lengthening of Y—Z, compared to **3** or other cases. At higher dielectric constant, the SN1-like transition state should be enhanced. The SCRF data predict about the same geometry for the transition state at DK = 24 (ethanol) as for DK <1.

For a stepwise ET process, it might be expected that an energy jump would be seen when the electron transfer to Y-Z occurred, with little change in the X—Y distance. The Y-Z distance might undergo an increase in bond distance, as an antibonding Y-Z orbital would be populated. It was difficult to get down to a structure resembling starting material in the irc scan, but in the vicinity of the transition state, the X—Y and Y—Z parabolas were similar. The parabolas for **1** were similar to the case of closure to a four-membered ring (**2**), and five-membered ring (**3**). For **1**, the imaginary frequency ( $\nu = -414 \text{ cm}^{-1}$ ) displayed motion of the developing bond atoms (X—Y) toward one another. Shaik, Schlegel and Wolfe do not believe that the ET process is stepwise for SN2 reactions, and that X—Y and Y—Z changes occur simultaneously with electron transfer, so an ET process might not show discontinuous X—Y and Y—Z changes.<sup>47,48</sup> This prediction remains to be seen.

Tunneling is an explanation now widespread for reactions in enzymatic chemistry.<sup>49-55</sup> Tunneling is expected for low mass atom transfers (e.g. hydrogen) in cases where the reaction barrier is narrow and location is uncertain with respect to

energy. However, R.P.Bell apparently regards every transition state to involve tunneling to some degree.<sup>56</sup> In the present case, the large  $X = (\text{NC})_2\text{CH}^\cdot$  fragment is hardly small. However, it is possible that an even smaller mass (than hydrogen) entity is transferred from C1 to C3, namely an electron. For **1**, there was no irc evidence for a particularly “sharp” transition state parabola, nor was there evidence for a truncated transition state parabola, as deemed necessary by some writers.<sup>53,57</sup> The irc parabolas for rapidly forming **1** and for the slowly forming **2** were similar.

The question arises whether the three-membered ring closure (**1**) enjoys some sort of quantum mechanical stabilization not present for **2** and the others, and also not present in the cyclopropane product. Inspection of visual representations of the LUMO, HOMO plus several lower energy filled transition state orbitals for **1-3** revealed similar forms.

The ease with which a three-membered transition state is located (as in **1**) vs. the great difficulty in locating a transition state for the four-ring case (as in **2**) suggests another avenue that may be explored. A common occurrence in searching for the four-ring transition state is “wrong number of imaginary vibrations”, commonly two or higher, often involving adjacent hydrogens. It is possible that the incursion of irrelevant bending or stretching modes or conformational excursions of the developing ring occur to short-circuit the approach to the transition state.<sup>54,55,58-59</sup> It is noteworthy that in every case where facile conformational changes are likely near the transition state e.g. **2**, **5**, twist-boat cyclohexane, and cyclooctane (transition state was never located), the transition state was located with difficulty and experimentally, the reaction is slow. The exception is **3**. Attempts to locate a transition state for **3** with the C2 geometry of the incipient ring ended up with the envelope conformation.

In contrast to the difficulty in locating the four-membered ring transition state (**2**), the rigid benzo derivative **14** allowed the transition state to be located in only two tries. The reacting carbon atoms are held planar. Although an anion assisted SN1 reaction is possible since the carbon(4)—chlorine bond is 2.49 Å in the transition state, and C1—C4 also relatively long (2.13 Å), inspection of the imaginary frequency ( $I = -405 \text{ cm}^{-1}$ ) reveals chlorine moving away from C4 and C1 and C4 moving together. The C4—Cl bond is orthogonal to the benzene ring. The overall reaction is more endothermic (2.8 kcal at the RHF/6-31G(d,p) level) compared to **2**, but the transition state is much higher in energy (23.6 kcal above starting material compared to ca. 15 kcal for **2**), so a more product-like transition state is predicted.

