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Desilylation-triggered Isomerization of a Molecular Capsule from an Open-type to a Collapsed-type Isomer

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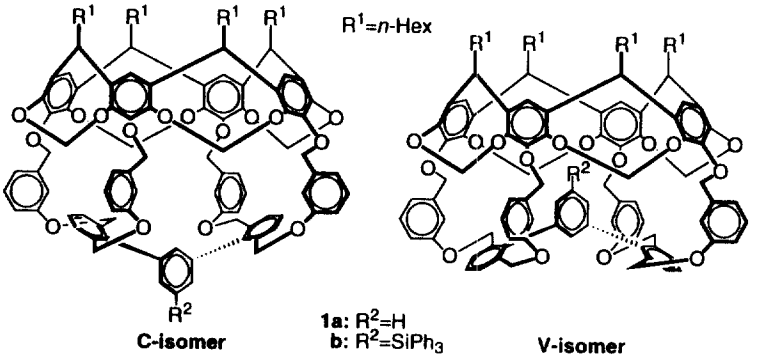
Abstract: Desilylation of a triphenylsilyl-substituted molecular capsule **1b**(C) bearing a large inner space afforded **1a**(C) with similar conformation, which underwent unidirectional and complete isomerization to a thermodynamically more favored isomer **1a**(V) with a collapsed inner space by gentle heating in $CDCl_3$.

Keywords: Carcerands; Deblocking; Isomerization; Kinetics

Whereas capsule-type molecules with various functions have been developed [1], there have been few examples of the molecules which undergo a drastic conformational change in response to the specific external stimulus [2]. If the size and shape of the endohedral space of molecular capsules can be altered by stimulation such as addition of a specific reagent, it will lead to the release of a guest from the host molecule in the responsive way. Recently, we reported the synthesis of capsule-shaped molecules **1**(R^2=H, *t*-Bu, Ph, and 4-*t*-BuC_6H_4) which exist as one of two possible conformational isomers depending on the steric demand of the substituent R^2, that is, a concave (C) isomer with an open-type structure and a convex (V) isomer bearing a rather collapsed inner space [3,4]. In this communication, we describe the flip-type isomerization of the molecular capsule **1a** from the C- to the V-isomer triggered by removal of a "conformationally locking" group.

In the previous paper [3], we reported that the V-isomer of **1** is thermodynamically more



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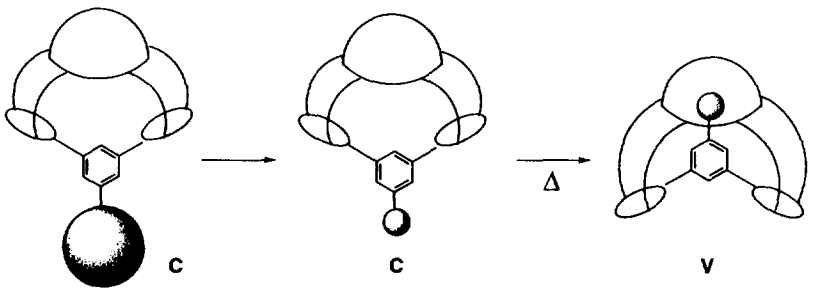
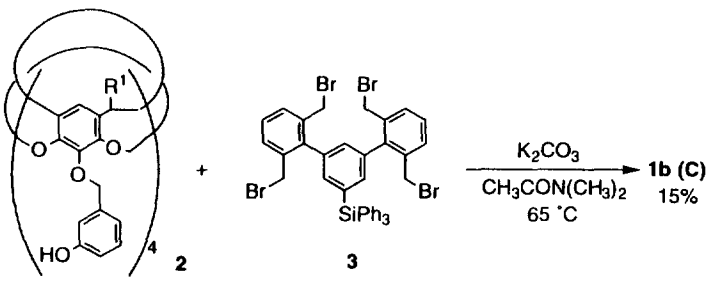
favorable than the corresponding C-isomer except when the substituent R^2 is an extremely bulky one such as a 4-*tert*-butylphenyl group. These findings led us to consider that if a sterically demanding R^2 substituent of the C-isomer is removed, the resulting C-isomer with a small substituent should isomerize to the corresponding V-isomer, which is thermodynamically more favorable (Scheme 1). In this case, the bulky substituent serves as a "conformationally locking" group. Here we employed a triphenylsilyl group as the locking group and desilylation reaction with a fluoride ion as the unlocking reaction to cause flipping of the *m*-terphenyl unit.

