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MPV-Reduction of C=O bond with *Al*-substituted-dialkylalan; A Theoretical Study on Relative Reactivity of Various Carbonyl Substrates

Keepyung Nahm

Department of Chemistry, Yeungnam University, Kyungbuk 712-749, Korea. E-mail: kpnahm@yu.ac.kr
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Relative reactivity of various carbonyl and acid derivatives in MPV-type (Meerwein–Ponndorf–Verley) reduction with an DIBAL(F) model has been studied *via* DFT and MP2 methods. Free energies of initial adduct formation (ΔG_{add}) of DIBAL(F) model and carbonyls are in the order of amide < ester < aldehyde < ketone < acid chloride; in the alan-amide adduct, the developed positive charge at carbonyl carbon is expected to be stabilized by amide resonance, but in the acid chloride adduct it is destabilized by inductive effect of chloride. However the TS barrier energies (ΔG_{TS}) for the MPV-type hydride reduction of the carbonyl adducts are in the order of aldehyde < ketone < acid chloride << ester < amide; presumably decreasing order of electrophilicity of carbonyl carbon at adducts, which is well correlated with experimental data. It is noted that the relative reactivity of carbonyl derivatives in MPV-type reduction with DIBAL(X) is not governed by the alan-adduct formation energies, but follows the order of electrophilicity of carbonyl carbon of transition states.

Key Words : *Al*-substituted-dialkylalan, MPV reduction, Carbonyl reduction, DFT, TS barrier

Introduction

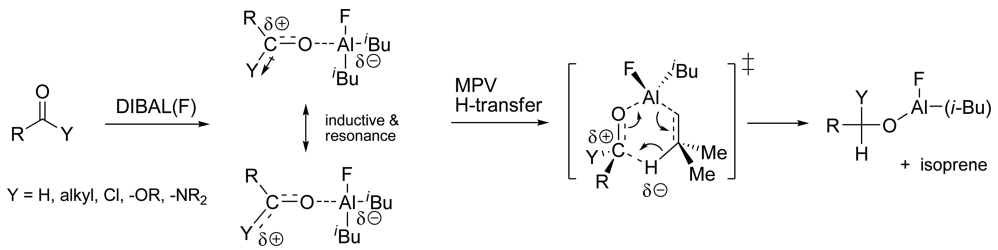
DIBAL(X), which is easily derived from DIBALH (diisobutylaluminum hydride) by substituting H with X,[1] has been applied successfully in reduction of carbonyl groups as MPV type reagents.[1b,2-4] DIBALH has two hydride sources; the hydride attached to Al and another hydride at iso-butyl group, whereas DIBAL(X) has only the latter hydride which behaves as a MPV type reagent. Introduction of electronegative substituent X groups, such as halides, alkoxides and amino groups, to DIBALH lowers the reactivity and shows selectivity in reduction. Among them, halogen substituted DIBAL(X) and those with inductive substituents such as trifluoromesylate and trifluoroacetate are more reactive than those of electron-rich alkoxy and amino substituents.[1b,5]

DIBALH reduces efficiently most of ketones, carbonyl acids and acid derivatives with H-Al even at low temperature.[6] However, reactivity of DIBAL(X) becomes lower; its MPV-type hydride reduces aldehydes and ketones efficiently at ambient temperature, and acid chlorides barely, but does not reduce carboxylic acids, esters, and amides. The relative reactivity of carbonyl compounds with DIBAL(X) is as follow; aldehyde > ketone >> acid chloride > ester > amide (Table 1).[1b,7]

The reactivity of the O=C(Y) bond toward nucleophiles is originated from its polarity. In general, electronegativity and resonance effect of the substituent Y, and the interaction between carbonyl oxygen electrons and Lewis acids exert powerful effect to the reactivity.[8]

Since DIBAL(X) is known to form a stable dimer and the dimer is not reactive in reduction,[9] the carbonyl-alan adduct formation could be an important factor in the reduction. Another factor is a TS barrier of the MPV-type hydride transfer of the adduct. One might expect both factors would control the reactivity of the reduction.[5]

