Organometallics **2004,** *23,* 2507−2509

Theoretical Study of Intramolecular [4 + 2] Cycloadditions of Iminoacetonitriles: A New Class of Azadienophiles for Hetero Diels−Alder Reactions

Ming-Der Su†

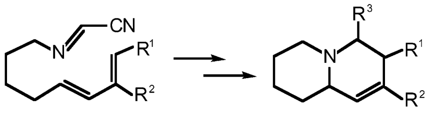
School of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 80708, Taiwan, Republic of China

Received December 1, 2003

Summary: The potential energy surfaces for intramolecular hetero Diels−Alder cycloaddition reactions have been characterized in detail using the B3LYP density functional method, including zero-point corrections. Fifteen isoelectronic species ($YCH{=}X(CH_2)_4CH{=}CHCH{=}CH_2$) were selected as model systems to investigate both the energetics of the reactions and the geometric structures of the species involved. The systems can be divided into three groups as follows: (I) X = N and Y = CN, OH, H, CH_3, Li; (II) Y = CB and X = N, P, As, Sb, Bi; (III) Y = CN and X = CH, SiH, GeH, SnH, PbH. The main findings are as follows. (1) The intramolecular hetero Diels−Alder reactions are predicted to take place through concerted but highly asynchronous transition structures in a fashion similar to some intermolecular hetero Diels−Alder reactions. (2) Our theoretical results for the geometries of the cycloadducts are in accordance with the experimental observations of Danheiser et al. (3) The substitution of a heavy heteroatom (i.e., X = SiH, GeH, SnH, PbH, P, As, Sb, Bi) for a nitrogen in the iminoacetonitrile exerts an important influence on both the activation energies of the transition structures and the reaction enthalpies of the cycloadducts.

The hetero Diels−Alder (DA) reactions are well-known[1] and have attracted much attention, especially in the past few years, because of the noticeable improvement in these reactions achieved by use of various heteroatoms.[2,3] Recently, Danheiser and co-workers reported some novel intramolecular hetero DA reactions.[2] In these [4 + 2] cycloadditions, iminoacetonitriles have been used as starting materials for the synthesis of nitrogen heterocycles (see Scheme 1). It is this fascinating experimental progress that has inspired this study. If iminoacetonitriles can successfully undergo such reactions, would it be possible to extend this to other analogues? Besides this, what are the structures and energetics of the transition states involved in the reaction? What effect does substitution have on the intramolecular DA reactions of iminoacetonitriles? What is the key factor in predicting the chemical reactivity of such hetero cycloaddition reactions? No quantum-chemical calculations for intramolecular hetero cycloaddition reactions have yet been carried out, let alone a systematic theoretical study performed of substituent effects on the reactivities of intramolecular [4 + 2] species. To elucidate the mechanism of the hetero DA reactions, 15 isoelectronic species ($YCH{=}X(CH_2)_4CH{=}CHCH{=}CH_2$) were selected as model systems to investigate both the energetics of the reaction and the geometric structures of the species involved. These systems can be divided into three groups as follows: (I) X = N and Y = CN, OH, H, CH_3, Li; (II) Y = CN and X = N, P, As, Sb, Bi; (III) Y = CN and X = CH, SiH, GeH, SnH, PbH. Our calculations strongly suggest that further development of intramolecular hetero DA reactions should soon be forthcoming and will open up new synthetic areas.

Scheme 1



Three regions on the potential energy surfaces are considered in this work: reactant, transition state, and cycloaddition product (see eq 1 in Table 1). For the group I systems, their geometries and energetics have been calculated using the hybrid density functional method B3LYP/6-311G(d).[4] For the group II and III systems, for reasons of consistency, B3LYP calculations were carried out with relativistic effective core potentials on group 14 and 15 elements modeled using the double-ζ (DZ) basis sets[5] augmented by a set of d-type polarization functions.[6] All these calculations are therefore denoted by B3LYP/LANL2DZdp. As a result, each model compound for group II and III systems contains 287 basis functions and 86 electrons. Vibrational frequencies at stationary points were calculated at the B3LYP level of theory to identify them as minima (zero imaginary frequencies) or transition states (one imaginary frequency). The relative energies are thus corrected for

---

[†] E-mail: midesu@cc.kmu.edu.tw.

[1] Borger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic: San Diego, CA, 1987.

[2] Amos, D. T.; Renslo, A. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2003**, *125*, 4970.

[3] For instance: (a) Beifuss, U.; Ledderhose, S. *J. Chem. Soc., Chem. Commun.* **1995**, 2137. (b) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1. (c) Schmittel, M.; Burghart, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2550. (d) Bland, D. C.; Raudenbush, B. C.; Weinreb, S. M. *Org. Lett.* **2000**, *2*, 4007. (e) Ujaque, G.; Lee, P. S.; Houk, K. N.; Hentemann, M. F.; Danishefsky, S. J. *Chem. Eur. J.* **2002**, *8*, 3423 and references therein.

