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Mechanism of halogen-catalyzed Mukaiyama aldol reactions: concerted or stepwise?

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Abstract

The halogen-catalyzed (I_2, Br_2, and Cl_2) Mukaiyama aldol (MA) reactions were investigated by ab initio MO calculations. The halogen-catalyzed MA reaction between a trihydrosilyl enol ether and formaldehyde favors a concerted pathway. In sharp contrast, the I_2-catalyzed reaction between 1-phenyl-1-(trimethylsilyloxy)ethylene and benzaldehyde favors a stepwise mechanism. The nature of the substituent strongly influences the type of mechanism involved.

The aldol reaction is one of the most versatile carbon–carbon bond forming processes and provides a synthetic pathway to β-hydroxycarbonyl compounds. In 1974, $TiCl_4$ was first reported by Mukaiyama as an effective catalyst for aldol reactions.[1] Since then, a wide range of other catalysts have been developed for Mukaiyama aldol (MA) reactions.[2] However, most of them suffer from drawbacks such as moisture sensitivity and high cost. Recently, iodine was found to be a practical and efficient catalyst for a variety of organic reactions.[3] In particular, iodine was applied as catalyst in the Mukaiyama aldol reaction reported by Phukan.[4] The advantages of using iodine as catalyst are threefold: (1) mild neutral conditions, (2) low cost, and (3) no stringent dry conditions are required.[4] To the best of our knowledge, the mechanisms of I_2-catalyzed reactions have not been investigated by quantum chemical calculations.

In this Letter, the mechanism of the Mukaiyama aldol reaction between a trihydrosilyl enol ether and formaldehyde catalyzed by I_2, Br_2, and Cl_2 is investigated by ab initio molecular orbital calculations. The reactivities of the different halogen catalysts were compared. In addition, our study was extended to the I_2-catalyzed MA reaction between 1-phenyl-1-(trimethylsilyloxy)ethylene and benzaldehyde, which is the exact system studied experimentally.[4] The mechanisms of uncatalyzed and metal chloride-promoted Mukaiyama aldol reactions have been reported recently.[5–7] While the uncatalyzed MA reactions favor a concerted mechanism,[5,6] the metal chloride promoted reactions prefer a stepwise process.[7] It is of interest to determine whether the halogen catalysts behave differently.

All equilibrium structures and transition states were fully optimized with the B3LYP[8] hybrid density functional theory. The 6-31G* (5d) basis set was used for all non-iodine atoms, while a similar double-zeta quality MIDI![9] basis set was employed for the iodine atom. Higher-level relative energies were obtained through MP2/6-311+G** calculations, based on the B3LYP/6-31G* optimized geometries. The diffuse functions for element iodine were not defined for the standard 6-311G** basis set. Based on the optimization of the energy of the iodine anion (I^-), an exponent of 0.028 has been derived for the diffuse *sp* functions of iodine in this study. Unless otherwise noted, the energies reported in the text correspond to the MP2/6-311+G** level, and include zero-point energy (ZPE) correction. The directly B3LYP/6-31G* calculated ZPEs were scaled by a factor of 0.9804.[10] All calculations were performed using the Gaussian 03 program.[11]