Aluminum behaves as a Lewis acid toward carbonyl groups. When the carbonyl group forms an alan-adduct, a positive charge will be developed at the carbonyl carbon. A carbonyl derivative which stabilizes better the positive charge will have tighter adducts with lower free energy for adduct formation; phenyl ketones would form more stable adducts than alkyl ketones and aldehydes. However, the next MPV hydride transfer process prefers the more electron-deficient carbonyl carbons. When the electrophilicity of carbonyl carbon of TS is higher, the hydride would be transferred more easily and the TS barrier will be lower. More tightly bound alan-adducts would have more electron



Scheme 1

Table 1. Selective reduction of carbonyl compounds and their mixtures with DIBAL(Cl) in ethyl ether[a] at 25 °C

Carbonyl	Time (h)	Yield %	(Ratio)	Ref
hexanal	1	100		7(b)
2-butanone	1	> 99		7(b)
hexanal + 2-heptanone	1	> 99	(100 : 0)	7(b)
hexanal + benzaldehyde	0.5	> 99	(3 : 97)	7(b)
cyclohexanone + cyclopentanone	3	> 99	(90 : 10)	7(b)
cyclohexanone + 2-heptanone	3	> 99	(99.9 : 0.1)	7(b)
2-heptanone + benzoyl chloride[b]	24	> 99	(98 : 2)	7(c)
2-heptanone + ethyl hexanoate	12	> 99	(100 : 0)	7(b)

[a]One equivalent of reagent for an equimolar of each carbonyl compounds. [b]with DIBAL(OH).

density around carbonyl carbon and have higher TS barrier, and a loose bound adduct will have a lower TS barrier.

Our previous calculation study showed that, among alan DIBAL(X) with various X, the alan which forms a lower energy adduct with a ketone has a lower TS barrier for hydride transfer.[5] Here we apply various ketones and acid derivatives as substrates with a DIBAL(F) model to verify the relative reactivity of various carbonyl substrates. To estimate both adduct formation energy and the TS barrier, we present a computational study of MPV-type reduction of carbonyl and acid derivatives and correlate the calculated energetics with experimental data.

Calculation Methods

The model carbonyl compounds are acetone, acetaldehyde, formaldehyde, acetyl chloride, methyl acetate, *N*-methyl acetamide and *N*,*N*-dimethyl acetamide. For the reduction of those carbonyl compounds with $^{i}Bu_2AlX$ (DIBAL(X)), we selected a model alan of ethyl(methyl)aluminum fluoride ((Et)(Me)Al(F)), **Alan(F**), where two iso-butyl groups were replaced by an ethyl and a methyl group for simplicity. Since *Al*-substituted dialkylalans are known not to exit as monomer but form dimer or higher oligomer and the aggregation of alans also influence the reactivity,[1,9] we calculated a dimer (**diAlan(F)**) of two (Et)(Me)Al(F). Then the adducts of the model carbonyl compounds and mono **Alan(F)** were calculated. Transition states for the MPV-type hydride-transfer were also located from the corresponding adducts, where the Et-hydride is transferred to a carbonyl carbon.

All calculations were performed with GAUSSIAN 09 package.[10] Most of the calculations were carried out by using the Becke3LYP hybrid functional and the 6-31+G(d) basis sets.[11-15] Frequency calculations have been carried out to determine all minima and transition states. Zero-point energies and thermal corrections were taken from frequency calculations and are not scaled.[11,14] Single-point energies were calculated at the M06-2X/6-31+G(d) level[16,17] with the geometries optimized at B3LYP/6-31+G(d) level. For M06-2X free energies, the B3LYP zero-point and thermochemical corrections were added to the M06-2X electronic energies.

Calculations on every carbonyl-alan adducts and TSs were performed at the MP2/6-31+G(d) levels of theory to evaluate the appropriate calculation level.[18] The calculation data using MP2 functional show the same trend and are very similar to those from M06-2X. Therefore the calculation results from 6-31+G(d) using M06-2X//B3LYP functional were described mainly throughout.