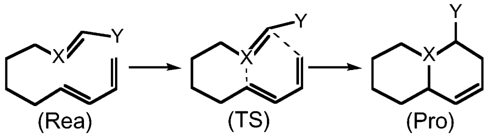
[4] (a) Becke, A. D. *Phys. Rev. A* **1988**, 38, 3098. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

[5] (a) Dunning, T. H., Jr.; Hay, P. J. In *Modern Theoretical Chemistry*; Schaefer, H. F., III, Ed.; Plenum: New York, 1976; pp 1−28. (b) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270. (c) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 284. (d) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.

[6] Check, C. E.; Faust, T. O.; Bailey, J. M.; Wright, B. J.; Gilbert, T. M.; Sunderlin, L. S. *J. Phys. Chem. A* **2001**, *105*, 8111.

10.1021/om030675l CCC: $27.50
Publication on Web 04/14/2004

Table 1. Relative Energies (kcal/mol) for the Process Reactant $YCH{=}X(CH_2)_4CH{=}CHCH{=}CH_2$ → Transition State → Product



(1)

group	system	$\Delta E^{\ddagger\ d}$	ΔH^{e}
I[a,c]	X = N, Y = CN	+22.80	−19.24
	X = N, Y = OH	+28.15	−15.18
	X = N, Y = H	+25.67	−20.56
	X = N, Y = CH_3	+30.04	−13.86
	X = N, Y = Li	+11.45	−3.215
II[b,c]	X = N, Y = CN	+21.49	−18.92
	X = P, Y = CN	+8.136	−31.71
	X = As, Y = CN	+7.376	−32.27
	X = Sb, Y = CN	+6.299	−33.34
	X = Bi, Y = CN	+6.384	−31.98
III[b,c]	X = CH, Y = CN	+20.89	−27.83
	X = SiH, Y = CN	+1.628	−49.09
	X = GeH, Y = CN	+2.143	−45.71
	X = SnH, Y = CN	+2.138	−43.70
	X = PbH, Y = CN	+2.050	−39.43

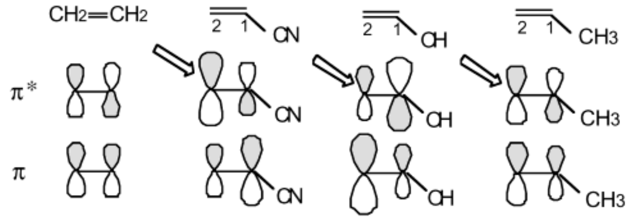
[a] At the B3LYP/6-311G(d) level. [b] At the B3LYP/LANL2DZdp level. [c] All optimized geometries can be found in Figures 1−15 (Supporting Information). [d] Activation energy at 0 K. [e] Reaction enthalpy at 0 K.

vibrational zero-point energies (ZPE, not scaled). All calculations were performed using the GAUSSIAN 98 package.[7]

The relative energies of the stationary points for eq 1 are collected in Table 1. Their calculated geometrical parameters are given in Figures 1−15 in the Supporting Information. The major conclusions drawn from the current study can be summarized as follows.[8]

(1) As seen in Table 1, our B3LYP/6-311G(d) calculations suggest that the barrier height for the intramolecular reactions of group I systems increases in the order (kcal/mol) CN (23) < H (26) < OH (28) < CH_3 (30). Moreover, the order of exothermicity of the cycloadditions follows a similar trend, namely (kcal/mol) H (−21) < CN (−19) < OH (−15) < CH_3 (−14). That is to say, the presence of electron-withdrawing substituents (such as CN) in the intramolecular dienophile can accelerate the process, whereas electron-donating substituents (such as OH) and alkyl groups (such as CH_3) give a higher barrier as well as a lower exothermicity for the intramolecular DA reaction. The reason for this can be easily understood in terms of the frontier molecular orbital (FMO) theory,[9] assuming a frontier interaction between the HOMO of the diene and the LUMO of the dienophile and taking into account the size of the frontier orbitals involved. As one can see in Chart 1, only the CN substituent strongly polarizes the π^* orbital toward C_2 (namely, the doubly bonded nitrogen position in iminoacetonitrile).[9] Thus, the simple FMO model presented here predicts high reactivity for iminoacetonitrile in an intramolecular DA reaction. Nevertheless, the exothermicity of the $[\pi^4s + \pi^2s]$ cycloaddition of the iminoacetonitrile molecule (X = N, Y = CN; see last column in Table 1) is relatively low when compared with those of other DA reactions,[10] which can be related to the difficulties associated with carrying out those types of additions.[2]

Chart 1



On the other hand, the energy data (Table 1) show that the DA reaction for the Li substituent is only slightly exothermic (−3.2 kcal/mol). However, its transition state barrier is 11 kcal/mol, smaller than those of above substituted azadienophiles by 7.2−19 kcal/mol. Consequently, if thermodynamics controls the process, our theoretical evidence indicates that the intramolecular DA reaction should not occur with a strongly electropositively substituted azadienophile.

