An experimental–theoretical approach to the kinetics and mechanism of Michael type addition: \(\alpha,\beta\)- Unsaturated tungsten Fischer carbene complex as the substrate

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Abstract

Through variable-temperature \(^1\)H and \(^{13}\)C NMR experiments and density functional calculations, the kinetics and mechanism of Michael type addition were investigated using alkynyl carbene \(A\) as the substrate. The two conformers of substrate \(A\) were distinguished from the \(^1\)H and \(^{13}\)C NMR spectra, and the calculated results showed that the \(syn\)-conformer is more stable than the \(anti\)-by 6.5 kJ mol\(^{-1}\) with the activation barrier between these two conformers as 62.5 kJ mol\(^{-1}\). The full reaction mechanism of Michael type addition was first presented to us, which differs from the previous solely based on the kinetic studies. It contains three elementary steps (see the scheme): (1) Formation of \(C_8-N_2\) bond via transition state \(TS_1\). (2) Conformation conversion from \(In_1\) to \(In_2\), which is very important but ignored before. (3) Intramolecular proton transfer via transition state \(TS_2\) forming the product. The first step is rate determining with an activation barrier of 73.0 kJ mol\(^{-1}\), very close to the experimental value of 89.6 kJ mol\(^{-1}\). The product \(P\) is dominant over \(P'\) in population contrary to the situation of tautomer \(B'\) over \(B\), which is caused by larger activation barriers to \(P'\) and the less stabilities of structures related to \(B'\) from the first transition state to the product.

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1. Introduction

In the past two decades, the chemistry of Fisher carbene complexes, especially the \( \alpha,\beta \)-unsaturated [1], has attracted increasing attention from various synthetic groups [2]. They are involved in the formation of phenol (Dötz product) [3] and indene derivatives [4]. They also act as the intermediates to pyridines [5], pyrroles [6], cyclopentenones [7], cyclopenta-[\( \beta \)]pyrans [8] and other heterocyclic complexes [9].

To the diverse reactions mediated with these Fischer carbene complexes, the mechanistic studies lag far behind the synthetic aspects [10]. Much progress has been made on the mechanisms for the hydrolysis of alkyl or aryl carbene complexes [11], the photocarbonylation of chromium carbene complex [12] as well as the Dötz reaction [13]. However, the mechanism of Michael type addition, a more general reaction, is still far from clarity. Based on the activation parameters using the pyrrolidine as the nucleophile, van Eldik et al. [14] followed a two-step mechanism with a zwitterionic intermediate involved, which was much more polar than the reactants. A small solvent dependence was observed probably due to the charge delocalization over the M(CO)\( _5 \) fragment (M = Cr, Mo or W) [15,16]. Large negative reaction constant (\( \nu = -2.95 \)) suggested the sensitivity of Michael type addition against the electronic effects [17]. The zwitterionic intermediate was unstable to detect experimentally. Moreover, the mechanism proposed above was solely based on the kinetic studies, which lacks direct proof and needs further investigation.

Recently, a series of \( \beta \)-pyrazolato-\( \alpha,\beta \)-unsaturated tungsten Fischer carbenes have been successfully produced in our group, see Scheme 1 [18]. To investigate the kinetics and mechanism of Michael type addition, the manuscript was organized as below: (1) Substrate A, which has different conformers, was subject to variable-temperature \( ^1 \)H and \( ^13 \)C NMR experiments. The interconversion process between the conformers of substrate A should be well understood before the investigation of Michael type addition. (2) The kinetics of Michael type addition was monitored under in situ \( ^1 \)H NMR technique and then the activation parameters were obtained. (3) The transition state was located for the conformers of substrate A by density functional calculations. (4) Mechanism of Michael type addition was proposed after geometrically optimizing a series structures and transition state searching. (5) The problem why the dominant tautomer B' will result in the minor product P was tackled.

2. Experimental

The alkynyl Fischer tungsten carbene complex A and 3-methyl-5-phenylpyrazole B were prepared and purified as described elsewhere [19,20]. The samples were dissolved in CDCl\( _3 \) for the NMR measurements, with the initial concentrations of A and B both as 0.04 mol L\(^{-1}\). All the NMR spectra were recorded on Bruker DRX-400 NMR spectrometer equipped with a 5 mm indirect detection probe with Z-gradient (chemical shifts were referred to TMS). To carry out the kinetic investigation, the \( ^1 \)H NMR spectra were acquired with time interval of 10 min. Net ethylene glycol was used as the thermometer substance calibrating the NMR measurement temperatures [21].