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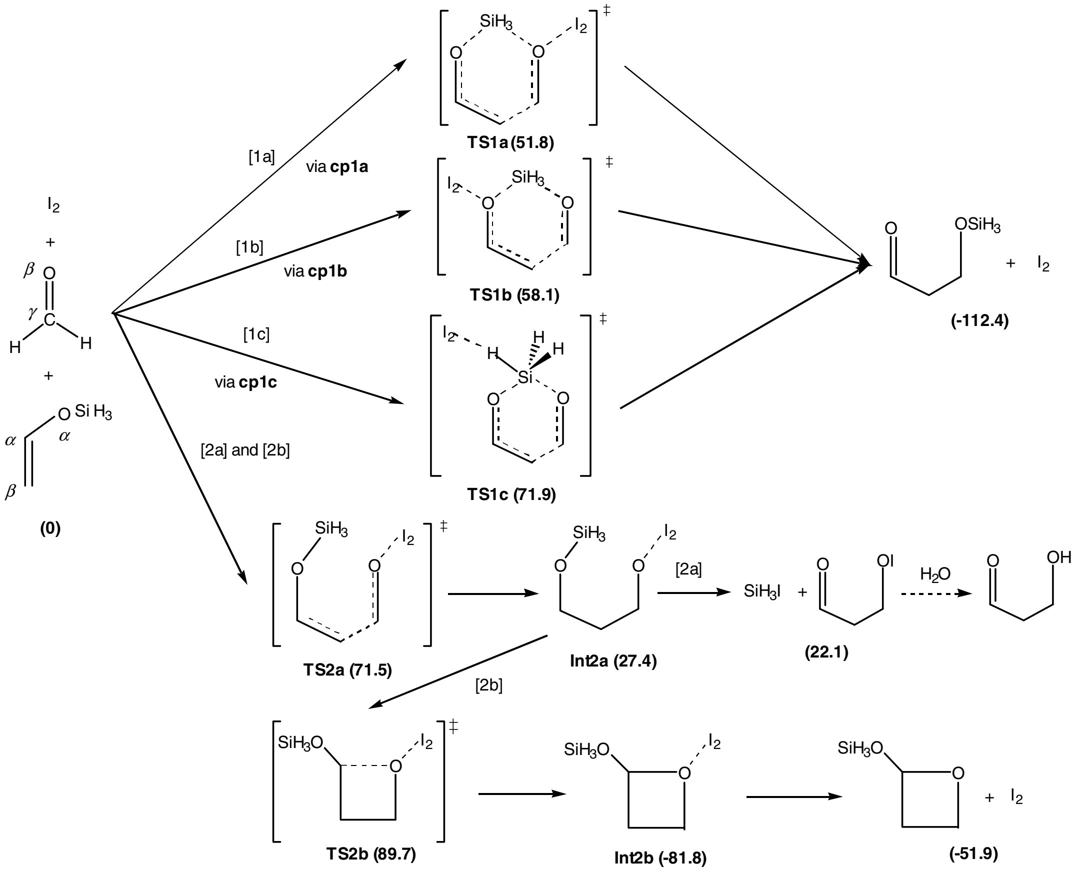
First, we explored in detail various plausible reaction modes, for the I_2-catalyzed aldol reaction. Five reaction pathways were considered, three concerted and two stepwise (Scheme 1). For the concerted pathways, [1a], [1b] and [1c], I_2 initially forms a stable complex via coordination with the oxygen (O_β) of formaldehyde (complex **cp1a**), the oxygen (O_α) of trihydrosilyl enol ether (complex **cp1b**), or with the hydrogen of the trihydrosilyl enol ether (complex **cp1c**), respectively. The calculated binding energies of **cp1a**, **cp1b**, and **cp1c** are −12.0, −20.0, and −3.6 kJ mol^{-1}, respectively. All three concerted pathways involve simultaneous C_β–C_γ bond formation and a SiH_3 shift from O_α to O_β in the transition state. As with the uncatalyzed MA reaction,[5,6] these concerted transition states have a boat-shape six-membered ring geometry. The chair-shape transition state does not exist. In the case of the uncatalyzed reaction, the chair-shape transition state is slightly higher in energy than the boat form by 9.1 kJ mol^{-1}. Not surprisingly, the calculated activation barrier for pathway [1c] is significantly higher (71.9 kJ mol^{-1}), via **TS1c**. On the other hand, reaction pathways [1a] and [1b] are energetically more competitive, with a slight preference for pathway [1a]. Pathway [1a] is inhibited by a moderate barrier of 51.8 kJ mol^{-1}, via transition state **TS1a**. For comparison, the uncatalyzed MA reaction has a higher barrier of 81.0 kJ mol^{-1} at the same level of theory. Coordination of I_2 to formaldehyde in **cp1a** lowers the LUMO energy by 1.88 eV. This leads to a more favorable HOMO–LUMO interaction in the I_2-catalyzed MA reaction. Previous study had shown that the silyl enol ether serves as a nucleophile while formaldehyde acts as an electrophile in the MA reaction.[6] The concerted pathways [1a]–[1c] are calculated to be strongly exothermic processes (−112.4 kJ mol^{-1}).

