

Reaction Pathway of Methylenation of Carbonyl Compounds with Bis(iodozincio)methane

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Abstract: About 40 years have passed since methylene dizinc reagent was discovered as a substitute for Wittig reagent. Density functional theory (DFT) calculations have been performed to understand the reaction pathways of methylenation of carbonyl compounds with bis(iodozincio)methane. The present computational/theoretical study concluded that the methylenation reaction with *gem*-dizinc reagent proceeds as a two-step reaction, that is, methylene addition (RDS) and olefination. In the first step, the nucleophilic attack of the CH₂ group enhanced by two Zn proceeds under the assistance of the electrophilic activation of the carbonyl group with the Zn atom. In the second step, the olefination is facilitated by both Zn atoms of the *gem*-dizinc reagent without an electron transfer process.

Introduction

A terminal alkene structure is frequently observed in natural products, and its selective preparation has been studied intensively. The Wittig reaction is one of the most commonly used reactions for this purpose. This ylide chemistry has been well studied from both synthetic and mechanistic aspects since it was developed by Nobel laureate Professor Georg Wittig.^{1,2} This prominent reaction looks perfect, but it still includes some drawbacks. First, the reaction often leads to an enolization of the carbonyl compound because the ylide exhibits an ordinary basicity. For example, treatment of α -tetralone with methylenetriphenylphosphorane gives a deprotonation reaction in the substrate that forms the enolate instead of leading to any alkene. Second, Wittig reagents often suffer from a lack of nucleophilicity, because the ylide is a relatively stable anion species. Actually, treatment of an ester with methylenetriphenylphosphorane often ends with a recovery of the starting material. To compensate these points, researchers have developed many types of olefination reagents including various organometallic compounds that were effective for the purpose. Among these reagents, *gem*-dimetallic compound and metal carbene complex were shown to be reliable.^{3,4}

Cainelli reported a *gem*-dimagnesium reagent prepared from diiodomethane and Mg/Hg for methylenation reactions of

ketones and aldehydes.^{5a} Fried,⁶ Miyano,⁷ and Nysted⁸ demonstrated more convenient methods for methylenation reactions of α -hydroxy ketones with *gem*-dizinc species. Further applications of methylenation from the viewpoint of titanium-mediated

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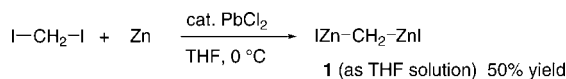
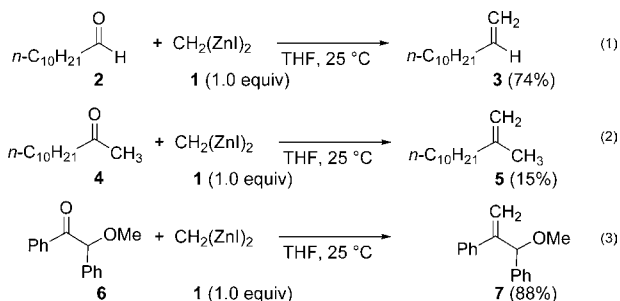
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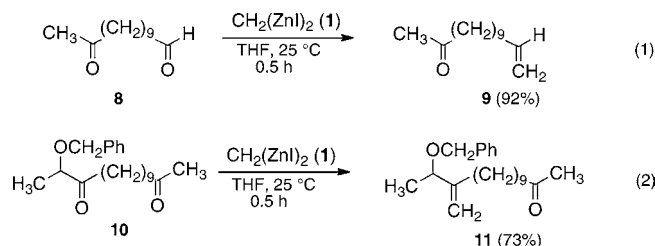
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Scheme 1. Preparation of Bis(iodozincio)methane (**1**) from Diiodomethane**Scheme 2.** Examples of Wittig-type Methylenation of Carbonyl Compounds with Bis(iodozincio)methane (**1**)

gem-dizinc chemistry have been investigated by Nozaki/Oshima/Takai,^{9,10} Eisch,¹¹ and Lombardo.¹² During the preparation process of *gem*-dizinc reagents, Takai and Utimoto discovered in 1994 that lead played an important role for the acceleration of further reduction of the carbenoid into *gem*-dizinc species.¹³ After extensive experimentation, in 1998, a general procedure for the preparation of bis(iodozincio)methane by a reduction of diiodomethane with zinc powder in the presence of lead catalyst (Scheme 1) was also shown.¹⁴ Structural studies for THF solution of bis(iodozincio)methane confirmed the monomeric structure of bis(iodozincio)methane.^{15,16}

