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Challenge To Detect 1,4-Zwitterions Spectroscopically in a Ketene−Alkene Reaction

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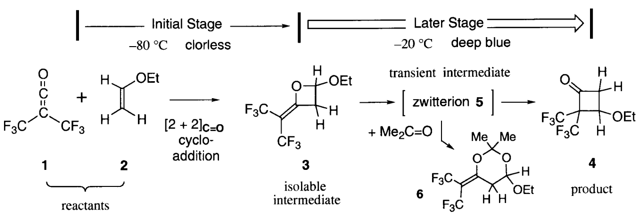
We wish to report the first example of detecting explicitly 1,4-zwitterionic intermediates in a ketene−alkene [2 + 2] cycloaddition. Also, we will show a striking result involving an unprecedented "1,4-zwitterion neutral dimer" in a new pathway of the ketene−alkene reaction. In ketene−alkene reactions,[3] the intervention of zwitterions has been suggested to avoid the *symmetry-forbidden* [2 + 2] cycloadditions.[3a] However, in our previous work, an entirely different mechanism was found.[4] In the reaction between a weight-measurable ketene, bis(trifluoromethyl)ketene (**1**),[5] and an activated alkene, ethyl vinyl ether (**2**), a concerted [2 + 2] cycloaddition takes place at the initial stage of the reaction (Scheme 1).[4] During the isomerization, α-methyleneoxetane (**3**) to cyclobutanone (**4**), the zwitterion (**5**) intervenes (Scheme 1). The intervention was established by an acetone-quench experiment to give a cycloadduct (**6**).[4] The sequence, **1** + **2** → **3** → **5** → **4** (not **1** + **2** → **5** → **4**), was elucidated in the acetone solvent by a monitoring experiment of the time course of the reaction (see Supporting Information).

Scheme 1



Although the existence was elucidated by our acetone-quench experiment,[4] the zwitterion still remains as merely a conceptual species. It is an open question whether the zwitterion occurs in a sufficient concentration in CH_2Cl_2 to become visible to the naked eye. A direct spectroscopic detection of the ion would be a much stronger argument than the quenching experiment with acetone.

The visible deep color at −20 °C prompted us to design a simple but unprecedented method for low-temperature UV−vis spectroscopy (see Figure 1). We used a quartz 5-mm-diameter NMR tube for low-temperature UV−vis spectroscopy to search for reaction intermediates, *keeping the concentration as high as that in the preparative experiments* (0.1−2.5 mol/L). To monitor each stage of the reaction under conditions of high purity, we used a vacuum-transfer system to deposit the two reactants and solvent in the tube *at separate positions* (Figure 1) of the inside wall of the tube at liquid nitrogen temperature. The reaction tube was sealed under vacuum to protect the reactants from moisture. The unreacted combinations were melted at −100 °C in an NMR probe or in a cryostat with a temperature-control (±0.1 °C) unit for low-temperature measurements by NMR (^1H and ^{19}F) and UV−vis spectroscopies, respectively.

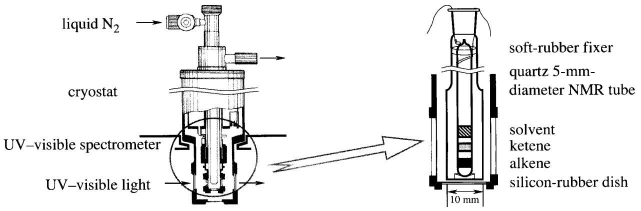


Figure 1. Low-temperature equipment for UV−vis spectroscopy. Detection of transient species under concentrations which are the same as those of preparative-scale experiments (0.1−2.5 mol/L).

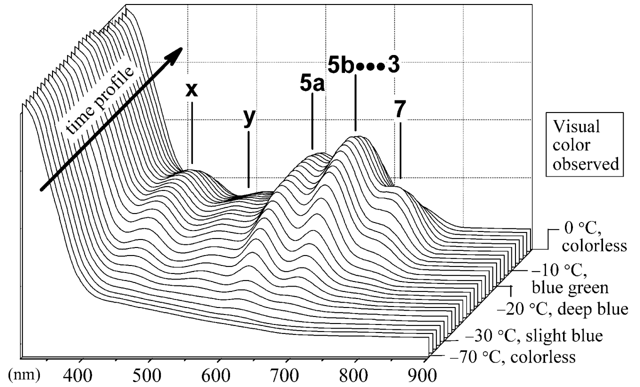


Figure 2. Dynamic detection of zwitterions (**5a**, **5b**, and **7**) by variable-temperature UV−vis spectroscopy. The figure presents a 3-D profile of the spectra on monitoring the later stages of the reaction in Schemes 1 and 2. The reaction was carried out in CH_2Cl_2 (0.1 mol/L) and, finally, led to the cyclobutanone (**4**) exclusively. The species **x** and **y** are tentatively assigned to geometric isomers of **5b**···**3**.