3. Calculation details

Density-functional calculations were performed at the gradient corrected approximation level, implemented in the Dmol3 program, CERIUS 2 of MSI [22]. Joubert and Maldivi [23] claimed that BP functional was superior to the conventional B3LYP functional when treating systems with heavy elements, confirmed by our pervious theoretical work [24]. Accordingly, BP functional was employed here along with the high precise basis set of DNP. All the elements were calculated with all electrons except W, whose core electrons were replaced by a simple effective core potential (ECP) with the valence electrons treated as 5s5p5d6s6p.

To describe the mechanism of Michael type addition as accurate as possible, the most precise transition state searching method in Dmol3 module was selected; i.e., complete linear synchronous transit/quadratic synchronous transit (complete LST/QST) protocol.

4. Results and discussion

4.1. The features of \( ^1 \)H and \( ^13 \)C NMR spectra

4.1.1. Interconversion between the conformers of substrate A

From the variable temperature \( ^1 \)H NMR spectra in Fig. 1, it was found that at the temperature range of \(-60 \) to \(-20 \)°C, the proton signals for methylene or methyl of ethoxyl (CH\( _2 \)CH\( _2 \)O) are separated into two groups, corresponding to the syn- and trans-conformer, respectively.

![Scheme 1. Synthesis of \( \beta \)-pyrazolato-\( \alpha,\beta \)-unsaturated carbenes.](image-url)
At $-60^\circ$C, the ratio of main/minor conformers is 4.6 based on the $^1$H NMR integrals. Variable temperature $^{13}$C NMR spectra also evidence the coexistence of two conformers: 284.9 and 289.8 ppm for carbene carbon in the main and minor conformers, 206.6 and 205.3 ppm for trans-CO, 197.7 and 196.9 ppm for cis-CO, 133.4, 132.1, 129.0, 120.1 and 132.9, 128.9, 122.0 ppm for phenyl carbons, 131.5 and 122.0 ppm for $\equiv$C(–Ph), 96.5 and 100.0 ppm for C($\equiv$C–Ph), 75.8 and 79.2 ppm for CH$_2$, 14.7 and 15.0 ppm for CH$_3$, respectively, see Fig. 2. The resonance of carbene carbon in the minor conformer is at lower field than that in the main one, which implies that the former is of more electron deficiency. The main conformer of alkynyl-substituted carbene complex A will adopt syn-configuration [25], confirmed by our latter calculated results with the syn-conformer stabilized by 6.5 kJ mol$^{-1}$ over the anti. At low temperatures, the interconversion process is quite slow, where the two conformers can be distinguished from $^1$H and $^{13}$C NMR spectra. As the temperature increases, $^1$H and $^{13}$C NMR signals become broadened and coalesced and finally turn out sharp, where the interconversion process proceeds fast on the NMR time scale.

4.1.2. Michael type addition

As Scheme 2 shows, 3-methyl-5-phenylpyrazole (B) and 3-phenyl-5-methylpyrazole ($B'$) are two tautomers, with $B'$ of higher proportion [26]. The Michael type addition of B and $B'$ leads to two products; i.e., P through reaction 1 and $P'$ through reaction 2, respectively.

The characterization of the products was performed by in situ $^1$H NMR spectroscopy, see Fig. S1, with the chemical shifts collected in Table 1. Compared to B or $B'$, the $^1$H NMR signals of methyl in the products shift upward due to the
electron donation by N-alkenylation of pyrazole [27]. The anisotropic shielding effect as another important factor exists in the phenyl ring of \( P \), which results in the up-field shifts of methyl in \( P \) (about 224 Hz) more obviously than in \( P_0 \) (about 4 Hz) [28]. It was observed from our \(^1\)H NMR spectra that the minor tautomer \( B \) will lead to the main product \( P \) whereas the main tautomer \( B_0 \) to the minor product \( P_0 \), and the reasons will be elaborated in Section 4.5.