Our group has already reported methylenation of various carbonyl compounds with bis(iodozincio)methane (**1**).^{14,17–19} Key examples are shown in Scheme 2. (1) An aldehyde **2** was converted into the corresponding alkene **3** with **1** at 25 °C (eq 1).^{14,17a} (2) A reaction of a normal ketone **4** with **1** gave the corresponding alkene only in poor yield at 25 °C (eq 2). In this case, an addition of β-TiCl₃ improved the yield dramatically (83%).¹⁴ (3) A reaction of a ketone carrying heteroatom at α-position **6** proceeded smoothly to give the alkene **7** at 25 °C

Scheme 3. Chemoselective Methylenation of Carbonyl Compounds

(eq 3).¹⁸ The details of these reactions are included in the Supporting Information.

The relative reactivity of carbonyl groups in the methylenation using **1** was emphasized by the selective reactions in Scheme 3. In the case of ketoaldehyde **8**, only aldehyde was converted into the methylene selectively with **1** (eq 1).¹⁴ In the case of diketone **10**, the ketone group carrying an alkoxy group at α-position was converted into methylene selectively (eq 2).¹⁸

This methodology has recently been extensively applied as a useful strategy in syntheses of natural products and functional molecules. However, no systematic computations have been performed to date on the detailed reaction mechanism of methylation reaction of carbonyl compounds, despite the fact that knowledge of the reaction pathway and of the origin of unique chemoselectivity would be helpful in improving the reactivity and selectivity of the reactions, as well as in designing more efficient reagents/reactions.

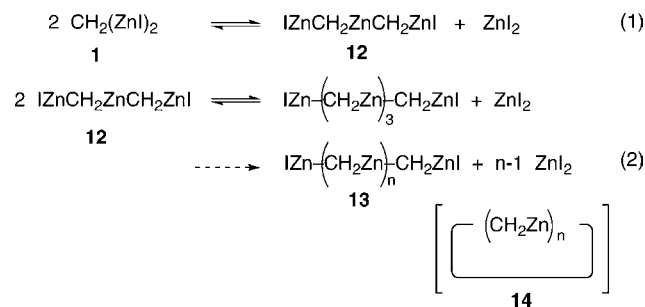
In the present Article, we present the first systematical computational/theoretical studies on the methylenation of carbonyl compounds with bis(iodozincio)methane. The purposes of our study are as follows: (1) to investigate the reaction pathways of methylenation of various carbonyl compounds in gas and in solution; (2) to investigate the geometrical features of the transition structures, intermediates, and products of methylenation; (3) to analyze the roles of the zinc atoms, the sort of halogen, and the effects of solvents and substituents adjacent to the carbonyl group in controlling the reactivity of methylenation; and (4) to investigate the mechanism and the factors responsible for the selectivity of methylenation.

Results and Discussion**Information about the Structure of Bis(iodozincio)methane**

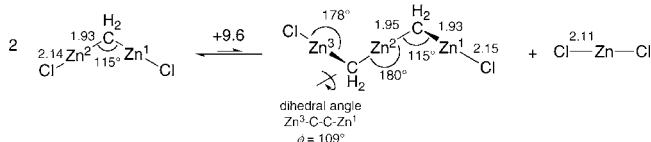
(1) in Solution. Bis(iodozincio)methane (**1**) in THF solution was prepared by the treatment of diiodomethane with zinc powder in the presence of lead(II) chloride (Scheme 1).^{13,14} The concentration of **1** in the obtained THF solution was determined by ¹H NMR spectra.^{14,15} The broad singlet signal in the high field area (−1.0 to −1.7 ppm) was reasonably assigned as a signal of a methylene, which was substituted with two electron positive zinc atoms. The corresponding signal was depended on temperature: a broad singlet (−0.9 ppm) at 20 °C, a broad singlet (−1.34 ppm) at −20 °C, and a sharp singlet (−1.56 ppm) at −60 °C. The structure of zinc reagent **1** in THF should be discussed by considering a self-transmetalation between the molecules of **1**, that is, Schlenk equilibrium (Scheme 4). The Schlenk equilibrium of **1** induces not only a dimeric compound **12** (eq 1) but also a polymeric linear compound **13** or a cyclic compound **14** (eq 2). As we reported previously, further information by SANS, AXS, and EXAFS strongly supports the conclusion that the resulting mixture of Scheme 1 contained monomeric **1** predominantly without aggregation.^{15,16} Heating or concentration of THF solution of **1** causes a formation of

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Scheme 4. Possible Schlenk Equilibrium of Bis(iodozincio)methane (1)



Scheme 5. Schlenk Equilibrium of Bis(chlorozincio)methane^a



^a Energy changes at the B3LYP/631SVPs level are shown in kcal/mol, and bond lengths are in angstroms. See Computational Methods and Chemical Methods for details.

polymethylene dizinc **13** or **14**. A DFT calculation in Scheme 5 implied also the monomeric structure of bis(chlorozincio)methane. The following theoretical/computational studies were performed on the basis of the monomeric structure **1**.