For the stepwise mechanism, two reaction modes, [2a] and [2b], were considered (Scheme 1). These two pathways have been studied recently for the metal chloride-promoted MA reactions.[7] Both stepwise pathways involve the formation of a common intermediate (**Int2a**) in the first step. **Int2a** lies 27.4 kJ mol^{-1} above the reactants + I_2. The C_β–C_γ bond formation process requires an activation barrier of 71.5 kJ mol^{-1}, via transition state **TS2a**. For pathway, [2a], intermediate **Int2a** undergoes a SiH_3 elimination to form $IOCH_2CH_2CH{=}O$, which then undergoes hydrolysis to give the final hydroxyl product. The first step, via **TS2a**, is the rate determining step for pathway [2a]. For pathway, [2b], intermediate **Int2a** undergoes ring closure of the C_α–O_β bond, via **TS2b**, to yield a [2+2]-cycloaddition adduct **Int2b**. This ring closure step, which has a significant barrier of 62.3 kJ mol^{-1}, is the rate determining step of pathway [2b]. Overall, pathway [2a] is energetically more favorable than [2b]. Interestingly, for the



Scheme 1. Various reaction pathways for the I_2-catalyzed aldol reaction between trihydrosilyl enol ether and formaldehyde. Relative energies (kJ mol^{-1}) calculated at the MP2/6-311+G**//B3LYP/6-31G*+ZPE level are given in parentheses.

metal halide-promoted reactions, the [2+2]-addition process has a very small activation barrier for the ring closure step.[7] It is important to note that there are two stable conformations of the trihydrosilyl enol ether, cis and trans, with almost identical energy.[5,6] Only the reaction energies associated with the *trans* enol ether are reported here.

It is clear from Scheme 1 that pathway [1a] is the lowest in energy of the five considered. Hence, the halogen-catalyzed Mukaiyama aldol reaction between trihydrosilyl enol ether and formaldehyde is predicted to favor a concerted pathway. This finding is somewhat surprising as most of the catalyzed (or promoted) MA reactions are thought to involve a stepwise mechanism.[12]

We have explored also the effect of other halogen catalysts, namely Br_2 and Cl_2, on the model MA reaction. The calculated relative energies of the various transition states (**TS1a**, **TS1b**, **TS1c**, **TS2a** and **TS2b**) of the five reaction pathways are summarized in Table 1. The mechanisms of the Br_2- and Cl_2-catalyzed aldol reactions are identical to that of I_2 discussed above. In particular, the concerted pathway [1a] is the most favorable pathway in all three halogen-catalyzed systems. Br_2 is predicted to have similar reactivity to I_2. The calculated barriers are just 2–4 kJ mol^{-1} higher compared to the corresponding I_2 values. Thus, Br_2 is predicted to be an efficient catalyst as well. On the other hand, Cl_2 is calculated to have a significantly larger energy barrier in all five pathways considered (Table 1). Hence, the predicted catalyst reactivity is in the order: $I_2 > Br_2 > Cl_2$. This is in accordance with the halogen ability in activating formaldehyde. In brief, our computational results support the experimental finding that iodine is a versatile catalyst for Mukaiyama aldol reactions.

