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A 'sugar-coated' carbene precursor: a single crystal X-ray diffraction and NMR study†

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Abstract

For the first time, the inclusion complex of any diazirine with a cyclodextrin was studied by single crystal X-ray diffraction. This and 2D NMR spectroscopy were employed to elucidate the structure in both the solid state and solution. An opposite orientation of the guest inside the host molecule was revealed. Moreover, crystallization of the neat guest enabled the first X-ray diffraction of a dialkyl-substituted diazirine. © 2000 Published by Elsevier Science Ltd.

Solid state reactions within crystals or confined spaces often differ remarkably from corresponding reactions in solution by surpassing them in selectivity, yield, and ease of workup.[1] It has been shown lately, that upon inclusion of diazirines into cyclodextrins the chiroptical properties of an inherently achiral carbene precursor[2] as well as its reactivity can be altered dramatically.[3] Furthermore, it has been demonstrated in a model system that it is feasible to exploit the encapsulation of a diazirine by generating carbenes that react chemospecifically to monofunctionalize cyclodextrin hosts in the solid state[4] and in solution.[4,5] Monofunctionalized cyclodextrins possess interesting properties for chiral discrimination and as enzyme mimics.[6] To understand and control the selectivity of photochemical reactions and to further develop selective systems, intimate knowledge of the arrangement and structure of the supramolecular aggregates has to be obtained. Toward this end, the structure of 2-azi-5-hydroxyadamantane[7] (**1**) and its inclusion complex (**1**@**7-Cy**) with β-cyclodextrin (**7-Cy**) have been studied in the crystal state as well as in aqueous solution. To our knowledge, only four diazirines have been examined by single crystal X-ray diffraction analysis.[8] These diazirines, however, bear either a heteroatom or an aromatic moiety attached to the three-membered ring and, therefore, do not reflect accurately the structural and electronic properties of the adamantyl system. Though the parent 2-aziadamantane

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† Dedicated to our colleague Dr. Andreas Werner, who was killed in a motorcycle accident.

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has been studied thoroughly spectroscopically and theoretically,[9] experimental verification of the geometry is still lacking. This issue is the first to be addressed in this communication.

Due to the rigidity of the adamantane skeleton, the OH substituent should not have a pronounced effect on the geometry of the diazirine. Geometry optimization of **1** and of 2-aziadamantane at the RHF/6-31G* level of theory yields the same dimensions for the diazirine ring.[10] Therefore, it is reasonable to compare the structure of **1** with the unsubstituted system. The results of X-ray diffraction analysis of diazirine of **1**[11] as well as theoretical data for 2-aziadamantane (taken from Ref. 9a), are listed in Table 1.

Table 1
Calculated geometry of 2-aziadamantane and theoretical and experimental data of **1**

	r (N=N)/Å	r (C-N)/ Å	θ (N-C-N)/ °
RHF/6-31G*[9a]	1.203	1.441	49.4
1 RHF/6-31G*	1.203	1.441	49.4
1 experimental	1.239(0.0015)	1.474(0.0014)	49.69(0.07)

Supramolecular inclusion does not seem to affect the geometry of the diazirine.[12] Unfortunately, the nitrogen atom positions inside the cyclodextrin cavity are too diffuse to allow for monitoring of small changes induced by complexation.[13]

1@7-Cy crystallizes in a 2:2 stoichiometry with two cyclodextrin molecules facing each other via their wider apertures (Fig. 1).[14] The cages thus formed can accommodate two adamantyl guests. The dimeric units crystallize in a chessboard arrangement[15] forming slightly distorted bilayers. Two molecules of **1** face each other at a distance of approximately 11 Å with the diazirine rings well inside the cavity of the cyclodextrins. The adamantyl OH–hydrogen binds to one O6–H on the outside of the narrower rim of a cyclodextrin in the next layer of dimers at a distance of 2.75 Å. Therefore, this hydrogen bond participates in the tail-to-tail arrangement between the cyclodextrin bilayers.