A Theoretical/Computational Study for Methylenation of an Aldehyde or a Ketone with 1. Having obtained the structural information of bis(iodozincio)methane reagent **1** that is likely to be experimentally relevant, we performed DFT calculations to investigate the reaction pathway of the methylenation reaction with monomeric **1**.

Computational Methods and Chemical Models. All calculations were carried with the Gaussian 03 program package.²⁰ The global reaction route mapping method (GRRM)²¹ based on Gaussian 03 was utilized for locating all local equilibrium structures and TS structures and for geometry optimization. The molecular structures and harmonic vibrational frequencies were obtained using the hybrid density functional method based on Becke's three-parameter exchange function and the Lee–Yang–Parr nonlocal correlation functional (B3LYP).²² We used Ahlrichs' SVP²³ all-electron basis set for Zn, Br, and I atoms and 6-31G* for the other atoms (denoted as 631SVPs in the text). Our preliminary computation results showed that most methylenation intermediates and transition states optimized by

using B3PW91/631SVPs²⁴ and B3LYP/631SVP(6-31+G*&SVP) were quite analogous to those obtained with B3LYP/631SVPs. We therefore selected B3LYP/631SVPs as our main method/basis sets for the present computations. Geometry optimization and vibrational analysis were performed at the same level. All stationary points were optimized without any symmetry assumptions, and characterized by normal coordinate analysis at the same level of theory (number of imaginary frequencies, NIMAG, 0 for minima and 1 for TSs). The intrinsic reaction coordinate (IRC) method was used to track minimum energy paths from transition structures to the corresponding local minima.²⁵ We employed CH₂(ZnCl)₂ as chemical models for the dizinc compounds with and without 1–3 molecules of Me₂O or THF coordinated to the zinc atom. Replacement of CH₂(ZnCl)₂ with CH₂(ZnBr)₂ or CH₂(ZnI)₂ does not much affect the geometry of intermediates/TSs or their energy profiles, so we chose CH₂(ZnCl)₂ as the dizinc species (details in the Supporting Information).

Reaction Pathway of Methylenation of Aldehydes with Bis(chlorozincio)methane. The gas-phase calculations indicated that CH₂(ZnCl)₂ exists as a dogleg form structure **RT1-a0**, and we confirmed that the dogleg geometry is the global minimum by making an artificial Cl-bridged rhombic (Zn(μ-Cl)Zn) geometry of the reagent by first placing a Cl atom at the midpoint of both Zn atoms. Geometry optimization then caused smooth migration of the bridged Cl atom without energy barrier to form the planar sector structures. The results of several examinations indicated that the reaction pathway of methylenation of formaldehyde shown in Figure 1 is the most probable. In this pathway, the addition of CH₂(ZnCl)₂ to formaldehyde occurs first to form an association complex **CP1-a0** with little change of the geometry. The formation of this intermediate causes the C=O bond length (1.22 Å) to be elongated by less than 1% as compared with the length in the reactants (**RT1-a0**). The methylene group bounds to the two Zn atoms can migrate smoothly along the intrinsic reaction coordinate to the carbonyl carbon atom with an activation energy of 29.5 kcal/mol. On the basis of the degree of elongation of the CH₂–Zn¹ and C=O bond lengths in the TS (7% and 6%, respectively), as well as the short length of the forming CH₂–C(=O) bond (2.19 Å), we consider this TS to be rather late. As the CH₂ group migrates to the carbonyl carbon atom, the resultant alkoxide group becomes attached to the Zn¹ atom to produce the adduct, ClZn²–CH₂CH₂O–Zn¹Cl (**IM1-a0**). The stabilization energy is very large (–39.8 kcal/mol) because of the formation of two Zn–O bonds, and the product provides a precursor for the olefination.