By the use of the apparatus, the reaction was traced by variable-temperature UV−vis spectroscopy, where the zwitterion is thought to be involved. Figure 2 demonstrates a striking result! Absorption at extraordinary long wavelengths (>600 nm) was observed. This is the first detection of such large wavelengths in a simple nonconjugated system as that composed of **1** and **2**. Those absorptions are ascribed to zwitterions, but a decisive statement requires calculated authentic spectroscopic data.

In accordance with recent computational methods,[6] the geometry of the zwitterion was determined, and subsequently, its λ_{max} value was calculated. Two geometric isomers (**5a** and **5b**) were obtained. For **5a**, λ_{max} = 621 nm was computed, which is in good agreement with the present observed value, λ_{max} = 615 nm. For **5b**, the calculated data, λ_{max} = 677 nm, are comparable with the present

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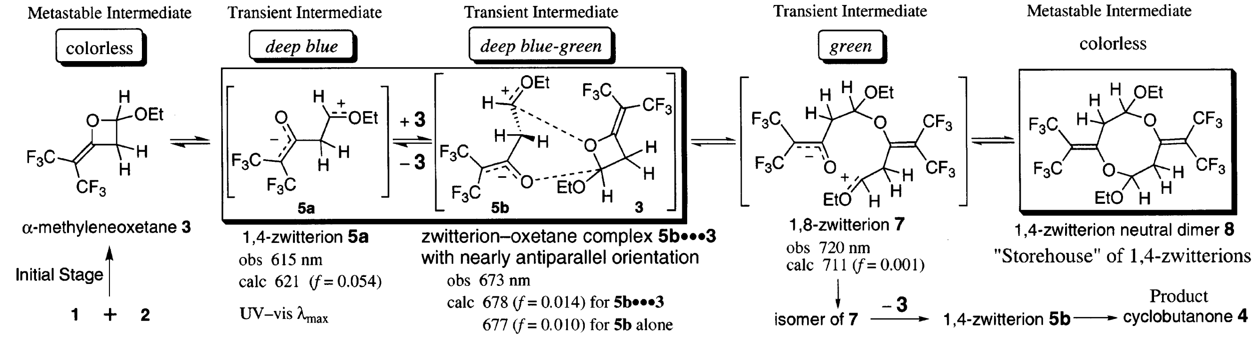
Scheme 2. Later Stage of the Reaction in Scheme 1



observed ones, $\lambda_{max} = 673$ nm. Although good correspondence of λ_{max} values was obtained, zwitterions **5a** and **5b** are 13.8 and 15.1 kcal/mol less stable than the α-methyleneoxetane **3**. The significantly large instability of **5a** and **5b** is apparently inconsistent with the observation of them in Figure 2.

The α-methyleneoxetane **3** was calculated to have a large dipole moment, $\mu = 6.76$ D.[7] By the same computational method, tremendously large dipole moments of the zwitterions **5a** and **5b**, $\mu = 17.90$ and 13.64 D, respectively, were obtained. Remarkable dipole−dipole attraction results from the association of **3** and **5**. Even at the large separation of 4 Å, stabilizing energies of −27.2 and −20.7 kcal/mol were calculated for the antiparallel orientations of **3** + **5a** and **3** + **5b**, respectively;[8] the association energy of two molecules of **3** amounts to −10.2 kcal/mol. We are inclined to correlate these species with UV−vis absorptions (Figure 2), for example, **5b···3** (also stabilized by a hydrogen bond)[9] with $\lambda_{max} = 678$ nm ($f = 0.014$). These dipole−dipole stabilizations facilitate the C−O bond cleavage in the conversion of **3** to **5** (+13.8 kcal/mol).

