BULLETIN

OF THE

KOREAN CHEMICAL SOCIETY

ISSN 0253-2964 BKCSDE 20(12) 1377-1578
Volume 20, Number 12 December 20, 1999

Communication

HF and MP2 Calculations on the Transition States of S_N' O-Cyclizations

Gyoosoon Park[*] and Soo Gyeong Cho[†,*]

Department of Chemistry, Kookmin University, Seoul 136-702, Korea
[†]Agency for Defense Development, P.O. Box 35-5, Yuseong, Taejon 305-600, Korea

Received August 23, 1999

Bimolecular nucleophilic substitution with allylic rearrangement (S_N2') has been of synthetic and mechanistic interest for years.[1,2] Intramolecular cyclization *via* S_N2' mechanism is one of effective and general approaches to synthesize various heterocycles.[3] Recently, Zhao and coworkers[4] have demonstrated the intramolecular S_N' O-cyclizations of alkoxides are efficient methods for tetrahydrofurans (THFs), which are common structure present in a variety of natural products and diverse synthetic intermediates.[5]

This synthetic scheme is quite a useful methodology in synthesizing other novel compounds because the products contain the vinyl moiety, which can be utilized to perform necessary synthetic modifications. If a large substituent is present in the terminal vinyl group, S_N' O-cyclization become possibly stereoselective. However, the stereoselectivity in S_N' O-cyclizations should largely depend upon the natures of transition states including steric hindrance.[6] First, the large substituent attached to the terminal position of the vinyl group provides steric hindrance enough to differentiate a route to produce one isomer from that to produce the other isomer. However, this differentiation is impossible to obtain, if (1) the steric hindrance is relieved by an internal rotation, and (2) each reaction route can proceed to two different isomers via two different modes, *i.e.* syn and anti attacks. Thus, which mode is more favorable between syn and anti attacks is an important issue that should be addressed in the first place. If a substantial energy difference is present between two modes of attacks, a stereoselective product may be obtained due to the different size of terminal groups. On the other hand, if the energy difference between two modes is almost negligible, one can hardly expect stereoselectivity in S_N' O-cyclizations.

Thus, we have carried out *ab initio* studies to investigate the transition states of the S_N' O-cyclization, which may provide useful information regarding stereochemical outcomes in this reaction. Our study is particularly focusing on the energy difference between syn and anti modes of attacks. *Ab initio* calculations were carried out using the GAUSSIAN-94 programs[7] on a CRAY machine. (*E*)- and (*Z*)-6-Chlorohex-4-enolate anion ($Cl\text{-}CH_2CH{=}CH\text{-}(CH_2)_3\text{-}O^-$, **1**), which are model compounds with a basic skeleton to undergo the S_N' O-cyclization, were selected. Transition structures (TSs) were optimized with the 6-31+G(d) basis set[8] at the HF and MP2 levels of theories without restricting any symmetry. TSs were found by using the eigenvector following routine of Baker.[9] Vibrational frequencies were calculated at both HF and MP2 levels to confirm whether optimized TSs are true transition states, which should have only one negative imaginary frequency.[10] Electron correlation effect was incorporated at the second order Møller-Plesset perturbation theory[11] either with full optimization or at the HF-optimized geometries.

We have initiated our studies by performing HF/6-31+G(d) calculations. We have attempted to locate the TSs for the S_N' O-cyclization from (*E*)- and (*Z*)-**1** by varying skeletons of both isomers of **1**. Two stable TSs of each isomer are illustrated in Figure 1. The geometric nature of the TSs seems to be a typical example of concerted S_N2' mechanisms, and clearly shows that the Cl atom departs simultaneously as the O anion attacks. During the cyclization, the newly forming THF ring maintains an envelope conformation where the C2 atom is on the tip of the envelope, and resides away from the newly forming vinyl substituent at the C4 position. Although we can also locate additional TSs with posing the C2 atom to the near side of the vinyl substituent, they are of course energetically unfavorable when compared with those conformations depicted in Figure 1.