Closure to a three-membered is also predicted for free-radicals (in contrast to carbanions) (cf. **15** and **16**, Scheme 3), but the energy is high. The higher energy required for the  $X = \text{CH}_2$  (**16**) than for  $X = (\text{NC})_2\text{C}^\cdot$  (**15**) is surprising. The spin densities

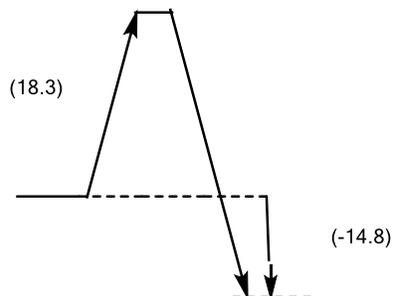
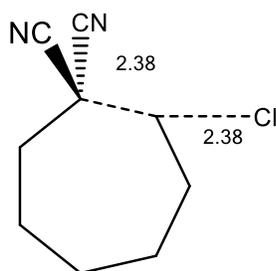
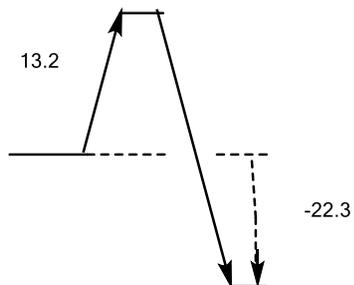
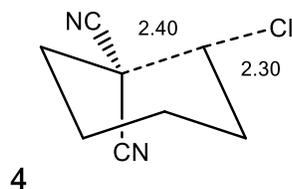
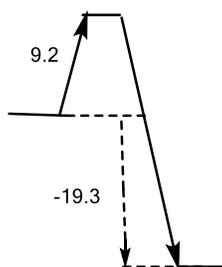
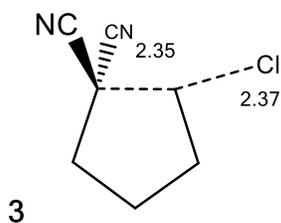
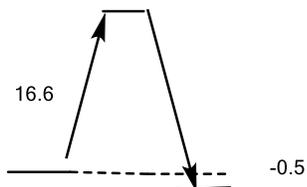
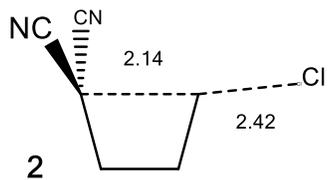
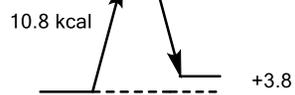
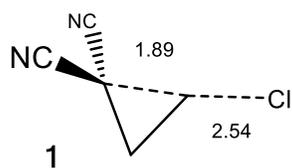
in the transition state are shared by X and Z (Cl). The transition state resembles products much more than for **1**.

In conclusion, the examples of **9** to **12** as well as **13** illustrate that factors totally unrelated to the X—Y and Y—Z force constants *per se* are predicted to affect the earliness or lateness of the transition state. The earliness/lateness of the transition state seems dictated by thermodynamic energy of starting material and product alone. While it is possible that the energy of the transition state itself (cf. **1**) plays no role in the earliness or lateness of that same transition state, this lack of influence strains credulity. Further, changes in the molecule external to the X—Y and Y—Z bond force constants, e.g. gem dimethyl substitution, affect the earliness or lateness of the transition state, solely by affecting the energies of the starting material and product (cf. **9** – **12**). The question arises: Are the balances in X—Y and Y—Z “built in” the methods of transition state determination? The method for locating transition state geometry in Gaussian is complex, but seems generally in accord with transition state theory, and, tangentially, with the Hammond postulate. The slavish agreement with the Hammond postulate, thus, may be pre-determined by the calculation method. What the molecules actually do in the transition state remains to be seen.<sup>54,57</sup>

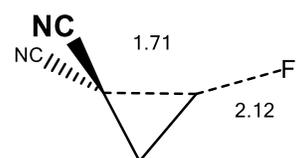
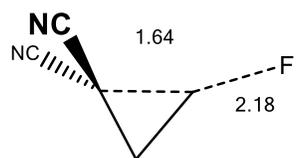
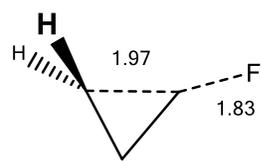
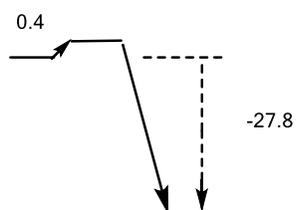
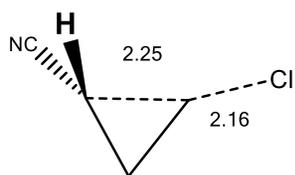
### Computational Methods