Scheme 1



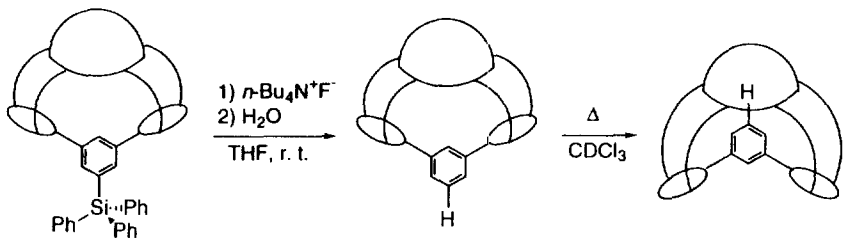
The capsule-shaped molecule **1b** [5] with a triphenylsilyl group was synthesized by coupling reaction of the capping unit **2** and the bottom unit **3** in the presence of potassium carbonate in 15% yield (Scheme 2). The comparison of the ^{1}H NMR spectrum of **1b** with that of the non-capped precursor **3** indicated that **1b** exists exclusively as the C-isomer. For example, signals due to the protons on the triphenylsilyl group of **1b** appeared between 7.17 and 7.58 ppm, almost the same chemical shifts as those for the corresponding protons of **3** (between 7.03 and 7.58 ppm).

Scheme 2



Desilylation reaction of **1b** with tetrabutylammonium fluoride in THF at room temperature afforded **1a** without the R^2 substituent, which was isolated in 88% yield as a 10:1 mixture of the C- and V-isomers after working up and chromatographic purification with careful avoidance of heating (Scheme 3). These isomers **1a**(C) [5] and **1a**(V) showed very different chemical shifts in the ^{1}H NMR spectra. Especially, the R^2 proton of **1a**(C) and **1a**(V) resonated at 7.62 and 6.02 ppm, respectively, in $CDCl_3$. The thermodynamically unfavorable isomer **1a**(C) has never been obtained by the coupling method outlined previously [3]. These results demonstrate that the employment of a removable bulky substituent as a "conformationally locking" group provides a useful strategy to synthesize an unstable conformational isomer.

Scheme 3



1b (C) 1a (C) 1a (V)

Whereas the "unlocked" C-isomer **1a**(C) was found to be conformationally stable at room temperature, upon heating it underwent the unidirectional and complete isomerization to the corresponding V-isomer through the flipping of the *m*-terphenyl unit as expected [6]. The predominant thermal stability of the V-isomer over the C-isomer is also illustrated by the results of the molecular mechanics calculations (Macromodel V6.5 program [7]) for the model compounds of **1a**(C) and **1a**(V) where the hexyl groups attached to the calixresorcarene units are replaced by the methyl groups. The global energy minimum structures of these isomers (Figure 1) were obtained by the MM3* (GB/SA $CHCl_3$) force field [7] with the aid of the low mode conformational search algorithm [8], and it was found that the V-isomer is thermodynamically more stable than the C-isomer by 8.22 kJ mol^{-1}. The lowest energy structure of the C-isomer indicates that one of the aromatic rings of the *m*-terphenyl unit tends to fill the void in the inner phase when the molecule is alone.

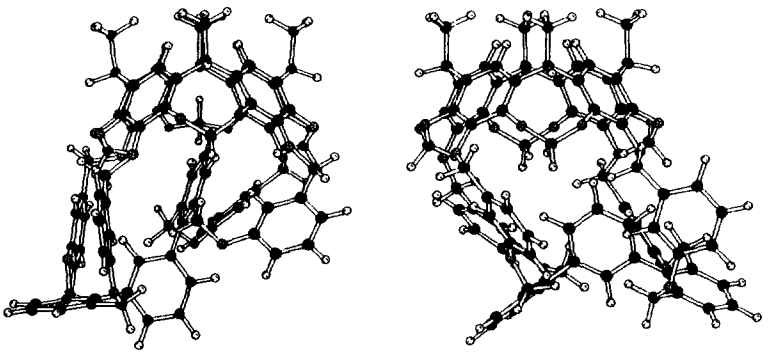


Figure 1.
Lowest energy structures of the model compounds of **1a**(C) (left) and **1a**(V) (right).

The kinetic studies of this thermal isomerization were effected by ^1H NMR measurements in $CDCl_3$. The disappearance and appearance of the signals for the acetal methylene protons at the calixresorcarene units of the C- and V-isomers, respectively, were monitored at four temperatures in the range of 60-110 °C. At each temperature, the data gave a good first-order plot, from which the rate constants were calculated (Table 1). The activation parameters were obtained by use of Arrhenius and Eyring equation as shown in Table 2. This isomerization involves the simultaneous rotation of two biphenyl bonds of the 2,6-dialkyl-3'-arylbiphenyl units. These activation parameters are similar to the reported values for several 2,6,2'-trisubstituted biphenyl derivatives such as 2-carboxy-6-nitro-2'-alkoxybiphenyls [9], indicating that they are hardly affected by the presence of the capping unit. The small negative value of the activation entropy of **1a** is probably due to the decrease in the mobility of the biphenyl moieties at the transition state as is in the case with other 2,6,2'-trisubstituted biphenyls.

