Highly regio- and enantioselective thermal [2 + 2] cycloaddition of coumarin in a crystalline inclusion complex under high vacuum†

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Coumarin and thiocoumarin, which are usually thermally unreactive for dimerization, were dimerized in their inclusion crystalline complexes under thermal and high vacuum conditions.

Cycloaddition reactions are among the powerful reactions available to organic chemists. The productive interplay between theory and experiment has resulted in sophisticated models, which often allow one to predict reactivity, regioselectivity and stereoselectivity for given cycloaddition partners. According to the Woodward–Hoffmann rules,[1] a concerted [2 + 2] reaction is forbidden in the ground state. Besides those catalyzed by transition metal or Lewis acid,[2,3] they are typically confined to strongly electrophilic olefins and cumulenes,[4] such as fluorinated ethylene, ketene, and propadiene.

Coumarin and its derivatives are of wide interest due to their abundant optical[5] and biological properties.[6] Although they have been extensively studied in solutions, self-assembled monolayers, polymeric films, as well as in crystals or crystalline inclusion complexes,[5] so far no data on thermal [2 + 2] cycloaddition of coumarin are available. However, our recent research shows that coumarin molecules can undergo a thermal [2 + 2] cycloaddition in crystalline inclusion complexes under high vacuum conditions (Scheme 1). Analogous results can also be found in thiocoumarin crystalline complexes. This finding might provide new impetus for applying high vacuum as an effective tool in organic solid chemistry and supramolecular chemistry. Furthermore, with the widespread application of organic materials in molecular electronic devices,[7] it merits much attention from molecular device engineers preparing thin films with high vacuum vapor phase deposition technology.
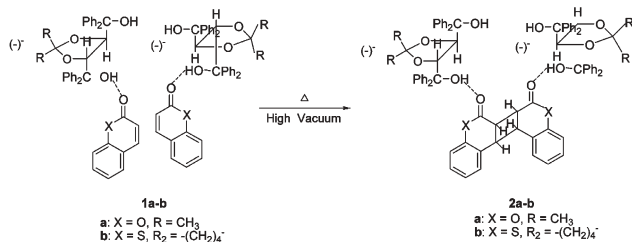
The study of the thermal [2 + 2] cycloaddition of **1a** was prompted by the discovery of its excellent single-crystal-to-single-crystal photodimerization property, which is likely to be used for optical data storage.[5a] In the course of preparing films for data storage by the physical vapor deposition (PVD) method, we found that the chemical composition of films changed quite noticeably and the obtained IR data were in agreement with those reported for its photodimerization complexes **2a**. This unexpected phenomenon seemed to be in conflict with the Woodward–Hoffmann rules, which inspired us to further investigate the reason for it.

Complex **1a** was obtained by co-crystallization of (−)-TADDOL[8] ((R,R)-(−)-trans-4,5-bis(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxacyclopentane) (1.0 g, 2.15 mmol) with coumarin (0.36 g, 2.47 mmol) from ethyl acetate–hexane (1 : 5, 10 mL).[5a] The crystal structure was determined, and was consistent with a previous report,[5a] therefore no details are presented here. Following common practice, the thermal dimerization of **1a** was carried out in a conventional PVD apparatus. When the vacuum arrived at 3.0×10^{-4} Pa, the temperature was increased by slowly raising the electric current through the tungsten filament surrounding the crucible. A constant temperature (about 85 °C) was maintained for about 10 min to afford the thermal cycloadduct. As shown in Fig. 1, the characteristic IR absorptions of the thermal products (Fig. 1B) were in good agreement with those of the standard sample **2a** (Fig. 1C). For the thermal products, the $v_{C=C}$ absorption of the pyrone ring in monomer **1a** at 1563 cm^{-1} disappeared, the $v_{C=C}$ absorption of the aromatic ring
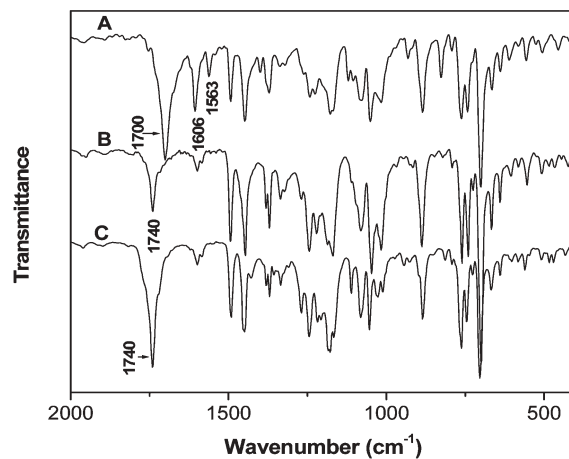
Scheme 1