Gaussian 03 was used.<sup>60</sup> The transition states were located first using rhf/3-21G method and basis set, on guesses as to what the transition state might look like. The “noeigentest” technique was NOT used, except for **14**. The calculation was moved up in stages first to RHF/6-31G(d,p), then to B3LYP/6-31G(d,p). In some cases, the MP2 method was used, but frequencies were impossible. The B3LYP/cc-pVZT technique was used for some of the data in Scheme 5. MP2/cc-pVZT was impossible on our system.<sup>11</sup> Irc scans were attempted in major cases, plus additional reach to the starting material or product. In general, the “sum of electronic and thermal free energies” calculation from frequency calculations was used to evaluate the energetics (data of table I and schemes 1-5), where possible. For MP2 and B3LYP/cc-pVZT calculations, this was impossible, and thus Hartree Fock energies or MP2 energies were used.

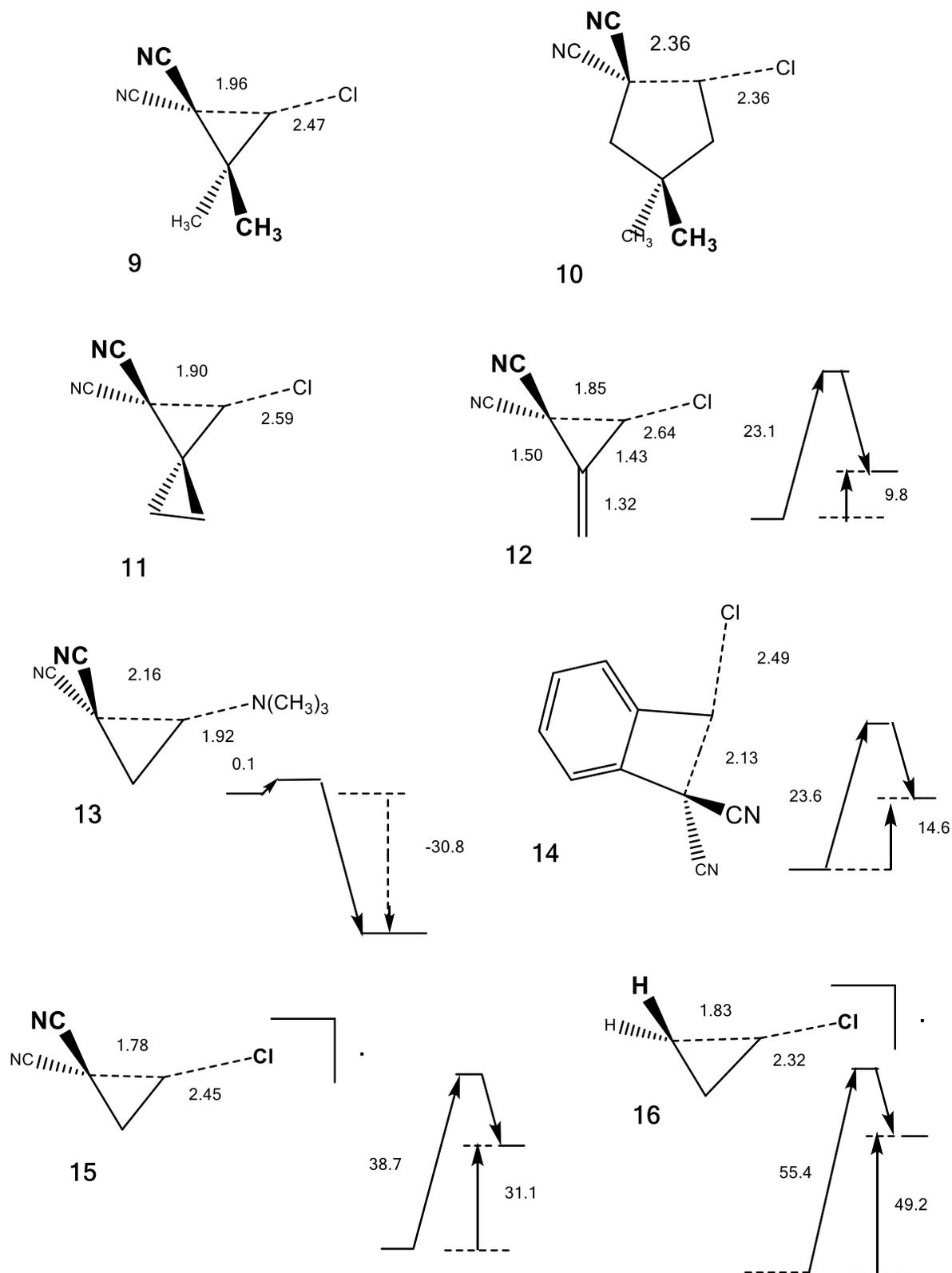
**Scheme 1: Interatomic Distances (Angstroms) in the Transition State (B3LYP/6-31G(d,p) data)  
"Activation Energies" and Energies of Overall Reaction (kcal)**



