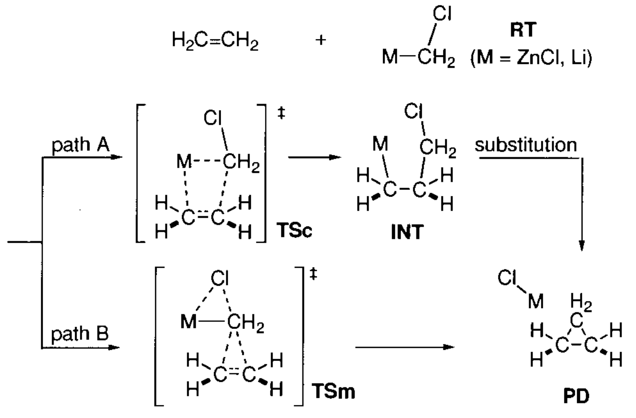
Theoretical Studies on Cyclopropanation Reaction with Lithium and Zinc Carbenoids

Atsushi Hirai, Masaharu Nakamura, and Eiichi Nakamura*
Department of Chemistry, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033

(Received June 5, 1998; CL-980431)

Theoretical studies on cyclopropanation of ethylene with lithium carbenoid and zinc carbenoid (Simmons-Smith reagent) revealed two competing pathways, methylene transfer and carbometalation. Both processes are fast for the lithium carbenioid, while only the former is fast enough to be experimentally observable for the zinc carbenoid.

Metal carbenoids are important intermediates for cyclopropane ring synthesis,[1] among which α-halolithium and α-halozinc reagents, the latter known as the Simmons-Smith reagent, have been frequently used for practical synthesis.[2-4] Two reaction pathways have long been discussed for the cyclopropanation reaction, i.e., carbometalation and methylene transfer pathways (Scheme 1, path A and B).[5,6] In the carbometalation pathway (path A), [2 + 2] addition of the ethylene occurs to produce an intermediate **INT** through a four-centered transition structure **TSc**. Subsequent intramolecular substitution reaction of **INT** affords a cyclopropane product. On the other hand, in the methylene transfer pathway (path B), [2 + 1] addition takes place to provide a cyclopropane ring in one step through **TSm**.



Scheme 1.

Wittig reported an experimental proof of path B for the cyclopropanation with zinc carbenoid[5] while Hoffmann recently determined that the two reaction pathways compete in the cyclopropanation with lithium carbenoids.[7] The reasons for such metal-dependent dichotomy still remain unclear, however. The most recent theoretical analysis revealed the role of Lewis acid assistance of the cyclopropanation with zinc carbenoid,[8] which is essential not only in cases where a Lewis acid is added intentionally but also when it is generated autocatalytically by the cyclopropanation itself.[9] To solve such long standing questions on the diversity between paths A and B in the light of our continuing interest on olefin carbomatalation reaction,[10] we performed quantum mechanical studies on cyclopropanation reaction of ethylene with lithium and zinc carbenoids.[11]

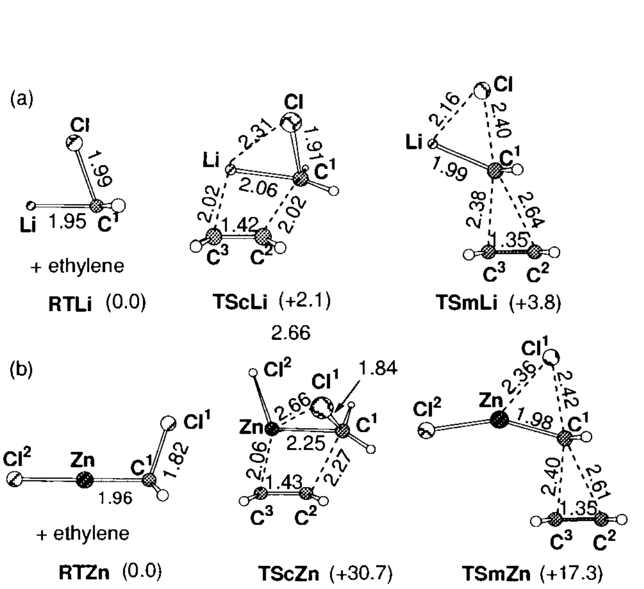


Figure 1. Stationary points of reaction of (a) lithium carbenoid with ethylene (B3LYP/6-31G* level) and (b) zinc carbenoid with ethylene (B3LYP/631A level). Bond lengths are in Å, and energies of TSs based on reactants (in parentheses) are in kcal/mol.