Considering the reaction channel to **4**, there might be another transient species involved. The antiparallel orientation of **5b···3** is ready to make an intermolecular C−O bond. In fact, the one-center addition TS and the subsequent 1,8-zwitterion **7** were calculated (see Supporting Information). The cation and anion centers in the 1,8-zwitterion **7** are close conformationally to each other, and they would be linked by a second covalent bond.

When the reaction of **1** + **2** was carried out at the high concentration of 2.0 mol/L in the polar solvent $EtNO_2$ ($\mu = 3.70$ D), the neutral dimer **8** was detected at −20 °C by NMR spectroscopy; also in CH_2Cl_2 or hexane as solvent, formation and decay of the dimer was observed. The isolated dimer **8** [NMR ($CDCl_3$, −40 °C): δ_C 31.28 (t, 2 C), 85.09 (sept, $^2J_{CF} = 32.1$ Hz), 96.37 (d, 2 C), 107.32 (sept, $^2J_{CF} = 34.2$ Hz), 154.74 (sept, $^3J_{CF} = 2.3$ Hz), 156.24 (sept, $^3J_{CF} = 2.1$ Hz); δ_F (external C_6F_6) −58.39 (qt, $^4J_{F,F}$ and $^5J_{F,H}$), −56.51 (q, $^4J_{F,F}$), −56.05 (qt, $^4J_{F,F}$ and $^5J_{F,H}$), −55.79 (qt, $^4J_{F,F}$ and $^5J_{F,H}$); δ_H 3.22 (dm, $^2J = 17.7$ Hz), 3.30 (dm, $^2J = 17.7$ Hz), 5.53 (dd, $^3J = 3.8$, 2.1 Hz)] has been converted to cyclobutanone **4** exclusively in CH_2Cl_2 (0.1 mol/L). The dimer **8** has been concealed and overlooked for a long time. The dimer **8** [mp 34−36 °C (dec); *m/z* 500 (M^+, 29%)] was isolated at low temperatures but is not stable at higher temperature ($T = 273$ K). It is dissociated in CH_2Cl_2 or $EtNO_2$ (see Supporting Information II.3) to its fragment, oxetane **3** and zwitterion **5b**, which is cyclized easily to give **4** eventually. The stability may be assessed by comparing the calculated Gibbs free energies at $T = 0$ and 298 K (see Supporting Information). The reversibility renders the dimer a "storehouse" of the zwitterions and makes them observable.

Summarizing the results of our combined study of experiment and calculation, the main features of the reaction of **1** + **2** are depicted in Scheme 2. The ions **5a** and **5b···3** are formed and observed at $\lambda_{max} = 615$ and 673 nm, respectively, as well as other association complexes **x** and **y** (Figure 2). The 1,4-zwitterion is characterized unequivocally for the first time. Sacrificing one bond, the α-methyleneoxetane is transformed to the 1,4-zwitterion **5**, assisted by the dipole−dipole interchanges. Formation of the first covalent C−O bond leads to the 1,8-zwitterion **7** ($\lambda_{max} = 720$ nm). This ion either affords dimer **8** via ring closure or forms a conformational isomer which, finally, leads to cyclobutanone **4** via **5b**. The dimer is situated at one end of the equilibrium and ensures the observable concentrations of the zwitterions and the association complex. From the isomer, the cyclobutanone and the α-methyleneoxetane are generated.

In conclusion, zwitterions in ketene−alkene reactions are not virtual but spectroscopically observable real species.

Acknowledgment. This paper is dedicated to Professor Rolf Huisgen on the occasion of his 85th birthday (ref 1), and also to the memory of Mrs. Gertrud Huisgen who passed away on February, 27, 2005 (ref 2).

Supporting Information Available: NMR spectral charts for the dimer **8**, plots of reaction monitoring experiments, Cartesian coordinates of optimized geometries of all the species (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The μ value was calculated by MP2/6-311G**, which was shown to reproduce the experimental data well. Minato, T.; Yamabe, S.; Hasegawa T.; Machiguchi, T. *Tetrahedron* **1995**, *51*, 2507−2514.
(8) The interaction energy is given by $U_{dipole-dipole}(d) = -\mu_1\mu_2/4\pi\epsilon d^3$.
(9) See Scheme 3 in Supporting Information.

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