

An Endohedral Simple Enol: The First Isolation of a β -Unsubstituted Simple Enol Utilizing a Lantern-Shaped Molecular Framework

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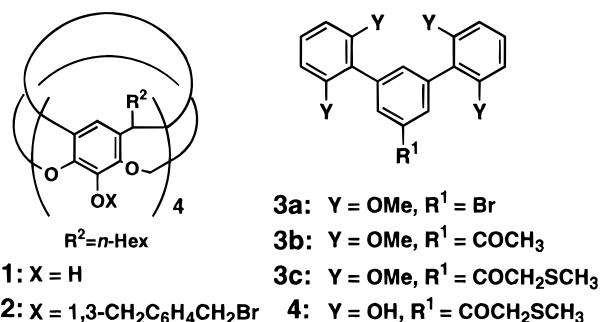
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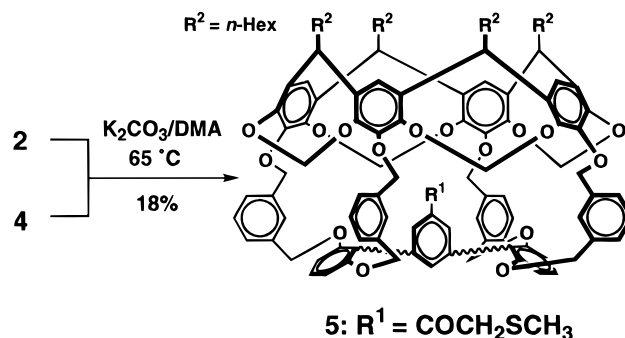
Capsule-shaped macromolecules with a three-dimensional closed-shell sphere have been receiving increasing attention because of their unique ability for molecular recognition as well as the expectation of the development of endohedral chemistry.¹ The application of their endohedral space as a reaction environment with special properties is a major area of current interest and importance. Various types of reactions of guest molecules incorporated in the capsules have been reported² and among them there is the generation of long-lived cyclobutadiene inside a hemicarcerand, which is highly reactive under normal conditions.^{2a} However, these capsule-type molecules have been designed primarily as a container molecule, and they are at a disadvantage with respect to functionalization of the endohedral surface. Recently, we reported the design and synthesis of lantern-shaped molecules which can fix an inwardly-directed functional group in its endohedral space.³ In this Communication, we describe the unique ability of this type of compound as a reaction field as well as a steric protection group.

When a lantern-shaped molecule of this type is applied to stabilization of a highly reactive species, it is expected that a monosubstituted compound of a reactive species can be obtained which otherwise requires more than two bulky groups to be stabilized. Simple enols are one of such species.⁴ It has been reported that small simple enols generated by double-bond migration of allylic alcohols can have a rather long lifetime under rigorously purified aprotic conditions, but they are observable only in dilute solution and cannot be isolated.^{4d} Whereas simple enols bearing more than two bulky aryl groups are sometimes isolable,^{4a–c} there has been no example of the isolation of a monosubstituted compound of this class. Furthermore, all the stable simple enols isolated so far have two substituents in the β -position of the hydroxyl group. In order to estimate the properties of the endohedral space of lantern-

Chart 1



Scheme 1



shaped molecules, we have examined the photochemical reaction of a methylthioacetyl-substituted compound, which is known to generate a simple enol along with thioformaldehyde.⁵ If this reaction occurs in the endohedral space, it is expected to afford a β -unsubstituted simple enol stabilized by the surrounding capsule cage.