Table1.
Rate Constants for the Isomerization of the Capsule-shaped Molecule **1a** in $CDCl_3$

T / K	k ($\times 10^{-4}$ min^{-1})
333	3.30
353	22.8
373	136
383	266

Table2.
Activation Parameters

Ea= 22.6 ± 0.3 kcal mol^{-1}
log$A$ = 26.1± 0.4
$\Delta H^{\ddagger}$ = 21.9 ± 0.4 kcal mol^{-1}
$\Delta S^{\ddagger}$ = - 9.0 ± 1.0 cal K^{-1} mol^{-1}

The CPK model examination indicates that the C-isomer of **1** can incorporate a molecule as large as benzene although its inner space may be self-filled in the absence of a guest molecule. The shape and volume of the inner space of the C- and V-isomers are considerably different from each other, and the isomerization from the C- to V-isomer would cause a drastic change of the complexing ability of the molecule. The desilylation-triggered isomerization of **1a** described here is implicative of a novel way to release a guest molecule from an inner phase of a capsule in response to addition of a specific reagent, a fluoride ion in the present case.

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References and Notes

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[5] **1b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89-0.93 (m, 12H), 1.30-1.46 (m, 32H), 2.12-2.21 (m, 8H), 4.14 (d, J= 7.3 Hz, 2H), 4.21 (d, J= 7.3 Hz, 2H), 4.67-4.72 (m, 4H), 4.85 (d, J= 16.9 Hz, 4H), 4.95 (d, J= 16.9 Hz, 4H), 4.96 (d, J= 12.6 Hz, 4H), 5.10 (d, J= 12.6 Hz, 4H), 5.26 (d, J= 7.3 Hz, 2H), 5.40 (d, J= 7.3 Hz, 2H), 6.70 (d, J= 7.8 Hz, 4H), 6.77 (s, 4H), 6.87 (s, 4H), 6.90 (d, J= 7.8 Hz, 4H), 7.17-7.24 (m, 10H), 7.39-7.47 (m, 11H), 7.56-7.58 (m, 7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.04 (q), 14.05 (q), 22.63 (t), 27.85 (t), 27.91 (t), 29.40 (t), 29.49 (t), 29.52 (t), 29.89 (t), 31.83 (t), 31.88 (t), 36.82 (d), 36.91 (d), 68.80 (t), 72.06 (t), 98.54 (t), 98.75 (t), 109.16 (d), 114.35 (d), 116.20 (d), 117.33 (d), 125.27 (d), 126.82 (d), 128.20 (d), 129.23 (d), 129.96 (d), 130.22 (d), 133.34 (s), 135.77 (s), 136.06 (d), 136.28 (d), 136.44 (s), 137.85 (s), 138.13 (s), 139.07 (s), 139.21 (s), 140.27 (s), 143.47 (s), 148.09 (s), 148.13 (s) 159.81 (s). **1a**(C): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89-0.93 (m, 12H), 1.25-1.45 (m, 32H), 2.14-2.19 (m, 8H), 4.13 (d, J= 7.2 Hz, 2H), 4.23 (d, J= 7.0 Hz, 2H), 4.67-4.72 (m, 4H), 4.81 (d, J= 16.2 Hz, 4H), 4.95-4.99 (m, 8H), 5.10 (d, J= 12.8 Hz, 4H), 5.30 (d, J= 7.0 Hz, 2H), 5.39 (d, J= 7.2 Hz, 2H), 6.69 (d, J= 7.3 Hz, 4H), 6.77 (s, 4H), 6.88 (s, 4H), 6.89 (d, J= 7.3 Hz, 4H), 7.17-7.25 (m, 12H), 7.50 (s, 1H), 7.62 (t, J= 7.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.04 (q), 14.05 (q), 22.64 (t), 27.86 (t), 27.91 (t), 29.38 (t), 29.50 (t), 29.52 (t), 29.92 (t), 31.83 (t), 31.89 (t), 36.83 (d), 36.92 (d), 68.55 (t), 72.01 (t), 98.51 (t), 98.75 (t), 108.89 (d), 114.40 (d), 116.08 (d), 117.25 (d), 125.15 (d), 126.88 (d), 128.43 (d), 128.82 (d), 129.20 (d), 130.56 (d), 136.37 (s), 138.55 (s), 139.07 (s), 139.23 (s), 139.37 (s), 140.28 (s), 143.47 (s), 148.15 (s), 148.21 (s), 159.83 (s).

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