According to HF/6-31+G(d) calculations, an anti attack is computed to be substantially more stable than a syn attack in

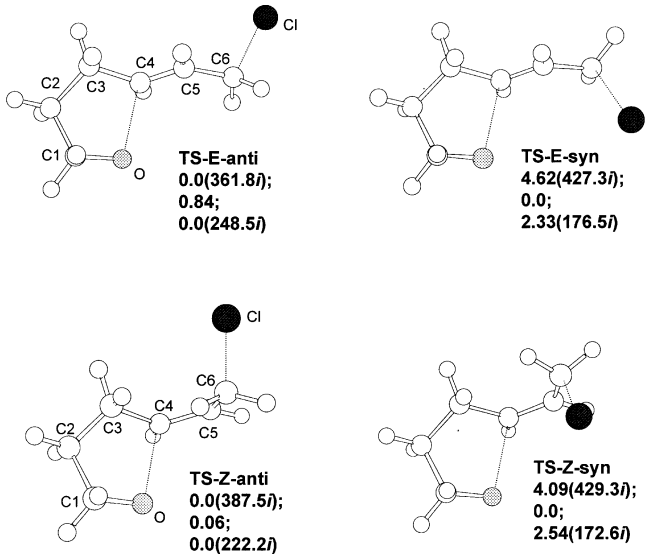

Figure 1. Geometries of four TSs, **TS-E-anti**, **TS-E-syn**, **TS-Z-anti**, and **TS-Z-syn**, optimized at the MP2/6-31+G(d) level with the atomic numbering scheme. HF-optimized TSs also have a similar trend with MP2-optimized geometries. The values are relative energy values calculated at the HF/6-31+G(d)//HF/6-31+G(d); MP2/6-31+G(d)//HF/6-31+G(d); MP2/6-31+G(d)//MP2/6-31+G(d) levels with the imaginary frequency in parenthesis. For a reference, absolute energy values (unit: a.u.) are -767.3119206; -768.4289331; -768.4365967 for **TS-E-anti**, and -767.3083241; -768.4275147; -768.4344466 for **TS-Z-anti**, respectively, at the HF/6-31+G(d)//HF/6-31+G(d); MP2/6-31+G(d)//HF/6-31+G(d); MP2/6-31+G(d)//MP2/6-31+G(d) levels.

both isomers. The energy differences between anti and syn attacks are 4.62 kcal/mol in the (*E*)-isomer, and 4.09 kcal/mol in the (*Z*)-isomer, respectively. If these large differences hold in a series of similar compounds with two different substituents at the C6 position, one may anticipate a large stereoselectivity of the products by eliminating a syn mode of attack.

Electron correlation is an important effect to describe various features of the reactions well. Especially, near TSs, where some bonds are forming or breaking partly, inclusion of electron correlation effect should be essential. Initially, we included electron correlation effect of the MP2 level of theory via single point energy calculation. This technique is a common methodology, especially when one should deal with a relatively large size of molecules like this case. In addition, this method is well proved in various types of reactions and compounds to provide very good results.[12] An argument to support single point energy calculations is (1) little changes of geometric features, but (2) a large difference in energies. However, we are surprised to find substantial changes in the relative stability between anti and syn attacks. Our MP2/6-31+G(d)//HF/6-31+G(d) calculations reverse the trend. Syn attacks are more favorable than anti attacks by 0.84 kcal/mol for the (*E*)-isomer, and 0.08 kcal/mol for the (*Z*)-isomer, respectively. If these values are true, one may not expect stereoselectivity from the S_N' O-cyclization.

Since the change due to the inclusion of electron correlation *via* single point energy calculation is so huge, and this change is of significant importance in understanding the stereochemical outcomes from the S_N2' O-cyclization, we pushed our computational level one notch up to move MP2/6-31+G(d) optimizations, which are almost the upper limit with our computational resources. We are only able to do these calculations by utilizing the keywords, verystingy and scf = direct. The MP2/6-31+G(d) calculations with full geometric optimizations and provide that an anti attack is more stable than a syn attack by 2.33 kcal/mol in the (*E*)-isomer, and 2.54 kcal/mol for the (*Z*)-isomer, respectively. These results are much smaller than those from the HF calculations by approximately 2 kcal/mol. Thus, electron correlation effect is profound in this particular reaction, and appears to play an important role to quantify stereoselectivity of a series of similar compounds accurately. Moreover, the MP2/6-31+G(d) results with full optimizations totally disagree with the energy differences obtained at the MP2/6-31+G(d)//HF/6-31+G(d) level. Although we are aware that our result may be atypical, it seriously warns that one may obtain illusive values in relative energies when electron correlation effect is included by

Table 1. Important geometric parameters in the TSs of the S_N' O-cyclization from (*E*)- and (*Z*)-**1**