Table 1
Calculated relative energies (kJ mol^{-1}) of various transition states for the X_2-catalyzed Mukaiyama aldol reactions between $CH_2{=}CHOSiH_3$ and $CH_2{=}O$[a,b]

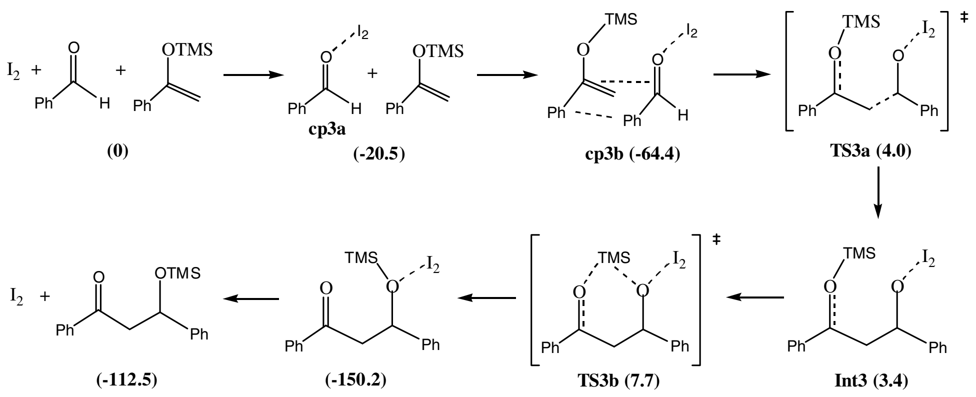
X_2	TS1a	TS1b	TS1c	TS2a	TS2b
I_2	51.8	58.1	71.9	71.5	89.7
Br_2	56.0	60.2	74.3	74.1	93.4
Cl_2	64.7	71.3	87.9	84.2	105.1

[a] MP2/6-311+G**//B3LYP/6-31G*+ZPE level.

[b] With reference to the total energy of $X_2{+}CH_2{=}CHOSiH_3{+}CH_2{=}O$.

Finally, we investigated a larger system which has been studied experimentally by Phukan,[4] namely the I_2-catalyzed reaction between 1-phenyl-1-(trimethylsilyloxy)ethylene (TMSE) and benzaldehyde. In this case, we were unable to locate a concerted transition state corresponding to pathway [1a]. This is perhaps not unexpected as the trimethylsilyl (TMS) group is too bulky to allow simultaneous carbon–carbon bond formation and a TMS shift in the concerted transition state. As a result, this I_2-catalyzed reaction proceeds via a stepwise mechanism with the formation of a zwitterionic intermediate. The schematic reaction profile of this stepwise process is given in Scheme 2. Optimized geometries of selected equilibrium and transition structures are shown in Figure 1. The first step corresponds to the formation of the C_β–C_γ bond to give an intermediate **Int3**, via transition state **TS3a**. This intermediate lies in an extremely shallow energy well, only 0.6 kJ mol^{-1} below **TS3a**. **Int3** readily undergoes a 1,5-TMS shift from O_α to O_β, via transition state **TS3b**, to form the final aldol product. A very small barrier of just 4.3 kJ is required for the TMS migration. **TS3b** is the highest point on the reaction profile and it lies 7.7 kJ mol^{-1} above the separate reactants + I_2. In other words, a very low overall activation barrier is required to drive this particular I_2-catalyzed reaction.

What is the source for the increased reactivity compared to the simple unsubstituted reaction (i.e., $CH_2{=}CHOSiH_3$ + $CH_2{=}O$)? A fairly stable pre-transition complex (**cp3b**) is formed between the enol silane TSME and the I_2-activated benzaldehyde ($I_2 \cdots PhCHO$, **cp3a**). This intermolecular complex **cp3b** is stabilized by π–π stacking interactions and is characterized by a rather large binding energy of 43.9 kJ mol^{-1}. The significantly larger interaction energy is attributed to the interaction of the two extended π systems.[13] In other words, the CC π bond of the enol silane and the CO π bond of benzaldehyde are involved in the π–π interactions. MP2 optimization of **cp3b** (Fig. 2) has confirmed the stacking geometry and strong interaction



Scheme 2. Schematic reaction pathway for the I_2-catalyzed aldol reaction between 1-phenyl-1-(trimethylsilyloxy)ethylene and benzaldehyde. Relative energies (kJ mol^{-1}) calculated at the MP2/6-311+G**//B3LYP/6-31G*+ZPE level are given in parenthesis.