(2) Considering the group II systems (group 15 elements) in Figures 6−10 (Supporting Information) and Table 1, it is apparent that the transition structures of the intramolecular DA reaction with Y = P, As, Sb, Bi substituents are highly asynchronous and are predicted to have very low activation energies (6.2−8.1 kcal/mol). Nevertheless, the B3LYP activation energy for the N-substituted system is about 14 kcal/mol higher than for reactions of pnicogen-substituted systems. Besides this, the reaction enthalpies for reactions with P, As, Sb, and Bi substituents are very close: approximately −32 kcal/mol. However, the reaction enthalpy for the DA reaction involving the N atom is less exothermic (−19 kcal/mol) than the others. This can be easily rationalized in terms of the bond changes that occur in these reactions. Taking a simple bond energy approach, the net bond change (kcal/mol) in the N-substituent reaction is the formation of a new C−N (69) and C−C (81) σ bond, while the C−N (79) bond and C−C (67) π bond are broken.[11] As a result, the formation of the relatively weak C−N σ bond at the expense of breaking the relatively strong C−N π bond leads to a less exothermic reaction. Furthermore, the intramolecular DA reactions for P, As, Sb, and Bi substituents are more exothermic than for the N substituent, a result of the

---

[7] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*; Gaussian, Inc.: Pittsburgh, PA, 1998.

[8] It should be mentioned here that the activation energy as well as the reaction enthalpy for the iminoacetonitrile (X = N, Y = CN) DA reaction at both b3LYP/6-311G(d) and B3LYP/LANL2DZdp levels are quite similar. Thus, it is believed that the current methods employed in this study should provide reliable information for the discussion of the nature of such intramolecular DA reactions.

[9] Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976.

[10] See: (a) Houk, K. N.; Gonzalez, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81. (b) Wiest, O.; Houk, K. N. *Top. Curr. Chem.* **1996**, *183*, 1 and references therein.

[11] Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987.

well-known much weaker C−Y π bond relative to the C−N π bond.[12]

(3) Considering the group III systems (group 14 elements) in Table 1, it is obvious that the predicted activation barriers for the intramolecular DA reactions with X = SiH, GeH, SnH, and PbH substituents (~2.0 kcal/mol) are significantly lower than the reaction with the CH substituent (21 kcal/mol). This strongly implies that the former species should undergo rapid intramolecular DA reactions at or below room temperature. Likewise, their intramolecular DA reactions are predicted to be much more exothermic (−39 to −49 kcal/mol) than that of the all-carbon dienophile (−28 kcal/mol). Again, as shown above, the weakness of the Y═C π bond, compared to the HC═C π bond, contributes to their reactivities as well as their thermodynamics.[12] Moreover, the large X═C bond lengths (see Figures 11−15 in the Supporting Information) probably also contribute to their low barrier heights. Namely, intramolecular butadiene must be strained to achieve simultaneous overlap at the two ends of a hetero dienophile. The strain is apparently larger in a short HC═C bond than in a long X═C bond.

(4) Comparing substituents in the same row in Table 1, it is evident that those in group III have lower activation barriers as well as higher exothermicity than those in group II. This strongly implies that the intramolecular hetero DA reactions should be more highly favored for a reactant containing a group 14 substituent than for one containing a pnicogen substituent from the same row. Again, this reflects the extremely weak π bond of the former compared to that of the latter.[12]

(5) Finally, as found by Danheiser and co-workers, in most experimental cases the cycloadduct with an exo-oriented cyano group is obtained as the major or exclusive product of the reaction.[2] Our computational results are in accordance with experimental observations.

In brief, our theoretical findings demonstrate that the activation energy is lowered and the reaction enthalpy becomes more exothermic for reactions involving a dienophile containing an electron-withdrawing group. Also, the substitution of a heavy heteroatom (i.e., X = SiH, GeH, SnH, PbH, P, As, Sb, Bi) for a nitrogen in the iminoacetonitriles exerts a significant influence on both the activation energy of the transition structure and reaction enthalpy of the cycloadduct.

It is hoped that this study can stimulate further research into the subject.

Acknowledgment. I am grateful to the National Center for High-Performance Computing of Taiwan for generous amounts of computing time. I also thank the National Science Council of Taiwan for financial support.

Supporting Information Available: Figures 1−15, giving calculated geometrical parameters for the stationary points given in eq 1. This material is available free of charge via the Internet at http://pubs.acs.org.

OM030675L

---

[12] Lide, D. R. and Frederikse, H. P. R. *CRC Handbook of Chemistry and Physics*, CRC Press: New York, 1998; pp 9−51.