4.2 Reaction rates and activation parameters based on NMR experiments

From the \(^1\)H NMR spectra of Michael type at different reaction times (Fig. 3), it can be seen that the concentrations of reactants and products will change as the reaction proceeds, reflected by the intensities of the corresponding peaks. The peaks at 4.72 and 4.70 ppm are assigned to the methylene protons of substrate \( A \) whereas at 4.56, 4.52 and 4.47, 4.44 ppm to the methylene protons of products \( P \) and \( P_0 \), respectively. The concentration of substrate \( A \) and its reciprocal were plotted against the reaction time (see Fig. 4). The inverse concentration can be expressed through the following equation

\[
1/[A] = kt + \text{Constant}
\]

where \([A]\) represents the concentration of substrate \( A \) and \( k \) the overall rate constant. Obviously, the reaction is second order, namely a bimolecular reaction. At each specified temperature, the ratio of \([P_0]/[P]\) (labelled as \( \theta \)) remains almost invariable within two half-lives, implying that reactions 1 and 2 proceed under the same mechanism. Accordingly, the rate constants of reactions 1 and 2; i.e., \( k_1 \) and \( k_2 \) can be obtained by the equations below

\[
k_1 = k/(1 + \theta)
\]

\[
k_2 = k\theta/(1 + \theta)
\]

The temperature dependences of \( k_1 \) and \( k_2 \) are summarized in Table 2. Within the Eyring transition state theory, the

<table>
<thead>
<tr>
<th></th>
<th>OCH(_2)</th>
<th>(OCH(_2))CH(_3)</th>
<th>4-H(pyrazole)</th>
<th>CH(_3)(pyrazole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( A )</td>
<td>4.72 and 4.70</td>
<td>1.58</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>( B (B') )</td>
<td>–</td>
<td>6.35</td>
<td>2.38</td>
<td>–</td>
</tr>
<tr>
<td>( P )</td>
<td>4.56 and 4.52</td>
<td>0.98</td>
<td>6.45</td>
<td>1.82</td>
</tr>
<tr>
<td>( P_0 )</td>
<td>4.47 and 4.44</td>
<td>0.91</td>
<td>6.23</td>
<td>2.37</td>
</tr>
</tbody>
</table>

Fig. 3. \(^1\)H NMR spectra for Michael type reaction at different times.
corresponding activation parameters were obtained and listed in Table 2. The Michael type addition reaction is characterized by low activation enthalpy ($\Delta H^\ddagger = 58.4$ and $52.6$ kJ mol$^{-1}$) and large activation entropy ($\Delta S^\ddagger = -109.6$ and $-131.0$ J mol$^{-1}$ K$^{-1}$), consistent with the results of van Eldik et al. [15,16]. $k_2/k_1$ decreases as 0.73 at $35^\circ C$, 0.69 at $40^\circ C$, 0.66 at $45^\circ C$ and 0.66 at $50^\circ C$, which indicates that reaction 1 is more favored over reaction 2 as the temperature goes up.

4.3. Theoretical investigation on the syn/anti interconversion of substrate A

At low temperatures, there exist two different conformers for substrate A, as observed in our $^1$H and $^{13}$C NMR experiments. For the two conformers, the calculated C–O distances of all the five carbonyls fall at ca. 1.60 Å, and all the W–C bond lengths are approximately at 2.08 Å except the one associated with the carbene carbon which falls at about 2.19 Å. The validity of our theoretical methods have been depicted in Section 3, which is further verified by optimizing (CO)$_2$W=CC(OEt)=C=R(R=1-t-Bu, 2=H, see Fig. S2) and then comparing the calculated geometric parameters with those from X-ray diffraction experiments, see the details in Table S1. As shown in Fig. 5, the syn-conformer is more stable than the anti by 6.5 kJ mol$^{-1}$. In the syn-conformer, the ethoxyl group falls almost within the C$_2$–C$_3$–C$_5$–W–C$_6$ plane, which can be deduced from the small C$_5$–W–C$_6$–O$_6$ dihedral angle of $-4.2^\circ$, whereas the ethoxyl group in the anti-conformer deviates greatly from the C$_2$–C$_3$–C$_5$–W–C$_6$ plane with the C$_5$–W–C$_6$–O$_6$ dihedral angle of $45.0^\circ$. Accordingly, the electronic donation from ethoxyl to the pz orbitals of carbene atoms will be more facilitated in the syn-conformer and thus stabilizes this conformer [29].