Among several possibilities for the olefination reaction from **IM1-a0**, we identified one TS, **TS2-a0**. The degree of shortening of the CH₂–CH₂ bond length (1.40 Å) in the TS (8%), together with the elongation of the CH₂–Zn² (2.18 Å) and CH₂–O (1.99 Å) bonds, clearly suggests that the TS is rather late. Because the elimination reaction is facilitated by the push–pull synergy of two Zn atoms in the reagent, the activation energy (+15.0 kcal/mol) seems to be reasonably low. The distinct and cooperative roles of the two Zn atoms are crucial for smooth olefin formation.

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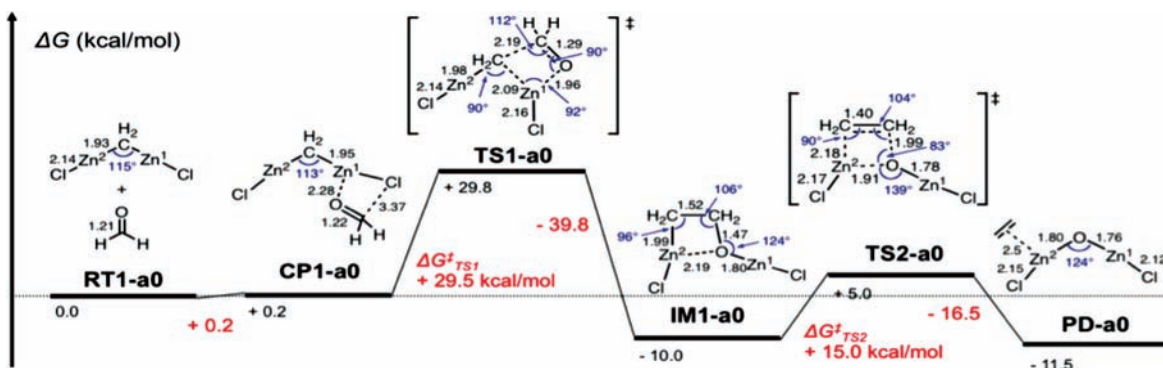


Figure 1. Addition/methylenation reaction of $\text{CH}_2(\text{ZnCl})_2$ with HCHO . Energy changes at the B3LYP/631SVPs level are shown in kcal/mol, and bond lengths are in angstroms.

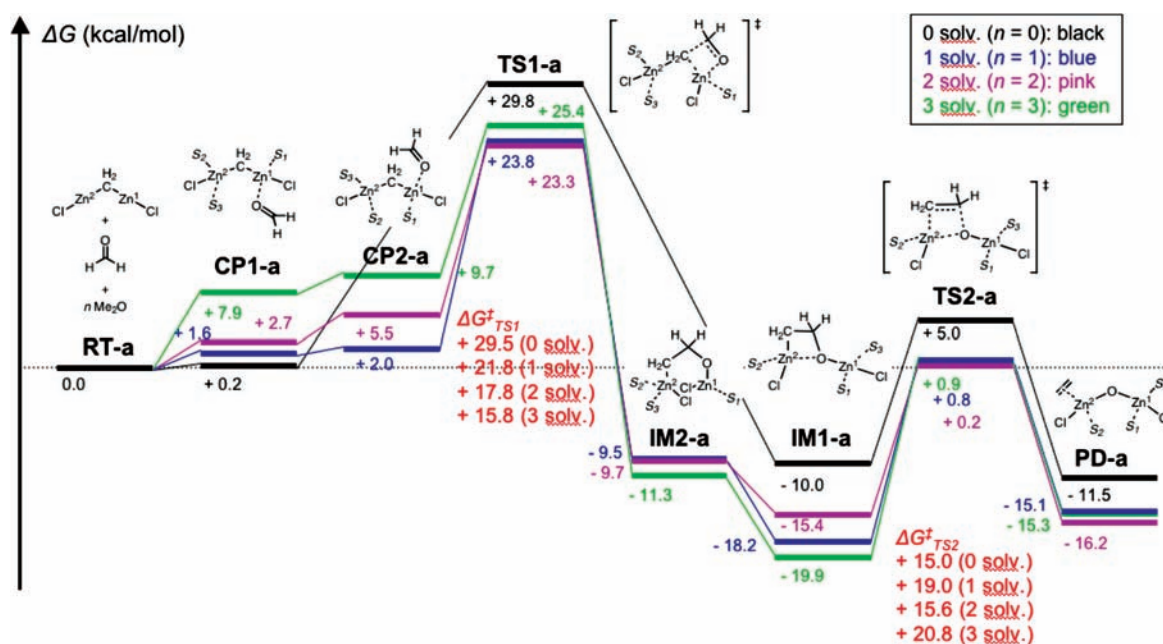


Figure 2. Energy diagram of the addition/olefination of $\text{CH}_2(\text{ZnCl})_2$ with 0, 1, 2, or 3 Me_2O solvent molecules (B3LYP/631SVPs). Energy changes at the B3LYP/631SVPs level are shown in kcal/mol.