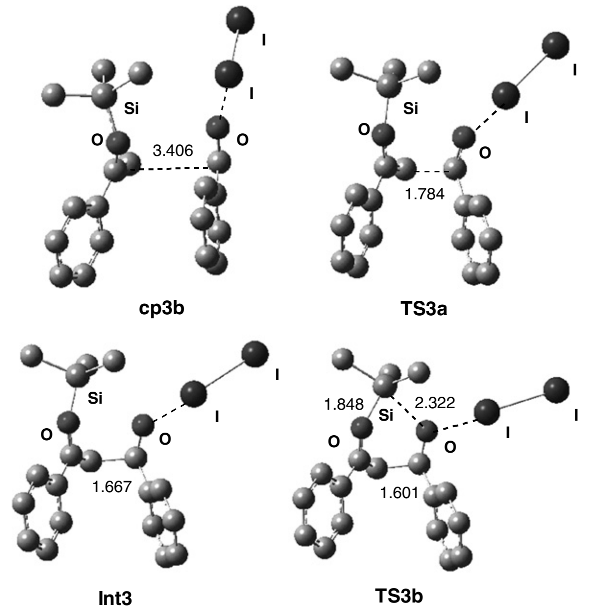


Fig. 1. Optimized (B3LYP/6-31G*) geometries related to the I_2-catalyzed aldol reaction between 1-phenyl-1-(trimethylsilyloxy)ethylene and benzaldehyde. Bond distances are given in Å. The hydrogen atoms are omitted for clarity.

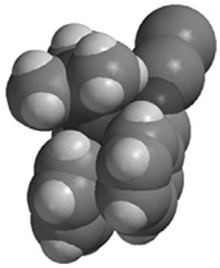


Fig. 2. The CPK model of the pre-transition state π–π intermolecular complex **cp3b**, based on MP2/6-31G* optimized geometry.

energy (-44.6 kJ mol^{-1}) of this pre-transition state π–π complex. The two phenyl units in **cp3b** are in close proximity with a separation of ~3.5 Å and the $C_\beta \cdots C_\gamma$ distance is 3.41 Å. The presence of the π–π attractive intermolecular force is supported by charge density analysis, based on the quantum theory of atoms in molecules (AIM).[14] In particular, a bond path and an associated bond critical point between C_β of enol silane and C_γ of benzaldehyde moiety have been located in **cp3b**. A similar pre-transition state complex is formed between $CH_2{=}CHOSiH_3$ and $CH_2{=}O\cdots I_2$ in the simple model MA reaction. However, the binding energy of this intermolecular complex is substantially less (16.2 kJ mol^{-1}). Thus, the formation of a stable pre-transition state π–π complex between the enol silane TMSE and the activated benzaldehyde ($PhCH{=}O\cdots I_2$) provides a key driving force for the facile aldol reaction. Essentially, the whole reaction profile is shifted downward as a result of the extra stabilization of the pre-transition state complex.

In conclusion, we have studied the mechanism of the halogen-catalyzed (I_2, Br_2, and Cl_2) Mukaiyama aldol reaction between a trihydrosilyl enol ether and formaldehyde. Five reaction pathways, three concerted and two stepwise reaction modes were considered. These halogen-catalyzed MA reactions with simple substituents prefer a concerted pathway. In distinct contrast, the I_2-catalyzed MA reaction between 1-phenyl-1-(trimethylsilyloxy)-ethylene and benzaldehyde prefers a stepwise mechanism. Hence, our computational results demonstrate that the nature of substituent may have a strong influence on the reaction mechanism involved.

Acknowledgments

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