	HF/6-31+G(d)				MP2/6-31+G(d)			
	TS-E-anti	**TS-E-syn**	**TS-Z-anti**	**TS-Z-syn**	**TS-E-anti**	**TS-E-syn**	**TS-Z-anti**	**TS-Z-syn**
Bond lengths[a]								
O-C4	2.260	2.055	2.238	2.083	2.105	2.166	2.136	2.205
C4-C5	1.362	1.374	1.367	1.377	1.376	1.372	1.377	1.374
C5-C6	1.414	1.436	1.417	1.435	1.447	1.461	1.452	1.463
C6-Cl	2.204	2.028	2.178	2.045	1.943	1.885	1.926	1.888
Bond angles[b]								
∠C1-O-C4	101.22	105.29	101.84	104.44	101.42	100.79	102.46	100.42
∠O-C4-C5	113.81	117.09	113.89	116.81	114.10	117.16	113.56	117.02
∠C3-C4-C5	123.49	121.09	126.29	124.93	121.60	121.04	124.02	124.30
∠C4-C5-C6	120.70	116.56	124.19	125.56	121.34	122.48	123.52	125.16
∠C5-C6-Cl	113.80	90.50	114.31	116.96	114.84	115.27	115.31	115.64
Torsional angles[b]								
O-C4-C6-C1	156.65	-11.93	-157.92	-1.58	159.96	-18.14	-153.59	-1.56

[a]Unit in Å. [b]Unit in deg.

single point energy calculations.

In order to understand these consequences due to electron correlation as well as the natures of TSs, we have examined the geometric features of the TSs. The geometric parameters including the distances of partly formed and broken bonds are summarized in Table 1. One of surprising geometric features we can immediately notice from the Table 1 is strikingly large discrepancies between HF and MP2 optimized geometries. In the TSs of anti attacks, partly formed O-C4 and partly broken C6-Cl bonds calculated at MP2/6-31+G(d) are about 0.1-0.2 Å smaller than those calculated at HF/6-31+G(d). On the other hand, in the TSs of syn attacks, MP2 calculated O-C4 bond is about 0.1-0.15 Å longer than the HF calculated one, while MP2 calculated C-Cl bond is about 0.15 Å smaller than the corresponding HF calculated bond. This geometric difference due to the inclusion of electron correlation effect is surprisingly large when compared with those published in other sources.[10,12] Considering small magnitudes of imaginary frequencies in this cyclization, we believe that an extremely flatness of the potential energy surfaces near TSs may cause to change the equilibrium geometries significantly due to the electron correlation. Thus, the use of geometries optimized at different levels also cause totally different relative energy values in this reaction.

In summary, the S_N' O-cyclizations proceed *via* a concerted intramolecular S_N2' mechanism with an anti alignment between attacking O anion and leaving Cl atom. HF/6-31+G(d) calculations predict that anti attacks are more than 4 kcal/mol favorable than syn attacks in both isomers. Electron correlation effect is significantly large. The energy differences between syn and anti attacks are reduced to be slightly more than 2 kcal/mol. MP2/6-31+G(d) calculations predict this energy difference is 2.33 kcal/mol in the (*E*)-isomer, and 2.54 kcal/mol in the (*Z*)-isomer, respectively. This energy difference is sufficient enough to be stereoselective in this cyclization, if a large substituent is present in a terminal position of the vinyl group. However, we were surprised to find that single point energy calculations utilizing the HF optimized geometries provide totally unacceptable energy differences in this particular reaction. This atypical result is probably attributed to an extremely flattened potential energy surface near TSs. Our study may serve as an excellent example that including electron correlation effect utilizing optimized geometries at insufficient levels of theories sometimes provides illusive results, if the potential energy surface is quite flat.