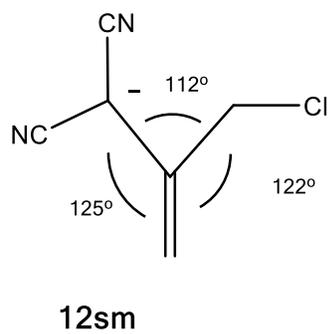
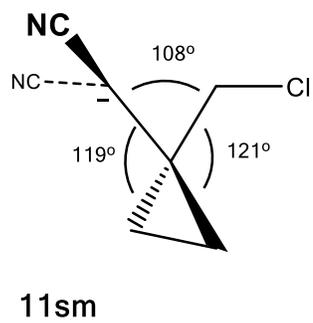
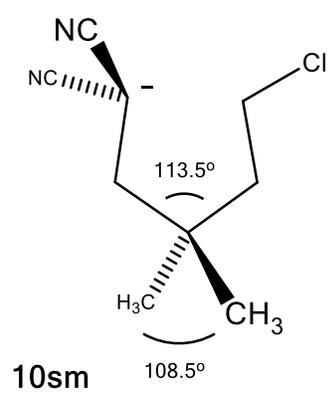
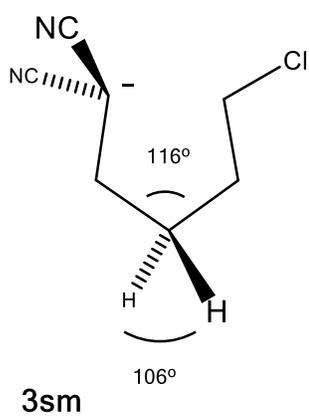
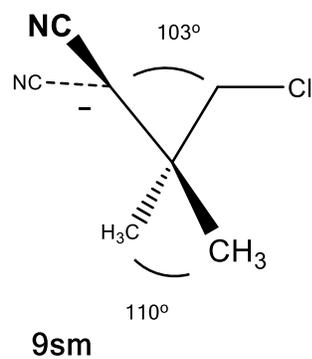
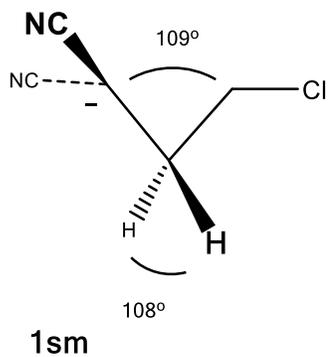
Scheme 2: Variations on the Theme



Scheme 3: Interatomic Distances in the Transition States for Substituted Ring Systems