For the solvent effects, the self-consistent reaction field (SCRF) technique with Thomasi's polarized continuum model using the polarizable conductor calculation model [SCRF-(CPCM)][19] for diethyl ether (ε = 4.24) was used at M06-2X/6-31+G(d)//B3LYP/6-31+G(d) level. Free energies are quoted at 298.15 K and 1 atm.

Results and Discussion

DIBAL(X) is known to form a stable dimer which has an (-Al-X-Al-X-) 4-memberbered ring structure and the dimer is not a reactive specie in reduction.[1] Therefore formation of the carbonyl-alan adduct between carbonyl oxygen and Al might be an important initial step in the reduction. Formation free energy for dimeric **diAlan(F)** from **Alan(F)** has been calculated to be as in Eq. (1); −33.37 (M06-2X), −33.67 (MP2) and −29.78 (M06-2X, CPCM in diethyl ether).[5]

$$\Delta G_{f,diAlan(F)} = (\Delta G_{diAlan(F)}) - 2\,(\Delta G_{Alan(F)}) \quad (1)$$

In the reduction process, dimeric **diAlan(F)** will be dissociated to two monomeric **Alan(F)**, which will be participated in the formation of carbonyl adducts. Therefore, the energy of **Alan(F)** is considered to be 1/2 of that of dimeric **diAlan(F)**. The free energy for the adduct formation ($\Delta G_{f,Add}$) with a monomeric alan is calculated as in Eq. (2). TS barriers with respect to the adduct (Eq. (3)) or to an alan and carbonyl (Eq. (4)) will be calculated as follows;

$$\Delta G_{f,Add} = (\Delta G_{adduct}) - (\Delta G_{keto} + 1/2\,\Delta G_{diAlan(F)}) \quad (2)$$

$$\Delta G_{(TS/Add)} = (\Delta G_{TS}) - (\Delta G_{adduct}) \quad (3)$$

$$\Delta G_{(TS/(Alan+keto))} = (\Delta G_{TS}) - (\Delta G_{keto} + 1/2\,\Delta G_{diAlan(F)}) \quad (4)$$

Formation of Adducts of Alan(F) and Carbonyl. The carbonyl models are acetone (**Keto(a)**),[5] acetaldehyde (**Keto(b)**), formaldehyde (**Keto(c)**), benzaldehyde (**Keto(d)**) and cyclopentanone (**Keto(e)**). The corresponding adducts with Al(F)(Et)(Me) (**Alan(F)**) are Al(F)(Et)(Me)(O=CR_1R_2), (**Add(a)-Add(e)**). The free energy for the adduct formation ($\Delta G_{f,Add1}$) with a monomeric alan is calculated as in Eq. (2).

Formation of each **Add(a)-Add(e)** is endothermic; $\Delta G_{f,adduct}$ = 4.94, 5.74, 7.70, 4.00 and 2.69 kcal/mol, respectively (Table 2). The calculated distances between Al and carbonyl oxygens in **Add(a)-Add(e)** are 1.997, 2.025, 2.051, 1.992 and 1.993 Å. It seems that acetone, cyclopentanone and benzaldehyde are bound more tightly to **Alan(F)** than acetaldehyde and formaldehyde.

Because of the eletrophilic nature of Lewis acid aluminum, a positive charge will be developed at the carbonyl carbon of the adducts. When the positive charge is better stabilized, more stable adduct would be formed. The phenyl group in