Fig. 1 The IR spectra of inclusion complexes **1a** before (**A**) and after (**B**) thermal dimerization, as well as the standard sample **2a** obtained by solid-state photochemical dimerization (**C**).

at 1606 cm^{-1} weakened greatly, and the most characteristic IR feature of the $v_{C=O}$ absorption at 1700 cm^{-1} vanished accompanied by a new $v_{C=O}$ absorption appearing at 1740 cm^{-1}.[5a] The weaker absorption intensity at 1740 cm^{-1} was attributed to the rupture of some hydrogen bonds between coumarin and (−)-TADDOL molecules, and coumarin was partly vaporised away. To further assess the thermal reaction products, the products in the crucible after heating under high vacuum were characterized by ^{1}H NMR, HPLC, MALDI-TOF, as well as ESI mass spectrography. The results indicated that the dimerization of **1a** did occur at high vacuum to give *anti* head-to-head dimers in about 30% yield and 99% ee.[9] Furthermore, to prove the intriguing reaction can occur widely, analogous experiments were used for thermal cycloaddition of the thiocoumarin crystalline complex **1b**. The corresponding homologous dimerization product **2b** was also obtained with high enantiomeric excess (> 95%).

The unexpected results observed in this system called for further investigation of the impact of H-bonds on the reactivity. Accordingly, experiments were carried out with coumarin or thiocoumarin solely as the reactant. However, no distinct transformation was observed under various thermal vacuum conditions. In addition, to further elucidate the role of the vacuum, experiments at ambient pressure and a lower vacuum (about 20 Pa) using an ordinary vacuum pump were developed. In contrast, inclusion complexes **1** did not undergo any dimerization reactions under these conditions over a temperature range from 50 to 150 °C. Moreover, with the temperature rising, the hydrogen bonds in complexes **1** ruptured almost completely. In contrast, when the system was kept at a higher vacuum (< 10^{-3} Pa), dimer **2** could be distinctly formed.