The activation barrier for this interconversion process is calculated at 62.5 kJ mol$^{-1}$, close to the value 59.8 kJ mol$^{-1}$ for an alkyl chromium Fisher carbene. The dihedral angle of W–C$_6$–O$_6$–C$_{10}$ changes from $-1.0^\circ$ in the syn-conformer to $78.7^\circ$ in the transition state TS and then to $-179.3^\circ$ in the anti-conformer. Compared to the two conformers, the W–C$_5$ and C$_6$–C$_7$ bonds in TS are strengthened somewhat at the expense of weakening C$_6$–O$_6$ bond (see the exact values in Fig. 5). The remaining part of the $\alpha\beta$-unsaturated Fisher carbene seems unaffected during the interconversion process.

Fig. 4. Plots of the concentration of substrate A and its reciprocal vs. the reaction time.

Table 2

<table>
<thead>
<tr>
<th>Temperature ($^\circ$C)</th>
<th>$k_1$ or $k_2$ ($10^3$ M$^{-1}$ s$^{-1}$)</th>
<th>$k$ (25 $^\circ$C) ($10^3$ M$^{-1}$ s$^{-1}$)</th>
<th>$\Delta H^\ddagger$ (kJ mol$^{-1}$)</th>
<th>$\Delta S^\ddagger$ (J mol$^{-1}$ K$^{-1}$)</th>
<th>$\Delta G^\ddagger$ (25 $^\circ$C) (kJ mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction 1</td>
<td>35</td>
<td>1.4</td>
<td>0.7</td>
<td>58.4</td>
<td>$-109.6$</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>2.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>3.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>4.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction 2</td>
<td>35</td>
<td>1.0</td>
<td>0.5</td>
<td>52.6</td>
<td>$-131.0$</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>1.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>2.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>2.9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.4. Theoretical investigation on the reaction mechanism of Michael type addition

4.4.1. Structures of reactants, intermediates and products

The adsorption structure of 3-methyl-5-phenylpyrazole B on α,β-unsaturated Fisher carbene A is marked as A/C0B, and the two intermediates as In1 and In2, respectively (see Fig. 6).

For substrate A, the calculated data show that the syn-conformer is slightly more stable than anti-conformer. Our X-ray diffraction and NMR experiments suggest the products adopt predominantly the anti-conformer. Accordingly, the interconversion between the two conformers of substrate A will take place due to the small activation barrier, and the mechanism of Michael type addition can be elucidated on the anti-conformers.

In structure A – B, the C8–N2 distance is optimized at a large value 4.308 Å. The geometries of B and A seem unaffected (see Table 3), which implies a weak adsorption with energy of 9.9 kJ mol\(^{-1}\). C7–C8 is characteristic of triple bond with the length of 1.230 Å.

The formation of In1 destroys the triple C7–C8 bond in substrate A with the length elongated to 1.329 Å. Meanwhile, the overlap of \(\pi\) electrons between the phenyl and alkyne (C7–C8) groups is significantly decreased, as concluded from the variation of the C7–C8–C9 angle (179.4–129.1°). Therefore, the stability of structure In1 is reduced compared to structure A – B, supported with the result that In1 is higher in energy than A – B.

In2 is in equilibrium with to In1. Their structures are very close to each other, which can be deduced from the geometric parameters (Table 3). The largest difference between

Fig. 5. Antisyn interconversion for α,β-unsaturated tungsten Fischer carbene A.

Fig. 6. Reaction mechanism of Michael type addition from theoretical calculations (energy units in kJ mol\(^{-1}\)).
Table 3
Geometric parameters of reactants, intermediates, products as well as the transition states of Michael type addition (bond lengths in Å and angles in °)

<table>
<thead>
<tr>
<th></th>
<th>A + B</th>
<th>A – B</th>
<th>TS₁</th>
<th>In₁</th>
<th>In₂</th>
<th>TS₂</th>
<th>P</th>
<th>A + B‘</th>
<th>A – B‘</th>
<th>TS₁</th>
<th>In₁</th>
<th>In₂</th>
<th>TS₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>W–C₆</td>
<td>2.199</td>
<td>2.212</td>
<td>2.293</td>
<td>2.347</td>
<td>2.350</td>
<td>2.275</td>
<td>2.239</td>
<td>2.199</td>
<td>2.214</td>
<td>2.304</td>
<td>2.350</td>
<td>2.341</td>
<td>2.275</td>
</tr>
<tr>
<td>C₆–C₇</td>
<td>1.419</td>
<td>1.411</td>
<td>1.373</td>
<td>1.322</td>
<td>1.325</td>
<td>1.395</td>
<td>1.456</td>
<td>1.419</td>
<td>1.411</td>
<td>1.374</td>
<td>1.322</td>
<td>1.323</td>
<td>1.389</td>
</tr>
<tr>
<td>N₁–N₂</td>
<td>1.353</td>
<td>1.353</td>
<td>1.349</td>
<td>1.368</td>
<td>1.359</td>
<td>1.346</td>
<td>1.371</td>
<td>1.350</td>
<td>1.351</td>
<td>1.351</td>
<td>1.369</td>
<td>1.477</td>
<td>1.470</td>
</tr>
</tbody>
</table>

Accordingly, it is the intermediate In₂ that climbs over the transition state TS₂ and reaches the final product P.