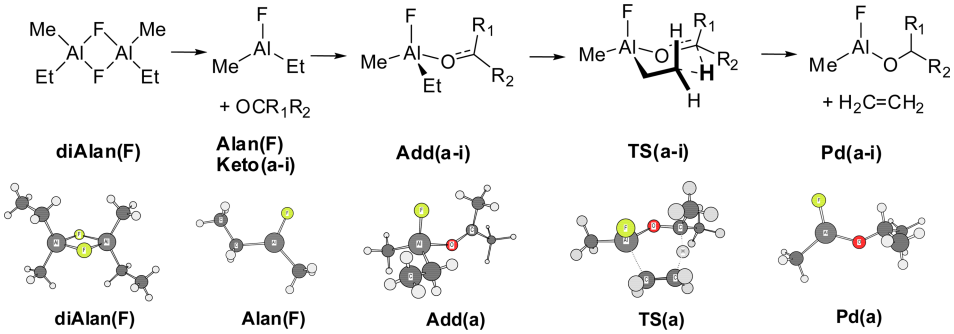


Figure 1. Model **Alan(F)**, adducts, TS and products, and several examples of calculated models.

Table 2. Relative formation energies for adducts and TS free energies for the reduction of carbonyl derivatives with **Alan(F)** at DFT and MP2 level calculation[a] (in kcal/mol)

Carbonyl	ΔG (Add)[b]	ΔG (TS/Add)[c]	ΔG (TS/(alan + keto))[d,e]
acetone (**keto(a)**)[f]	4.94 (5.39)	22.60 (24.53)	27.54 [26.19] (29.92)
MeCHO (**keto(b)**)	5.74 (4.96)	19.34 (24.23)	25.08 [22.96] (29.19)
H_2CO (**keto(c)**)	7.70 (8.39)	14.23 (19.25)	21.93 [18.80] (27.64)
PhCHO (**keto(d)**)	4.00 (3.77)	21.23 (23.62)	25.23 [22.10] (27.39)
cyclopentanone (**keto(e)**)	2.69 (3.54)	25.46 (24.61)	28.15 [27.54] (29.42)
MeCOCl (**keto(f)**)	11.38 (10.73)	20.24 (23.25)	31.62 [29.65] (33.98)
$MeCO_2Me$ (**keto(g)**)	4.33 (4.88)	34.09 (35.84)	38.42 [36.35] (40.72)
MeCONHMe (**keto(h)**)	-1.14 (-0.32)	41.55 (42.51)	40.41 [40.64] (42.19)
$MeCONMe_2$ (**keto(i)**)	0.22 (-2.67)	38.56 (40.81)	38.78 [38.26] (38.14)

[a]Numbers are calculated at M06-2X//B3LYP/6-31+G(d), and values in parenthesis are obtained at MP2/6-31+G(d). [b]Adduct formation energy with respect to a dissociated **Alan(F)** and carbonyl compound. [c]TS barrier with respect to the corresponding adduct. [d]TS barrier with respect to the sum of a dissociated **Alan(F)** and a carbonyl compound. [e]Values in bracket are calculated from CPCM-SCRF (diethyl ether) at M06-2X//B3LYP/6-31+G(d). [f]ref. (5).

benzaldehyde (**Keto(d)**) is a better electron donating group through resonance interactions than methyl (**Keto(b)**) and hydrogen (**Keto(c)**), and formation energy can be explained with the charge stabilization. However, in formaldehyde, the positive charge at a carbonyl carbon will be less stabilized and the adduct formation will be less favored.

Models of carboxylic acid derivatives are acetyl chloride (**Keto(f)**), methyl acetate (**Keto(g)**), *N*-methyl acetamide (**Keto(h)**) and *N*,*N*-dimethyl acetamide (**Keto(i)**). In adduct formation, the free energies for the acid chloride adduct (**Add(f)**) is calculated to be least favored (ΔG = 11.38 kcal/mol), which indicates the developing positive charge at the carbonyl carbon is not stabilized probably because of the inductive chloride. And the formation energy of methyl acetate adduct (**Add(g)**) is comparable to those of the ketones and aldehydes. (ΔG = 4.33 kcal/mol) On the other hand, formation energies of the acetamide adducts (**Add(h)** and **Add(i)**) are −1.14 and 0.22 kcal/mol which are favored. It can be rationalized by the amide resonance which stabilizes the developing charge at carbonyl carbon.