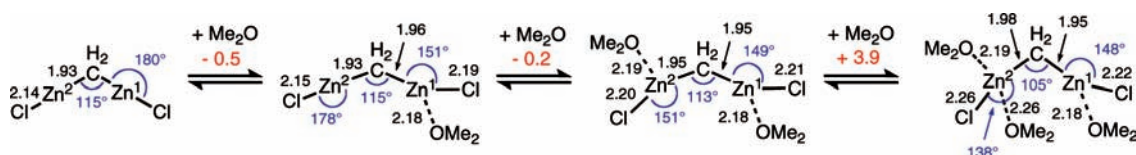


Figure 3. The stationary points of $\text{CH}_2(\text{ZnCl})_2$ for non-, mono-, di-, and trisolvated states at the B3LYP/631SVPs level with entropy term corrections.

Solvent Effects. Energy profiles in the olefination reactions of $\text{CH}_2(\text{ZnCl})_2$ with 0, 1, 2, or 3 Me_2O solvent molecules at the same level of theory are shown in Figure 2. Gibbs free energies of activation (298.15 K) from reactants (**RT-a**) for the first step are as follows: +29.8 kcal/mol (0 solvent); +23.8 kcal/mol (1 solvent); +23.3 kcal/mol (2 solvents), +25.4 kcal/mol (3 solvents), respectively. Solvation of the Zn atoms of **TS1-a** with Me_2O molecules led to stabilization of **TS1-a**. On the other hand, the solvation either does not change or may even destabilize the second step: +15.0 kcal/mol (0 solvent); +19.0 kcal/mol (1 solvent); +15.6 kcal/mol (2 solvents), +20.8 kcal/mol (3 solvents), respectively. In the case of the disolvated $\text{CH}_2(\text{ZnCl})_2$ pathway, the activation barrier for the first step is reasonably low and higher than that for the second step, in good agreement with the experimental fact that no methylene addition intermedi-

ate can be detected. The first addition step can be regarded as the RDS for the olefination reaction.

In harmony with the above analysis, we can expect a priori that $\text{CH}_2(\text{ZnCl})_2$ (**1**) with 2 Me_2O solvent molecules coordinated to the zinc atoms one by one is the most stable; however, we do not have enough evidence to neglect the possibility of the dizinc **1** with one Me_2O solvent molecular, and this was found to be the case in Figure 3. The GIAO-predicted chemical shift of the methylene proton (−0.92 ppm) of this disolvated $\text{CH}_2(\text{ZnCl})_2$ also showed good agreement with the experimental value (see Figure S1 in the Supporting Information) as compared to those of CH_3ZnLi with 0 (−0.07 ppm), 1 (−0.48 ppm), and 2 (−0.82 ppm) Me_2O solvent molecules coordinated to the zinc atom.

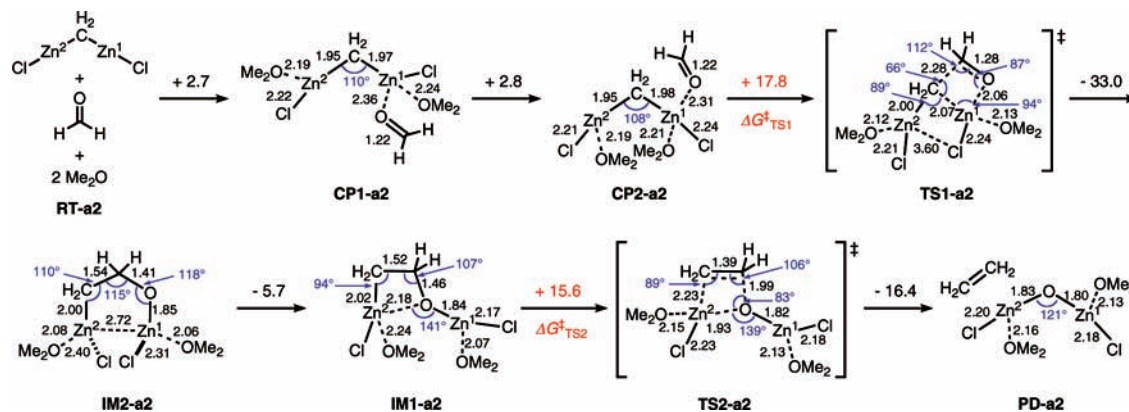


Figure 4. Addition/methylenation reaction of HCHO and $\text{CH}_2(\text{ZnCl})_2$ with 2 molecules of Me_2O . Energy changes at the B3LYP/631SVPs level are shown on the arrows in kcal/mol, and bond lengths are in angstroms.