To conclude, the Michael type addition (from step 1 to step 3) is exothermic with the calculated reaction heat as −81.7 kJ mol⁻¹. As the activation barrier of the first step is larger than that of the third step and the former is endothermic whereas the latter exothermic, it should be the first step as rate determining. The activation barrier of the first step is close to the experimental activation enthalpy of 89.6 kJ mol⁻¹, van Eldik et al. [14] used secondary amines as the nucleophiles to study the kinetics and also obtained that the first step is rate determining. A more systematic analysis of Michael type addition will be carried out in future work with different R¹, R² and R³ in pyrazole considered.

The Mulliken charges on pyrazolyl, W(CO)₅ and fragment 1 (including W(CO)₅, OEt, C₆, C₇ and C₈) increase in In₁ to 2.631 Å in In₂ and the angle of C₇–C₈–H₁ changing from 108.3° in In₁ to 77.2° in In₂.

Theoretical investigation on the reason why P is dominant over P'...
The energy difference between the tautomers $B$ and $B'_0$ is defined as $\Delta E_B$, and $\Delta E_{A-B}$, $\Delta E_{TS_1}$, $\Delta E_{In_1}$, $\Delta E_{In_2}$, $\Delta E_{TS_2}$ and $\Delta E_P$ for energy differences between the structures related to $B$ and $B'_0$, respectively (see the exact values in Table 4). As expected, $B$ is less stable than $B'_0$ with a calculated energy difference of 1.2 kJ mol$^{-1}$. The stabilities of the absorbed structures are the same in sequence. However, the situation changes from the first transition state, where $TS_1$ is found more stable than $TS'_1$ by 5.4 kJ mol$^{-1}$. The largest energy difference is for the two products, where $P$ is favored over $P'$ by 11.6 kJ mol$^{-1}$. For structures related to $B'_0$, the energy differences are reverse in sequence to the distances between the two phenyls, suggesting that it be the repulsion between these two bulk phenyls that reduces their stabilities.

5. Conclusions

1. By variable-temperature $^1$H and $^{13}$C NMR experiments, the syn- and anti-conformers of substrate $A$ were distinguished. The calculated results showed that the syn-conformer is more stable than the anti- by 6.5 kJ mol$^{-1}$, and that the activation barrier between these two conformers is 62.5 kJ mol$^{-1}$.

2. From kinetic analysis based on the $^1$H NMR experiments, Michael type addition is of second order, characterized by low activation enthalpy and significantly negative activation entropy.

3. The reaction mechanism of Michael type was proposed, which contains three elementary steps crossing over two intermediates and two transition states. Intermediates $In_1$ and $In_2$ are zwitterionic intermediates with the largest charge separation.

4. According to the calculated results, the first step is rate determining. The activation barrier of this step is calculated as 73.0 kJ mol$^{-1}$, very close to the experimental value of 89.6 kJ mol$^{-1}$.

5. The more population of product $P$ over $P'$ is caused by two reactions: (i) The smaller activation barrier of tautomer $B$ than $B'$ when reacting with substrate $A$. (ii) The less stabilities of the structures related to $B'_0$ from the first transition states.

Acknowledgements

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Appendix A. Supplementary data

References


[30] Following the reaction pathway, structures with N1 to attack substrate A were optimized. However, the reasonable configuration of the first intermediate cannot be reached no matter how we have tried, implying that it would not be N1 atom that acts as the nucleophilic center. Mulliken population analyses were performed on a series of substituted pyrazoles, showing that charges on N2 atoms are more negative than that on N1 atoms (−0.217 to −0.244 |e|) are more negative than that on N1 atoms (−0.125 to −0.155 |e|) in each case (the exact values can be found in Table S2). Accordingly, it is N2 atom that acts as the nucleophilic center.