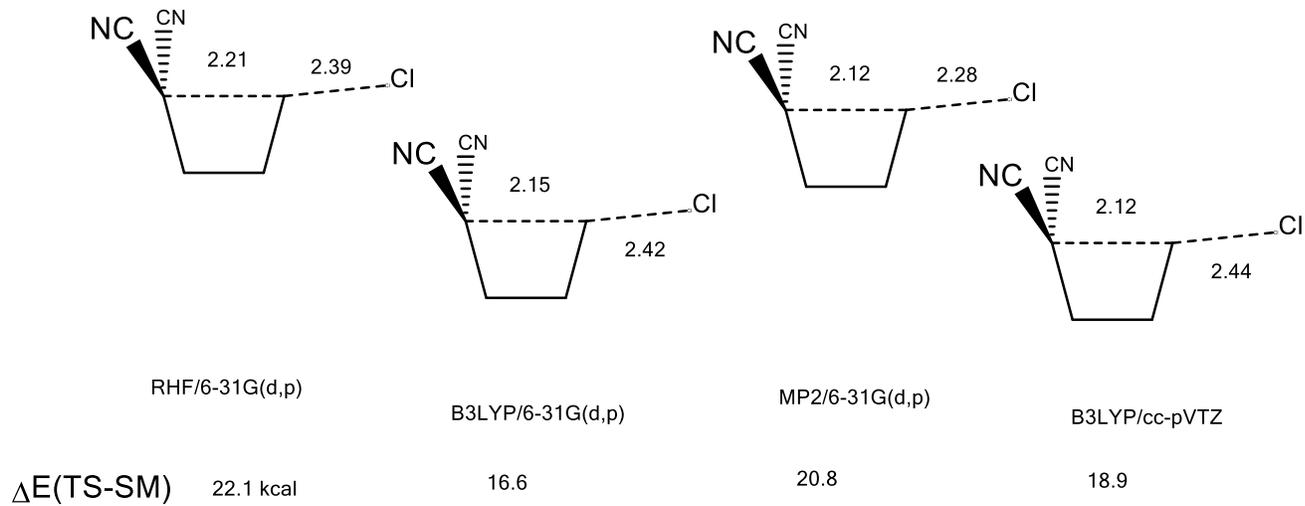
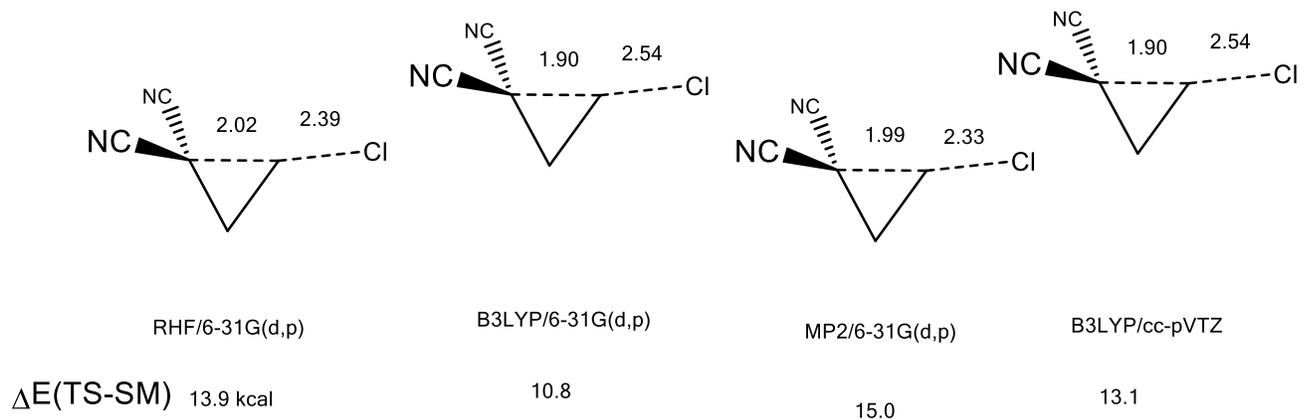


Scheme 4: Bond Angles in the Ground State



**Scheme 5: Energy differences between ground state and transition states and geometry of transition states at various levels of theory.**

Cyclopropane series:



## References

1. Leffler, J.E., *Science*, **1953**, *117*, 340-341.
2. Bronsted, J.N., *Rec. Trav. Chim.*, **1923**, *42*, 718.
3. Kornblum, N., Michel, R.E., Kerber, R.C., *J. Am. Chem. Soc.*, **1961**, *88*, 5660.
4. Kresge, A.J., *Chem. Soc. Rev.*, **1973**, *2*, 475.
5. Hammond, G.S., *J. Amer. Chem. Soc.*, **1955**, *77*, 334.
6. Evans, M.G., Polanyi, M., *J. Chem. Soc. Faraday Trans.*, **1936**, *32*, 1340.
7. Haddon, R.C., Tian, Z., Jiang, D-E., *J. Org. Chem.*, Apr. 2016, to be published.
8. Agmon, N., *J. Chem. Soc. Faraday Trans 2*, **1978**, *74*, 388-404.
9. Manz, T. Sholli, D., *J. Computational Chem.*, **2010**, *41*, 1528.
10. Pechukas, P., *Ann. Rev. Phys. Chem.*, **1981**, *32*, 159.
11. Trulahr, D.G., Garrett, B.C., Klippenstein, S.J., *J. Phys. Chem.*, **1996**, *100*, 12771.
12. Kreevoy, M.M., Trulahr, D.G., in "Investigation of Rates and Mechanism of Reactions," *Techniques of Chemistry*, 4th ed., Vol. VI, Part 1, Bernasconi, C. F. ed, Wiley, Interscience, NY, 1981.
13. Sola, M., *J. Phys. Chem.*, **1999**, *103*, 8847-8852.
14. J. Cioslowski, *J. Am. Chem. Soc.*, **1991**, *111*, 6756-6760.
15. Sola, M., Toro-Labbe, A., *J. Phys. Chem. A*, **1999**, *103*, 8847
16. Toro-Labbe, A., *J. Phys. Chem A*, **1999**, *103*, 4398.
17. Gellman, A., *J. Chem. Phys. B*, **2002**, *106*, 10509.
18. Gellman, A., *Acc. Chem. Res.*, **2000**, *33*, 19.
19. Gellman, A., Buelow, M.T., Street, S.C., Morton, T.A., *J. Phys. Chem. A*, **2000**, *104*, 2476.
20. Amat, L., Carbo-Dorea, R., Cooper, D. L., Allan, N. L., *Chem. Phys. Lett.*, **2004**, *393*, 40.
21. Sola, M., Mestres, J., Carbo, R., Duran, M., *J. Am. Chem. Soc.*, **1994**, *116*, 5909.
22. Haddon, R.C., Chow, S.Y., *J. Am. Chem. Soc.*, **1998**, *120*, 10494.
23. Nalewajski, R. F., Broniatowska, E., *Chem. Phys. Lett.*, **2003**, *376*, 33.
24. Arteca, G.A., Mezey, P.G., *J. Phys. Chem.*, **1989**, *93*, 4746.
25. Lah, Z.H., Field, R.V., *J. Chem. Phys.*, **2003**, *118*, 4037.
26. Petersson, G.H.A., Tensfeldt, T.E., Montgomery, J.A., *J. Am. Chem. Soc.*, **1992**, *114*, 6133.
27. Kingsbury, C., *J. Phys. Org. Chem.*, **2010**, *23*, 513.
28. Experimentally, the closure to a three-membered ring in a system very similar to **1**, i.e. 2-bromo-4,4-dicarbomethoxy-1,3-diphenylbutan-1-one, was complete before the first nmr point could be determined, a matter of a few minutes. The