References

1. For examples of S_N2' reaction see: (a) Magid, R. M.; Fruchey, O. S. *J. Am. Chem. Soc.* **1979**, *101*, 2107. (b) Kirmse, W.; Scheidt, F.; Vater, H.-J. *J. Am. Chem. Soc.* **1978**, *100*, 3945. (c) Ikota, N.; Ganem, B. *J. Am. Chem. Soc.* **1978**, *100*, 351. (d) Stork, G.; Kreft, A. F. *J. Am. Chem. Soc.* **1977**, *99*, 3850. (e) Dobbi, A. A.; Overton, K. H. *J. Chem. Soc., Chem. Com.* **1977**, 722. (f) Uebel, J. J.; Milaszewski, R. F.; Arlt, R. E. *J. Org. Chem.* **1977**, *42*, 585.
2. (a) Park, Y. S.; Kim, C. K.; Lee, B.-S.; Lee, I. *J. Phys. Chem.* **1995**, *99*, 13103. (b) Bach, R. D.; Wolber, G. J. *J. Am. Chem. Soc.* **1985**, *107*, 1352. (c) Yates, R. L.; Epiotis, N. D.; Bernardi, F. *J. Am. Chem. Soc.* **1975**, *97*, 6615.
3. For selected intramolecular S_N' cyclization see: (a) Marshall, J. A.; Bennett, C. E. *J. Org. Chem.* **1994**, *59*, 6110. (b) Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1994**, *59*, 1703. (c) Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.* **1988**, *53*, 1336. (d) Huffman, J. W.; Desai, R. C. *J. Org. Chem.* **1982**, *47*, 3254. (e) Chiche, L.; Coste, J.; Christol, H.; Pleant, F. *Tetrahedron Lett.* **1978**, 3251. (f) Stork, G.; Kreft, A. F. *J. Am. Chem. Soc.* **1977**, *99*, 3851. (g) Welch, S. C.; Hagan, C. P.; White, D. H.; Fleming, W. P.; Trotter, J. W. *J. Am. Chem. Soc.* **1977**, *99*, 549.
4. (a) Li, P.; Yang, J.; Zhao, K. *J. Org. Chem.* **1999**, *64*, 2259. (b) Li, P.; Wang, T.; Emge, T.; Zhao, K. *J. Am. Chem. Soc.* **1998**, *120*, 7391. (c) Wang, T.; Chen, J.; Zhao, K. *J. Org. Chem.* **1995**, *60*, 2668.
5. (a) Boeckman, R. H.; Goldstein, M. In *The Total Synthesis of Natural Products*, *Volume 7*; Apsimon, J., Ed.; John Wiley & Sons: New York, 1988; p 1. (b) Wierenga, M. In *The Total Synthesis of Natural Products*, *Volume 4*; Apsimon, J., Ed.; John Wiley & Sons: New York, 1981; p 263. (c) Rupprecechy, K. J.; Hui, Y.-H.; McLaughlin, J. L. *J. of Natural Product* **1990**, *53*, 237.
6. (a) Dorigo, A. E.; Houk, K. N. *Adv. Mol. Model.* **1988**, *1*, 135. (b) Eksterowicz, J. E.; Houk, K. N. *Chem. Rev.* **1993**, *93*, 2439. (c) Cho, S. G. *Bull. Korean Chem. Soc.* **1994**, *15*, 183. (d) Silvero, G.; Lucero, M. J.; Winterfeldt, E.; Houk, K. *Tetrahedron* **1998**, *54*, 7293. (e) Arrieta, A.; Cossio, F. P.; Lecea, B. *J. Org. Chem.* **1999**, *64*, 1831. (f) Tomoda, S.; Senji, T.; Kawamura, M.; Iketa, T. *J. Org. Chem.* **1999**, *64*, 5396.
7. Gaussian 94, Revision C.2.; Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A., Gaussian, Inc.: Pittsburgh, PA, 1995.
8. (a) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294. (b) Krishnan, R.; Frisch, M. J.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 4244. (c) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. *J. Chem. Phys.* **1982**, *77*, 3654.
9. Baker, J. J. *J. Comput. Chem.* **1986**, *7*, 385.
10. Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.
11. (a) Møller, C.; Plesset, M. *Phys. Rev.* **1934**, *46*, 618. (b) Pople, J. A.; Binkley, J. S.; Seeger, R. *Int. J. Quantum Chem.* **1976**, *10*, 1.
12. (a) Nagy, P. I.; Alagona, G.; Ghio, C. *J. Am. Chem. Soc.* **1999**, *121*, 4804. (b) Jursic, B. S. *J. Mol. Struct. (Theochem)* **1998**, *423*, 189. (c) Cho, S. G.; Rim, O. K.; Kim, Y.-S. *J. Mol. Struct. (Theochem)* **1996**, *364*, 59. (d) Bock, C. W.; George, P.; Glusker, J. P. *J. Org. Chem.* **1993**, *58*, 5816.