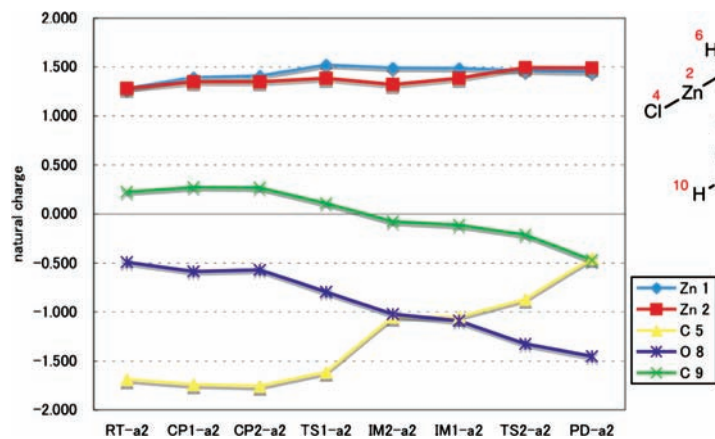


Figure 5. Charge changes in the methylenation of HCHO with $\text{CH}_2(\text{ZnCl})_2$.

We also carried out calculations employing the self-consistent reaction field (SCRF) method.²⁶ In this model, the solvent effect is represented by a dielectric continuum characterized by its relative static dielectric permittivity, ϵ .²⁷ A typical and experimentally used solvent, THF ($\epsilon = 7.58$), was chosen for the calculations. However, this SCRF calculation results in essentially no change to the energy profiles of the above calculations. In addition, replacement of Me_2O solvent molecules with THF does not also greatly affect the geometry of TSs/CPs/IMs and the energy profiles (Supporting Information).

Methylenation of Formaldehyde, Acetaldehyde, and Ketones. Reactants, complexes, TSs, and charge changes in the reaction of $\text{CH}_2(\text{ZnCl}\cdot\text{OMe}_2)_2$ with formaldehyde are shown in Figures 4 and 5.

This methylenation takes place as a single event, as indicated by the smooth charge changes during the reaction (Figure 5). Thus, the negative charge of the carbonyl oxygen increases monotonously from the reactant to the product, and the negative charge of the transferred CH_2 group decreases monotonously toward -0.5 in the product. The exchange of the electrons occurs exclusively between the CH_2 anion and the carbonyl oxygen, and the charges of both Zn atoms remain essentially

constant during the reaction. This is an indication of the absence of any oxidation/reduction process in this reaction and is markedly different from the case of carbene complex. Therefore, the addition/elimination processes seem to be facilitated by the push(Zn^2)–pull(Zn^1) synergy of two Zn metals in the reagent. NBO analysis²⁸ of **TS1-a2** indicates a large stabilization energy (21.6 kcal/mol) corresponding to the primary/secondary orbital interactions between the lone pair of carbonyl oxygen (donor NBO) and the vacant orbital of Zn^1 /the unoccupied σ -orbital of Zn^1 –Cl (acceptor NBO).

The reaction pathways of the methylenations of acetaldehyde and acetone, as shown in Figures 6 and 7, are similar to that of formaldehyde, but the activation energy of the $\text{CH}_2(\text{ZnCl})_2$ addition to acetone is much higher than those of the others because of the lower reactivity of ketone carbonyl carbon. The calculated result is consistent with the experimental fact that ketone substrates are inert/less reactive in the methylenation reaction in THF. Although the activation energy of acetone (26.8 kcal/mol) is rather high for the methylenation at room temperature, it indicates that the reaction of ketones with **1** would proceed by the activation with Lewis acid such as β - TiCl_3 ¹⁴ or thermal condition with THT or ionic liquid.²⁹ In another point of view, it is experimentally established that a chelatable atom