To obtain a deeper understanding of the mechanism of the unexpected thermal dimerization, comparative experiments for solid-state spin trapping have been carried out with α-phenyl-*N*-*tert*-butyl nitrone (PBN) as the spin trap. The corresponding electron spin resonance (ESR) spectra showed that when hydrogen bonds between the coumarins and (−)-TADDOL molecules existed, a significant nitroxide ESR signal was detected. On the contrary, no marked signal could be observed for the mixtures of coumarin/PBN (3 : 1) or (−)-TADDOL/PBN (3 : 1) (Fig. 2). These results clearly indicated that in the process of dimerization of complex **1a** there was significant formation of the trapped radical
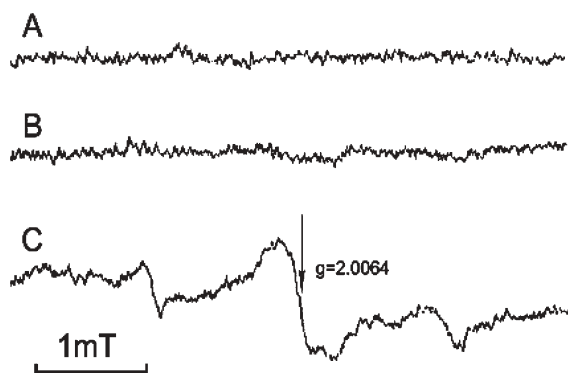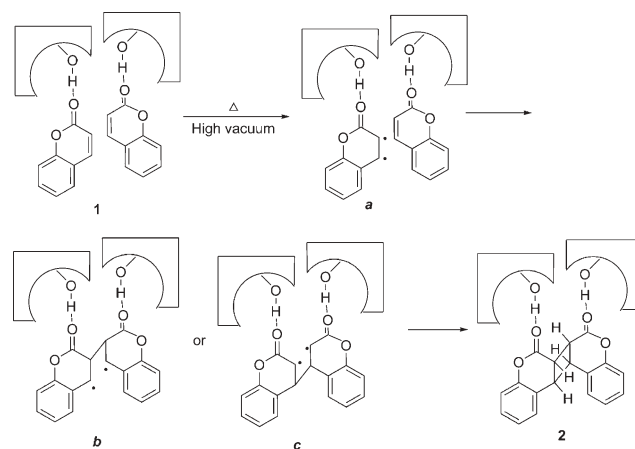
species, and that hydrogen bonds played an important role in this process. We presume that this unexpected reaction might take place *via* a stepwise radical mechanism (Scheme 2), as frequently found in the reaction of fluorinated ethylene.[4b]

Drawing inspiration from catalysts in nature,[10] chemists have developed a variety of synthetic small molecule catalysts to replace the traditional, metal-based catalysts in synthetic chemistry.[11] For our present system, it is clear that hydrogen bonds are critical factors for both the reactivity and stereochemistry. This could be further proved by density functional theory (DFT) theoretical studies. The calculated results indicated that the hydrogen bonds between coumarins and (−)-TADDOL played a key role in the formation of the reaction intermediates of coumarin dimerization.

The influence of high vacuum on the reactivity might be attributed to the decrease of the concentration of O$_2$ wrapped in the solid and adsorbed on the surface, which will make the intermediate radical have a long enough lifetime for ring closure to compete with expiration. Maybe high vacuum also has an effect on the reactivity of the inclusion complexes *via* the influence on the intermolecular interactions, however this needs to be further confirmed and elucidated. In addition, from our experimental observation, the reaction pathway was a solid–solid process, which can also be deduced from the enantioselectivity of the products. By virtue of the steering ability of host (−)-TADDOL molecules, the guest coumarin molecules in the crystalline inclusion complexes **1a** are organized with their reactive double bonds separated by 3.42–3.59 Å and parallel to each other,[5a] which is favorable for a topochemical reaction.[12,13] The perfect enantioselectivity of the thermal cycloaddition products should obviously be attributed to the chiral crystal environment and the presence of a rigid pyrone ring.[14]

In conclusion, we have demonstrated the [2 + 2] cycloaddition of coumarin in (−)-TADDOL inclusion complexes under high vacuum and heating conditions, affording *anti* head-to-head dimers in excellent stereoselectivity. Both the high vacuum conditions and the presence of (−)-TADDOL host molecules were found to be essential for this reaction. The formation of radical species has been confirmed with an ESR-spin trapping technique. Accordingly, a stepwise radical mechanism was proposed. With this example, we have illustrated the possibility of switching the reaction pathway from a thermally forbidden

Fig. 2 ESR spectra of the experimental products obtained from heating the mixture of (A) coumarin and PBN (3 : 1), (B) (−)-TADDOL and PBN (3 : 1), (C) complex **1a** and PBN (3 : 1). Experimental conditions: 80 °C, 3.0 × 10^{-4} Pa. PBN was used as the spin trap.

Scheme 2 Proposed reaction pathway for thermal [2 + 2] cycloaddition of coumarin in crystalline inclusion complexes at high vacuum.

concerted process to a highly stereoselective stepwise radical cycloaddition. Further studies on the mechanism and the effects of high vacuum on the crystal complex are in progress.

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