First, we examined the two reaction pathways in the cyclopropanaiton with lithium carbenoid, and found that the activation energies of the two pathways are very low and similar to each other. As shown in Figure 1a, the carbon atom of the lithium carbenoid in **RTLi** is almost *sp2* hybridized (dihedral angle H-C-Li-H = 178.0°), and has a structure with a character of a "lithium carbene complex". The TS of the carbometalation pathway **TScLi** is found to be in C_1 symmetry. Activation energy is 2.1 kcal/mol. In the methylene transfer pathway, concerted addition of methylene moiety of **RTLi** occurs and provides **PD** in a single step. The TS (**TSmLi**) is in C_s symmetry, and the activation energy is 3.8 kcal/mol, slightly higher than that of the carbometalation reaction. The similarity of the activation energies suggests that both pathways may compete in cyclopropanation with the lithium carbenoid, which is consistent with the Hoffmann experiments.[7]

Next, we investigated the reaction with zinc carbenoid (Figure 1b). The result revealed that the methylene transfer pathway is greatly favored. The TS of the carbometalation pathway (**TScZn**) is in C_1 symmetry (Figure 1b). Although **TScZn** has a geometry similar to **TScLi**, the activation energy is very high (30.7 kcal/mol). One of the reasons for the high activation energy is that a C-Zn bond is covalent in nature and little polarized. On the other hand, the activation energy of the methylene transfer pathway (**TSmZn**) is much lower (17.3 kcal/mol), which is a reasonable value for the cyclopropanation with zinc carbenoid in the light of experimental results.[3,12,13]

Intrinsic reaction coordinate (IRC) analysis from **TSmZn** back to reactants (data not shown) showed that the

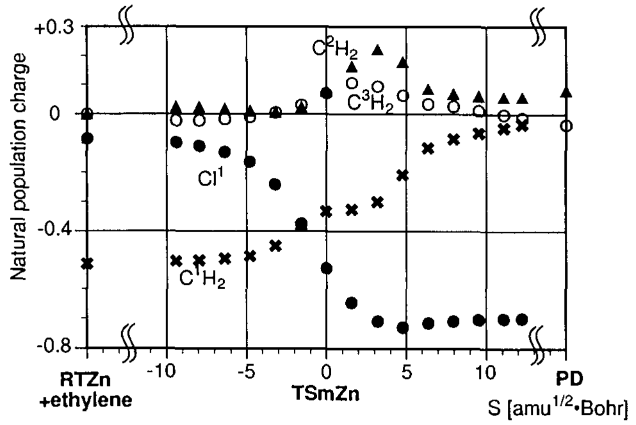


Figure 2. Natural population charge in IRC analysis near **TSmZn**.

approach of ethylene to the carbenoid carbon and cleavage of the C^1-Cl^1 bond occur in a concerted manner. No free carbene intermediate exists in the cyclopropanation.[14] In addition, the C^1-Cl^1 bond in **TSmZn** was elongated to 33%, though the C^1-Zn bond extended only 1% from those in **RTZn**.

The data in Figure 2 reveal that two independent events take place in the cyclopropanation. The first event takes place from reactant (**RTZn** + ethylene) to near **TSmZn** (Cf. at S = -1). The electron density at Cl^1 increases and those at C^2H_2 and C^3H_2 decrease. This change combined with the geometry of **TSmZn** indicates that the cyclopropanation is essentially an electrophilic attack to olefin.

The second event is involved in the reaction course after **TSmZn** (Cf. at S = 5). The electron densities at C^2H_2 and C^3H_2 increase again because of the C^1-Zn bond cleavage giving a neutral cyclopropane. Thus the methylene transfer pathway takes place through two stages; an S_N2 like displacement reaction by ethylene on halomethylzinc first, followed by cleavage of the C^1-Zn bond to give the cyclopropane ring.

In summary, the studies indicated that the favored reaction pathway of cyclopropanation crucially depends on the metal part of the carbenoid. With the lithium carbenoid, two paths have comparable activation energies. On the other hand, the carbozincation pathway is disfavored in the zinc carbenoid reagent, because the C-Zn bond is largely covalent in nature. The methylene transfer pathway involves an S_N2-like reaction on the methylene carbon, the ease of which depends largely on the polarization of the C-Cl bond. On this last point, the Lewis acid acts on the zinc carbenoid reagent to enhance the rate of the methylene transfer reaction.[8]

We thank Prof. R. W. Hoffmann for helpful discussion. This work was supported by Grant-in-Aid for Scientific Research on Priority Area (No. 283 "Innovative Synthetic Reactions") from Monbusho. Generous allotment of computational time from the Institute for Molecular Science is gratefully acknowledged.