It is noteworthy that amides form most favored adducts with an alan but acid chlorides form less stable adducts. The order of formation energies of each adducts is not correlated with the experimental order of the reduction reactivity.

MPV-reduction of Adducts. MPV-type TSs for H-transfer of adducts have half-chair-like 6-membered rings, with Al-CH_2-CH_2-H and C=O. And the fluoride of **Alan(F)** is located at the axial position at the ring. The methyl on Al resides at the equatorial position, and the substituents of aldehydes prefer to be located at the less hindered equatorial side.

Since the hydride is nucleophilic at the transition states, more electron deficient carbonyl carbon at TS is more reactive. The TS energy barrier with respect to an adduct (Eq. (3)) would represent the electrophilicity of the carbonyl carbon of the adduct. The barriers of **TS(a)-TS(e)** based on each **Add(a)-(e)** are 22.60, 19.34, 14.23, 21.23 and 25.46 kcal/mol, respectively (Table 2). Although formation of formaldehyde adduct (**Add(c)**) is not so favored, Add(c) has the lowest TS barrier, which indicates the free energy of adduct formation does not solely determine the reactivity, but the electrophilicity of carbonyl carbon affects the reactivity (Figure 2).

The TS energy barriers (Eq. (4)) calculated with respect to reactants (**Alan(F)** and **keto(a)-(e)**), will reflect the electrophilicity of both aluminum and the carbonyl carbon. The corresponding barriers are 27.54, 25.08, 21.93, 25.23 and 28.15 kcal/mol, respectively (Table 2). Those barriers (**TS(c)** < **TS(b)** < **TS(d)** < **TS(a)** < **TS(e)**) give a good correlation with the experimental reactivity.

In experiment, benzaldehyde is more reactive than hexanal (97:3) in reduction by DIBAL(Cl) (Table 1).[7] In gaseous phase calculation (Table 2), **TS(d)** of benzaldehyde has been calculated to have a higher energy barrier by 0.15 kcal/mol than **TS(b)** of acetaldehyde at M06-2X, but at MP2 level

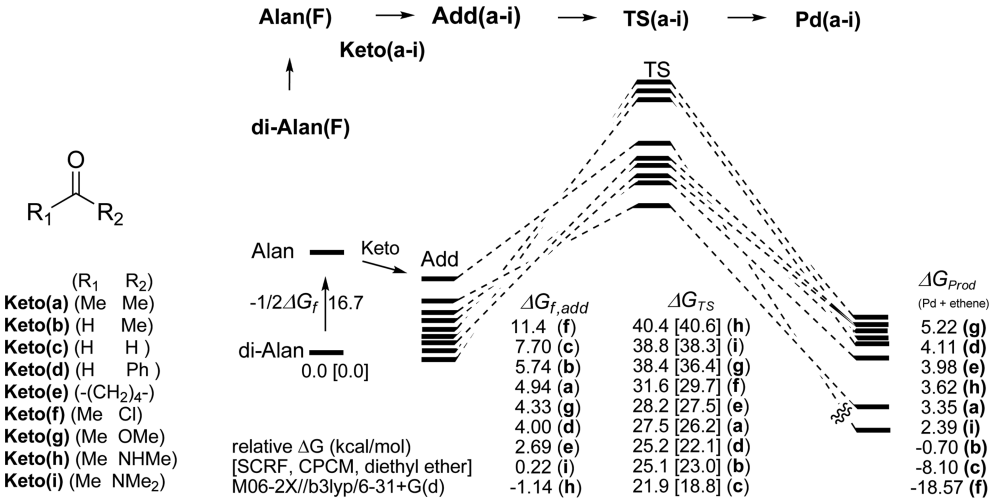


Figure 2. Energy profiles with respect to **diAlan(F)** and various carbonyl derivatives for the adduct formation and MPR-reduction (in kcal/mol, M06-2X//b3lyp/6-31+G(d)).