A capping unit **2** and a bottom unit **4** were prepared from resorcin[4]arene tetrol **1** and bromide **3a**, respectively (Chart 1). A lantern-shaped molecule **5** bearing a methylthioacetyl substituent was synthesized in 18% yield by the coupling reaction of both units in the presence of potassium carbonate in *N,N*-dimethylacetamide at 65 °C under high dilution conditions (Scheme 1), and its structure was confirmed by ¹H and ¹³C NMR spectra.⁶ We previously reported that there are two isomers (concave (C) and convex (V) ones) for this kind of lantern-shaped molecule (Chart 2), and their structures can be determined by the ¹H NMR chemical shifts of the protons on the R¹ group.³ In compound **5**, the signals of the methylene and methyl protons of the methylthioacetyl substituent were observed at δ 3.79 and 2.19 in CDCl₃ and δ 2.73 and -1.22 in toluene-*d*₈, respectively, indicating that in CDCl₃ **5** takes the C-conformation, where the methylthioacetyl group is located outside the capsule, whereas in toluene-*d*₈ **5** exists as a V-isomer, where the substituent is accommodated in the endohedral space. The structures of **5** in each solution were further supported by the NOE experiments as well as the measurements using shift reagents.⁶ In the present study, all photochemical reactions were carried out in toluene-*d*₈ to estimate the properties of the endohedral space of the lantern-shaped molecule.

The photochemical reactions (400 W medium pressure mercury lamp through Pyrex) and an aqueous filter solution of NiSO₄·CoSO₄ (280–360 nm) of the lantern-shaped molecule

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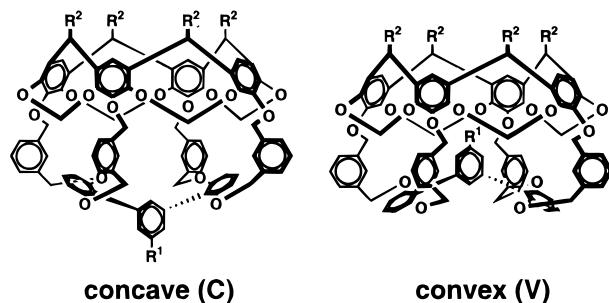
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(6) For the details, see the Supporting Information.

Chart 2



5 were carried out in toluene-*d*₈ in the presence of Danishefsky's diene **6** as a trapping reagent for thioformaldehyde. Monitoring of the reaction by ¹H NMR indicated that **5** was completely consumed within 4 min to afford enol **7**, which was isolated as white crystals in 71% yield by silica gel chromatography.⁷ This is the first isolation of a monosubstituted simple enol as well as of a β-unsubstituted simple enol. The corresponding acetyl derivative **9** (R¹ = COCH₃ in **5**, Scheme 1) was not detected. Thioformaldehyde formed in this reaction was trapped as enone **8**,⁸ which is considered to be derived by the hydrolysis of the Diels–Alder adduct of thioformaldehyde with Danishefsky's diene **6**. As a control experiment, the reaction of **3c** without the capsule framework was carried out under the same conditions. Irradiation of **3c** for 3 h gave the acetyl derivative **3b** in 73% yield with the recovery of **3c** (25%).

The lantern-type enol **7** showed its parent peak in the high-resolution FAB MS. The ¹H NMR measurements established that enol **7** is a V-isomer both in CDCl₃ and toluene-*d*₈, showing no solvent-dependent conformational change such as was observed for **5**. In CDCl₃, two signals due to vinylidene methylene protons of the enol moiety were observed at δ 0.51 and 3.33 with a coupling constant of 2.5 Hz, which agrees with that between geminal protons of olefins. The upfield shift of the methylene protons of enol **7** compared with those of the transient enol of acetophenone measured by the CIDNP method (δ 4.5)⁹ is consistent with the structure of **7** being a V-isomer. In the IR spectra, the OH stretching absorption of enol **7** was observed at 3551 cm⁻¹ in CH₂Cl₂. The OH bands of vinyl alcohol in Ar matrix¹⁰ and the enol of acetone in gas phase¹¹ are reported to be 3625 and 3628 cm⁻¹, respectively, and assigned as the free OH stretching vibration of simple enols. Although the slight low wavenumber shift of ca. 80 cm⁻¹ observed for **7** suggests possible existence of a very weak intramolecular hydrogen bonding with the surrounding ether