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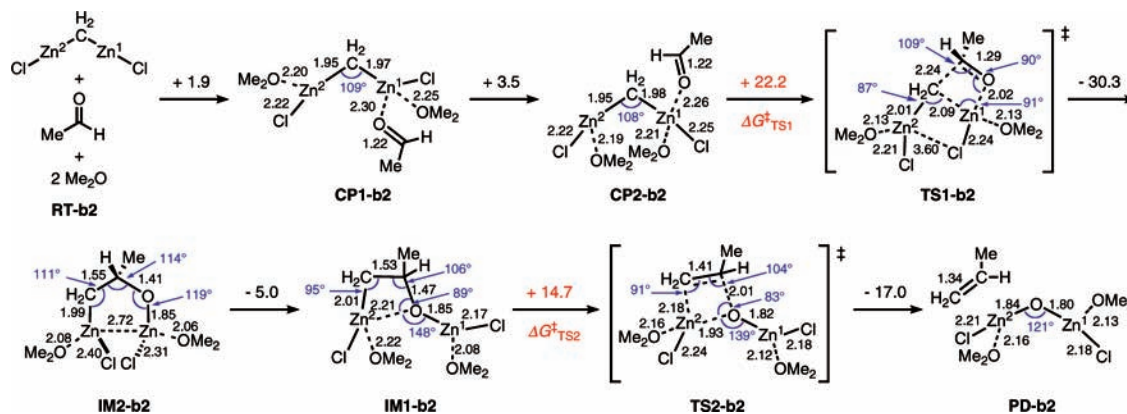


Figure 6. Addition/methylenation reaction of CH_3CHO and $\text{CH}_2(\text{ZnCl})_2$ with 2 molecules of Me_2O . Energy changes at the B3LYP/631SVPs level are shown on the arrows in kcal/mol, and bond lengths are in angstroms.

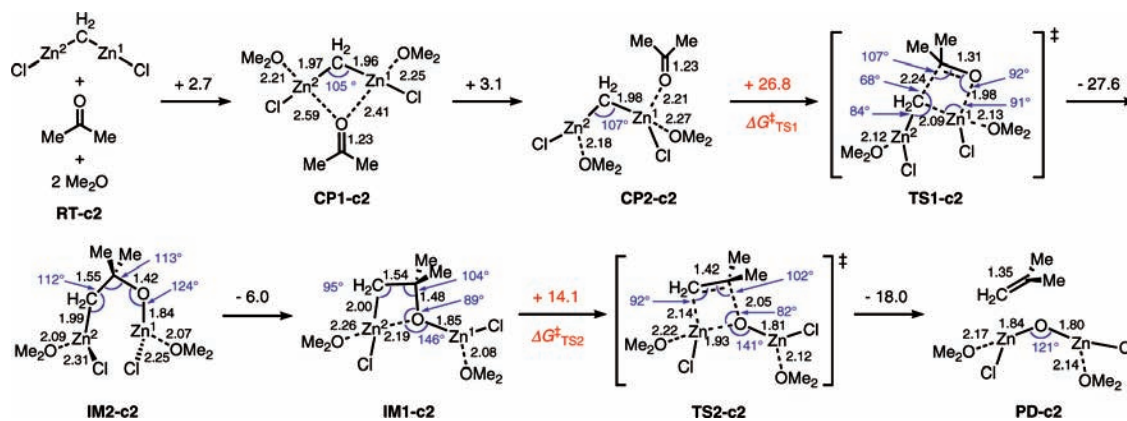


Figure 7. Addition/methylenation reaction of CH_3COCH_3 and $\text{CH}_2(\text{ZnCl})_2$ with 2 molecules of Me_2O . Energy changes at the B3LYP/631SVPs level are shown on the arrows in kcal/mol, and bond lengths are in angstroms.