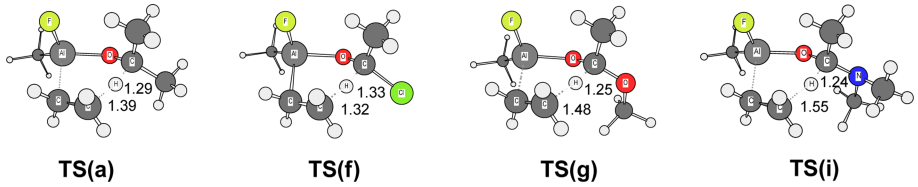


Figure 3. Selected MPV-type transition states (bond lengths around hydrides, in angstrom).

TS(d) is expected to be lower by 1.80 kcal/mol and predicts the product ratio of 95:5. In ether solution (CPCM), **TS(d)** is predicted to be lower by 0.86 kcal/mol (ratio of 80:20).

Cyclopentanone is experimentally more reactive than 2-heptanone (~99:1) in DIBAL(Cl) reduction. Calculated barrier of **TS(e)** for the reduction of cylcopentanone with respect to reactants has been compared with that of acetone (**TS(a)**); in gaseous phase, **TS(e)** is higher than **TS(a)** by 0.61 kcal/mol at M06-2X (E_{TS} = 28.15 *vs* 27.54 kcal/mol at M06-2X) and in ether solution, by 1.35 kcal/mol (27.54 *vs* 26.19 kcal/mol in ether). Both calculations predict acetone is more reactive than cyclopentanone. However, at MP2 level, **TS(e)** is expected to be lower than **TS(a)** by 0.50 kcal/mol (29.42 *vs* 29.92 kcal/mol), where the product ratio will be 70:30 (cyclopentanone : acetone).

Activation barriers for hydride transfer of TS of an acid chloride, an ester and amides (**TS(f)-TS(i)**) with respect to reactants are much higher (over 10 kcal/mol) than that of **TS(a)** (E_{TS} = 31.62, 38.42, 40.41 and 38.78 versus 27.54 kcal/mol, respectively, **TS(a)** << **TS(f)** << **TS(g)** < **TS(i)** < **TS(h)**). The amide resonance which helps the adduct formation favored, is functioned reversely in the hydride transfer at the TSs, where the electrophilicity at the carbonyl carbons is decreased by the resonance. With these high TS barriers the reduction will not be performed at ambient reaction condition.

On the other hand, benzoyl chloride among 2-heptanone is slightly reduced experimentally with DIBAL(OH). (ratio of 98:2, Table 1) The barrier for hydride transfer at **TS(f)** of acetyl chloride is calculataed to be higher only by 3.5-4 kcal/mol than that of acetone (**TS(a)**); 4.08 kcal/mol at M06-2X (E_{TS} = 31.62 *vs* 27.54 kcal/mol) and 3.49 kcal/mol at diethyl ether solution (E_{TS} = 29.65 *vs* 26.19 kcal/mol). Therefore, relative reactivity of acetone and acetyl chloride is expected to be the ratio of 99.95:0.05. Acid chlorides might be reduced with DIBAL(X) at an appropriate reduction condition.

At TSs of the ester and the amides, the bond distance between the carbonyl carbon and hydride (d_1) was measured to be ~1.24 Å and that between hydride and ethyl carbon (d_2) to be in the range of 1.48-1.55 Å. Those for TSs of acetone and acetaldehyde are d_1 = 1.29-1.30 Å and d_2 = 1.32-1.39 Å, respectively. The formers are expected to have late TSs compared to the latters.