(7) **7**: white crystals, mp 163.0–165.0 °C dec; IR (CH₂Cl₂) νOH 3551 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.51 (d, *J* = 2.5 Hz, 1H), 0.87–0.91 (m, 12H), 1.26–1.54 (m, 32H), 2.24–2.27 (m, 8H), 3.33 (d, *J* = 2.5 Hz, 1H), 4.58 (d, *J* = 7.2 Hz, 4H), 4.64 (d, *J* = 12.8 Hz, 4H), 4.71 (t, *J* = 8.1 Hz, 2H), 4.83 (t, *J* = 8.1 Hz, 2H), 4.98–5.10 (m, 14H), 5.54 (d, *J* = 7.2 Hz, 2H), 6.53 (d, *J* = 8.4 Hz, 4H), 6.99 (s, 4H), 7.02 (t, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 7.3 Hz, 4H), 7.16–7.38 (m, 16H). HRMS (FAB) *m/z* 1680.7898, calcd for C₁₀₈H₁₁₂O₁₇ 1680.7900. Anal. Calcd for C₁₀₈H₁₁₂O₁₇·H₂O: C, 76.30; H, 6.76. Found: C, 76.60; H, 7.10.

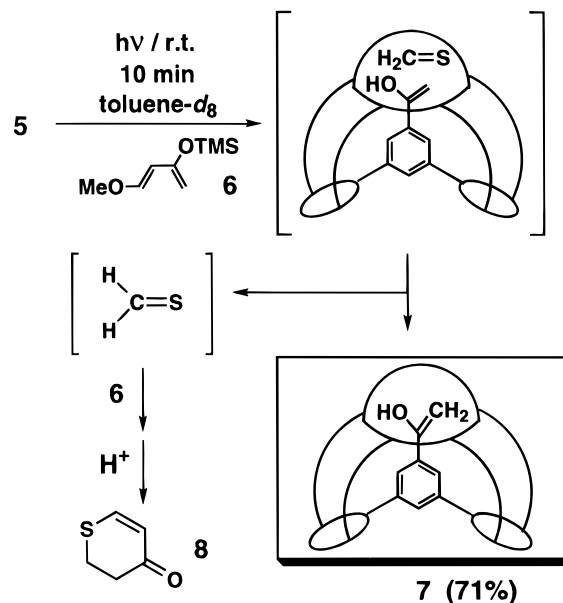
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Scheme 2



oxygens, it is unlikely that this effect is a major factor of the stability of **7**.

The endohedral enol **7** is stable in CDCl₃ at room temperature, and, even in the presence of trifluoroacetic acid, the ketonization to the corresponding acetyl derivative **9** took 3 days. The upfield shift experienced by the methyl protons of the acetyl moiety of **9** (δ 0.02) in comparison with the corresponding *m*-terphenyl **3b** (δ 2.60) indicates that **9** is a V-isomer. The fact that **7** showed such remarkable stability while it finally underwent complete ketonization indicates that thermodynamically the keto form is more stable than the enol form and the high stability of enol **7** originates from the steric protection effect due to the enclosure by the capsule framework. The observation presented here also gives the direct evidence for the occurrence of Norrish type II photocleavage in a β-keto sulfide; an enol is a kinetic product in the reaction, and it tautomerizes to the corresponding ketone, a thermodynamic product.

In summary, we have demonstrated that the capsule cage can provide a unique reaction environment for the endohedral functionality, because its interior is separated from a bulk phase. The lantern-shaped molecular framework has been found to be very effective for the stabilization of a highly reactive species such as a monosubstituted simple enol having two β-hydrogens. The behavior of thioformaldehyde generated in the cage is also of interest, which is currently under investigation.

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Supporting Information Available: An experimental procedure for the synthesis of **5**, physical and spectral data for **5**, **7**, and **9**, and the results of differential NOE and shift reagent experiments for **5** (5 pages). See any current masthead page for ordering and Internet access instructions.

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