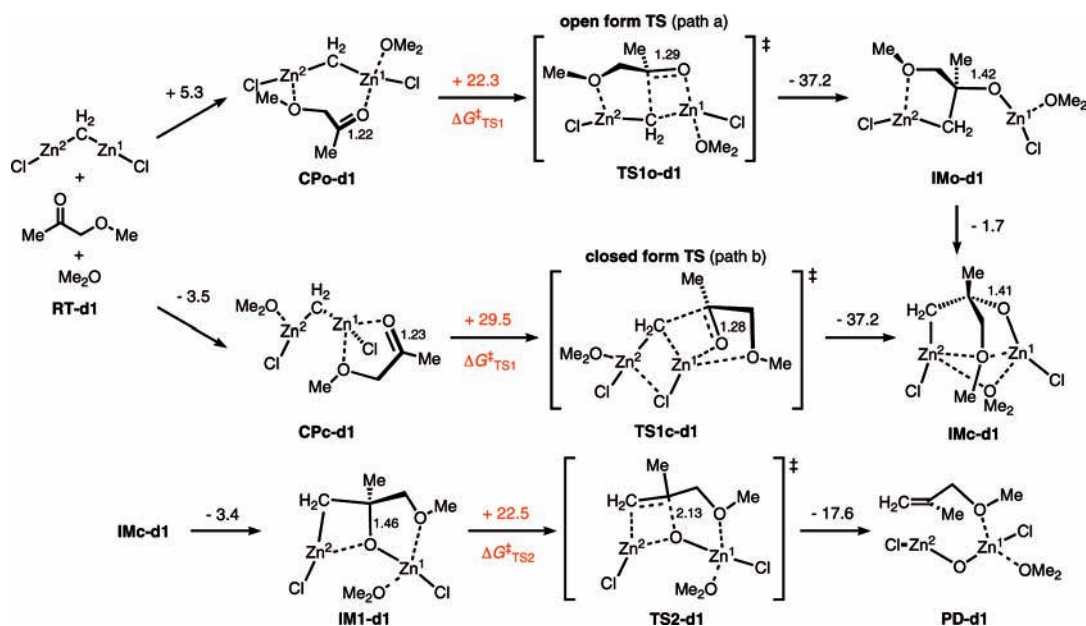


Figure 8. Addition/methylenation reaction of α -methoxyacetone and $\text{CH}_2(\text{ZnCl})_2$ with 1 molecule of Me_2O . Energy changes at the B3LYP/631SVPs level are shown on the arrows in kcal/mol (detailed bond lengths and angles are described in the Supporting Information).

such as O and N at the α -position of ketone carbonyl efficiently accelerates the methylenation (Schemes 2 and 3). Here, we employed α -methoxyacetone as a minimum chemical model for α -heteroatom-substituted ketones. We identified two plausible

pathways for the methylene addition reaction through **TS1o-d1** (“open form” TS) and **TS1c-d1** (“closed form” TS) in terms of the methylene addition process (Figure 8). The activation energy of “open form” TS is lower than that of acetone, because

the methylene addition reaction is facilitated by the α -heteroatom chelation (push) effect at the Zn^2 atom and by an entropy factor.

As the CH_2 group migrates to the carbonyl carbon atom in both cases, the resultant alkoxide group becomes attached to the Zn^1 atom to produce intermediates with large stabilization energies, **IMo-d1**, **IMc-d1**, **IM1-d1**. The formation of the intermediate, **IM1-d1**, causes the C–O bond (1.46 Å) to be elongated due to the double coordination/activation with both Zn^1 and Zn^2 . To reach the TS of the olefination, the Zn^2 –O– Zn^1 becomes detached, and the C=C double bond is formed with an overall energy loss of 22.5 kcal/mol. The olefination through **TS2-d1** generates a product, **PD-d1**, which is –17.6 kcal/mol lower in energy than **TS2-d1**.

Conclusion

About 40 years have passed since methylene dizinc reagent was proposed as a substitute for Wittig reagent. Many chemists have studied how to make the reagent more useful for organic synthesis.³ It has been experimentally established that the reactivity of **1** to carbonyl compounds could be well tuned by various additives, and the highly chemoselective methylenation has been realized. As a practical and useful synthetic method for methylenation reaction, we believe that bis(iodozincio)methane will benefit in many synthetic projects. In this study, we first carried out a structural study about bis(iodozincio)methane (**1**) in solution by means of NMR, SANS, AXS, and EXAFS spectroscopies to understand the reagent nature completely.¹⁵ On the basis of the information thus obtained, a computational/theoretical study was able to begin with monomeric bis(iodozincio)methane. Results disclosed that (1) the methylenation reaction with *gem*-dizinc reagent proceeds as a two-step reaction, that is, methylene addition (RDS) and olefination, (2) the methylene addition can be explained in terms of an ordinary nucleophilic mechanism, that is, the electrophilic

activation of the carbonyl group with the Zn cation and the nucleophilic attack of the CH_2 group activated by two Zn, (3) the olefination is facilitated by both Zn atoms of the *gem*-dizinc reagent without an electron transfer process, in sharp contrast to other olefination reactions, and (4) *gem*-dizinc reagent is inert or less reactive to ketones, and the smooth methylenation of ketones is likely to be aided by a high reaction temperature or a chelatable atom such as O or N at the α -position of the ketone carbonyl group. This structural and theoretical information benefits not only these methylenations but also other synthetic applications of bis(iodozincio)methane.³⁰ Work to clarify the reaction pathways of bis(iodozincio)methane (**1**) such as 1,4-addition and transmetalation, both theoretically and experimentally, is also in progress in our group.³¹

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Supporting Information Available: Procedure for the theoretical/computational study and molecular modeling coordinates. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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