The reduced products of ketones and aldehydse are alkoxy-alans, Al(F)(Me)(OCHR_1R_2). The reduced products of the acid derivatives are similar, Al(F)(Me)(OCH(R_1)-Me), except the reduced product of acetyl chloride. The initial product of acetyl chloride, Al(F)(Me)(OCH(Cl)-Me), could not be located, but the C-Cl bond is cleaved and the product further converts to acetaldehyde which forms the adduct of Al(F)(Me)(Cl) (OCH-Me). The reduced initial products of the acid derivatives will be further reduced to the alkoxides.[6b]

In summary, the DFT calculation shows that the reduction of aldehydes by DIBAL(X) is the fastest with activation barrier of 22-25 kcal/mol, and the reduction of ketones has higher barriers by 2-3 kcal/mol than those of aldehydes. Acid chlorides are expected to have the next higher barriers

by 6.5 kcal/mol than those of aldehydes. And the TS barriers of esters and amides are expected to be much higher by 13-20 kcal/mol than those of aldehydes. It is noted that the increasing order of TS barriers of MPV-type hydride transfer with DIBAL(F), aldehyde < ketone < acid chloride << ester < amide, is the decreasing order of electrophilicity of carbonyl carbon at adducts, and it matches well with experimental relative reactivity of carbonyl and acid derivatives, but the order of formation energies of alan-adduct does not match with the experimental reactivity order.

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Supporting Information. Cartesian coordinates for the calculated structures and ZPE-corrected free energies of Alan(F), dimer-Alan(F) and TS from DFT calculations are available *via* the Internet at http://journal.kcsnet.or.kr.

References

1. (a) Nguyen, S. T. *Tetrahedron: Asymmetry* **2005**, *16*, 3460. 3. (b) Cha, J. S. *Org. Process Res. Dev.* **2006**, *10*, 1032.
2. Meerwein, H.; Schmidt, R. *Liebigs Ann. Chem.* **1925**, *444*, 221.
3. Ponndorf, W. Z. *Angew. Chem.* **1926**, *39*, 138.
4. Verley, M. *Bull. Soc. Chim. Fr.* **1925**, *37*, 871-874.
5. Nahm, K.; Cha, J. S. *Bull. Korean Chem. Soc.* **2013**, *34*, 2335.
6. (a) Ziegler, K. *Angew. Chem.* **1964**, *76*, 545. (b) Winterfeldt, E. *Synthesis* **1975**, 617. (c) Miller, A. E. G.; Bliss, J. W.; Schwatzman, L. H. *J. Org. Chem.* **1959**, *24*, 627. (d) Ziegler, K.; Schneider, K.; Schneider, J. *Justus Liebig's Ann. Chem.* **1959**, *623*, 9. (e) Ziegler, K.; Martin, H.; Krupp, F. *Justus Liebig's Ann. Chem.* **1960**, *629*, 14. (f) Carey, F. A.; Sundberg, R. J. In *Advanced Organic Chemistry: Part B*, 5th ed.; Plenum: 2007; p 396.
7. (a) Cha, J. S. *Bull. Korean Chem. Soc.* **2007**, *28*, 2162. (b) Cha, J. S.; Kwon, O. O.; Kwon, S. Y.; Kim, J. M.; Seo, W. W.; Chang, S. W. *Synlett* **1995**, 1055. (c) Cha, J. S.; Kwon, O. O.; Kim, J. M.; Chun, J. H.; Lee, Y. S.; Lee, H. S.; Cho, S. D. *Bull. Korean Chem. Soc.* **1997**, *19*, 236.
8. (a) Wiberg, K. B. *Acc. Chem. Res.* **1999**, *32*, 922. (b) Wiberg, K. B.; Marquez, M.; Castejon, H. *J. Org. Chem.* **1994**, *59*, 6817. (c) Carey, F. A.; Sundberg, R. J. In *Advanced Organic Chemistry: Part B*, 5th ed.; Plenum: 2007; p 319.
9. Kow, R.; Nygren, R.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 826.
10. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; *et al. Gaussian 09*, Revision C.01; Gaussian, Inc.: Wallingford, CT, 2010.
11. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
12. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372.
13. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
14. Bauschlicher, C. W., Jr.; Partridge, H. *J. Chem. Phys.* **1995**, *103*, 1788.
15. Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502.
16. Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215.
17. Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157.
18. Head-Gordon, M.; Head-Gordon, T. *Chem. Phys. Lett.* **1994**, *220*, 122.
19. Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995.