- isomerization of the cis 2-benzoyl-3,3-dicarbomethoxy-3-phenylcyclopropane to the trans isomer was slower, with a half-life of a day or so.
29. Becke, A.D., *J. Chem. Phys.*, **1993**, *98*, 1372.
  30. Lee, C., Yang, W., Parr, R.G., *Phys. Rev. B*, **1988**, 785.
  31. Carey, F. A., Sundberg, R. J., *Advanced Organic Chemistry, A*, 3rd ed., Plenum Press, New York, NY, 1990, pp 211-215. Carey provides a compendium of ring closure rates vs. ring size.
  32. De Meijer, A., *Angew. Chem. Intern. Ed. Engl.*, **1979**, *18*, 809. Also ref. 31, p.7.
  33. Burkert, U., Allinger, N.L., *Molecular Mechanics*, ACS Monograph 177, American Chemical Society, Washington, DC, 1982, p. 89-91, p. 118.
  34. In the case of the seven-membered ring, starting with the classical "deformed chair" conformation was not successful. Eliel, E.L., *Stereochemistry of Carbon Compounds*, McGraw-Hill Book Co., New York, 1962, p. 252.
  35. Onsager, L., *J. Am. Chem. Soc.*, **1938**, *56*, 1436.
  36. Kirkwood, J.G., *J. Chem. Phys.*, **1934**, *2*, 351.
  37. Beesley, R.M., Ingold, C.K., Thorpe, J.F., *J. Chem. Soc.*, **1915**, *107*, 1080.
  38. Ingold, C.K., *J. Chem. Soc.*, **1921**, *119*, 305.
  39. An enthalpy-entropy argument has also been convincingly applied: Allinger, N.L., Zalkow, V., *J. Org. Chem.*, **1960**, *25*, 701.
  40. For a discussion of various interpretations: Eliel, E.L., ref. 33, pp 97-202.
  41. Ingold, C.K., *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, NY, 1953, pp. 345-350.
  42. Pocker, Y., Ciula, J.C., *J. Am. Chem. Soc.*, **1988**, *110*, 2904-9.
  43. Shaik, S., Shurki, A., *Angew. Chem. Intern. Ed. Engl.*, **1999**, *38*, 587-625.
  44. Naray-Szabo, G., Ferenczi, G.G., *Chem. Rev.*, **1995**, *95*, 829-47.
  45. Dahlberg, D.G., Kuzenko, M.A., Chang, Y., Kresge, A.J. Powell, M.T., *J. Am. Chem. Soc.*, **1983**, *105*, 5387-90.
  46. Smith, P.J., Wilcox, C.S., *Tetrahedron*, **1991**, *47*, 2617.
  47. Shaik, S., Schlegel, H.B., Wolfe, S., *Theoretical Aspects of Organic Chemistry: The SN2 Mechanism*, Wiley-Interscience, New York, 1992.
  48. Ebersson has concluded that there is no simple way of distinguishing electron transfer mechanisms from two-electron processes: Ebersson, L., *Electron Transfer Reactions in Organic Chemistry*, Springer-Verlag, Berlin 1987, pp 191-199.
  49. Tunneling is invoked in hydrogen transfers in enzymatic reactions: See Thornton, C.K. Thornton E.R., in *Transition States in Biochemical Processes*, Gandour R, Schowen, R.L., eds, Springer Science and Business Media, 1978, Ch. 2, as well as other chapters.
  50. Johannsson, L., Hay, S., Scrutton, N.S., *Physical Chemistry Chemical Physics*, **2015** *17*, 30775.

51. Matta, Cherif , *Quantum Biochemistry: Electronic Structure and Biological Activity*, Wiley-VCH, Weinheim, 2014. Ch 1.
52. Quirk, D.J., Northrup, D.B., *Biochemistry*, **2001**, *40*, 847.
53. Suhnel, J., Schowen, R.L. in *Enzyme mechanism from Isotope Effects*, Cook, P.F. Ed., CRC Press, Inc., Boca Raton, FL, 1991, p. 17
54. Recrossing the barrier is another factor, investigated in detail by Truhlar and coworkers, Pu, J., Gao, J. Truhlar, D.G., *Chem. Rev.*, **2006**, *106*, 3140.
55. Grote, R.F., Hynes, G.T., *J. Chem. Phys.*, **1980**, *73*, 2715. This theory represents an alternative to tunneling.
56. Bell, R.P. *The Tunnel Effect in Chemistry*, Chapman and Hall, London, New York, 1980.
57. Westheimer, F.H., *Chem. Rev.*, **1961**, *61*, 265.
58. Ritchie, C.D., *Physical-Organic Chemistry*, 2nd ed., Marcel Dekker, Inc., NY, 1990, pp 297-306.
59. Anslyn, E.V., Dougherty, D.A., *Modern Physical Organic Chemistry*, University Science Books, Sausalito, CA, 2006, pp 375-376.
60. Gaussian 03, Revision C.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Wallingford CT, 2004.