References and Notes

1 P. Helquist, in "Comprehensive Organic Synthesis", ed. by B. M. Trost, I. Fleming, C. H. Heathcock, S. V. Ley, R. Noyori, L. A. Paquette, G. Pattenden, S. L. Schreiber, M. F. Semmelhack, and E. Winterfeldt, Pergamon Press (1991), Vol. 4, Chap. 4.6, p. 951.

2 H. E. Simmons, T. L. Craims, S. A. Vladuchik, and C. M. Hoiness, *Org. React.*, **20**, 1 (1973). A. Streitwieser, Jr., and C. H. Heathcock, in "Introduction to Organic Chemistry, third edition", Macmillan Publishing Company (1989), Chap. 11, p. 268.

3 S. E. Denmark and S. P. O'Connor, *J. Org. Chem.*, **62**, 584 (1997). E. C. Friedrich, S. E. Lunetta, and E. J. Lewis, *J. Org. Chem.*, **54**, 2388 (1989). A. B. Charette and H. Juteau, *J. Am. Chem. Soc.*, **116**, 2651 (1994). A. B. Charette, S. Prescott, and C. Brochu, *J. Org. Chem.*, **60**, 1081 (1995).

4 J. G. White, T.-S. Kim, and M. Nambu, *J. Am. Chem. Soc.*, **119**, 103 (1997). A. G. M. Barrett and K. Kasdorf, *J. Am. Chem. Soc.*, **118**, 11030 (1996).

5 G. Wittig and F. Wingler, *Chem. Ber.*, **97**, 2146 (1964).

6 F. Bernardi, A. Bottini, and G. P. Miscione, *J. Am. Chem. Soc.*, **119**, 12300 (1997).

7 H. C. Stiasny and R. W. Hoffmann, *Chem. Euro. J.*, **1**, 619 (1995).

8 E. Nakamura, A. Hirai, and M. Nakamura, *J. Am. Chem. Soc.*, **120**, 5844 (1998).

9 S. E. Denmark and S. P. O'Connor, *J. Org. Chem.*, **62**, 3390 (1997).

10 K. Kubota and E. Nakamura *Angew. Chem. Int. Ed.*, **36**, 2491 (1997). M. Nakamura, M. Arai, and E. Nakamura, *J. Am. Chem. Soc.*, **117**, 1179 (1995). M. Nakamura, E. Nakamura, N. Koga, and K. Morokuma, *J. Chem. Soc. FaradayTrans.*, **90**, 1789 (1994). E. Nakamura, S. Mori, M. Nakamura, and K. Morokuma, *J. Am. Chem. Soc.*, **119**, 4887 (1997).

11 We used the density functional B3LYP method implemented in Gaussian 94 program (GAUSSIAN 94, revision E.1, M. J. Frisch, et al., GAUSSIAN Inc.; Pittsburgh, PA, USA, 1995). Ahlrichs's SVP (A. Schäfer, H. Horn, and R. Ahlrichs, *J. Chem. Phys.*, **97**, 2571 (1992).) basis set was used for zinc atom and 6-31G* basis set for other atoms (denoted here as B3LYP/631A).

12 The calculated ^{13}C kinetics isotopes effect (KIE) with tunnel correction of the two TSs **TScZn** and **TSmZn** is as follows: C^1; 1.029, C^2; 1.027, C^3; 1.071 in **TScZn**, C^1; 1.066, C^2; 1.003, C^3; 1.008 in **TSmZn** (scale factor of 0.9804; M. W. Wong, *Chem. Phys. Lett.*, **255**, 391 (1996); E. P. Wigner, *Z. Phys. Chem.*, **B19**, 203 (1932). J. Bigeleisen, *J. Chem. Phys.*, **17**, 675 (1949).). The trend in KIEs for **TSmZn** differs significantly from that of **TScZn**, and will be a measure to experimentally differenciate the two pathways.

13 The activation energy for $IZnCH_2I$ is 13.1 kcal/mol (B3LYP/631A).

14 Elongating the C^1-Cl bond without ethylene, we obtained a zinc carbene complex structure, which was however a TS of chlorine atom exchange reaction (the vector of negative frequency shown by arrows).