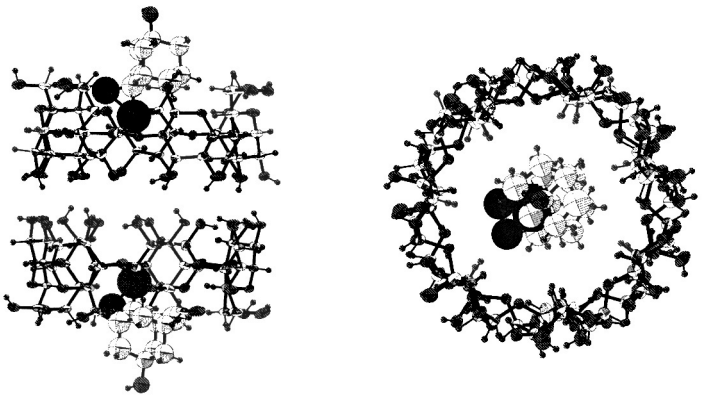

Figure 1. Single crystal X-ray structure of **1@7-Cy**. View along (right) and through (left) the cyclodextrin dimer

The arrangement in solution was determined by 2D rotating-frame Overhauser effect spectroscopy (ROESY) in D_2O.[16] The observed crosspeaks between the adamantyl protons and the cyclodextrin's inner protons, H-3 and H-5, reveal an encapsulation of **1** inside the hydrophobic cavity of **7-Cy**. The intermolecular NOE of the cyclodextrin's inner protons, H-3 and H-5, by the adamantane's CH_a (next to the diazirine ring) and CH_2 signals is stronger upon H-3 (3.81 ppm) than H-5 (3.74 ppm) in all cases.[17] No enhancement was observed for **7-Cy**'s CH_2-6 at 3.83 ppm. This clearly shows that the adamantane moiety is located at the wider opening of the toroidal-shaped host molecule. No crosspeak can be detected between H_f and the cyclodextrin's H-5. The inner protons H-3 and H-5 experience an upfield shift of 0.12 and 0.07 ppm, respectively. This shift can be attributed to the anisotropy of the diazirine's N–N double bond. The proposed arrangement of **1@7-Cy** in solution is consistent with these findings (Fig. 2).

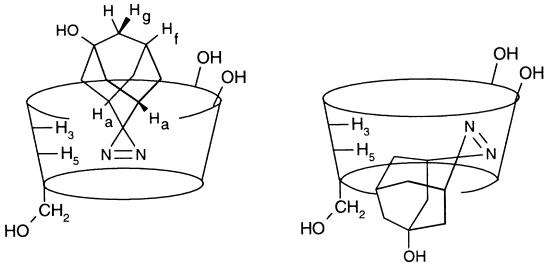

Figure 2. Proposed arrangement of **1@7-Cy** in solution as determined by NMR spectroscopy (left) and in the solid state (right)

The observed switch of orientation is a rare phenomenon[18,19] and can be explained by the different effects of the hydrogen bond in solution and in the solid state. In solution, the complex formation is driven by entropic factors and unspecific hydrophobic interactions between the apolar cavity of the cyclodextrin and the hydrocarbon skeleton bearing the apolar diazirine function.[20] Presumably, the adamantyl OH stays solvated and does not enter the apolar cavity of the host. In contrast, the arrangement in the solid state indicates that hydrogen bond formation between the adamantyl OH and the cyclodextrin's O6–H, providing approximately –6 kcal mol^{-1} per interaction,[21] becomes the structure-determining factor for the orientation of the guest inside the crystal. The adamantyl OH–hydrogen bond probably accounts for both the complexation of the guest at the primary side of the cyclodextrin and the chessboard arrangement of the cyclodextrin dimers. These factors govern the inclusion mode of the guest within the host and are consistent with the different forces involved in solution and in the solid state.[18,22] The observed structural findings are expected to provide an enhanced understanding for the design of chemoselective systems for the innermolecular[23] photochemistry of cyclodextrin complexes with diazirines.

Supplementary material: The single crystal X-ray data files have been deposited at the Cambridge Crystallography Data Centre, Cambridge, UK, as structures CCDC 137063 and CCDC 137064.

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11. Crystal data for $C_{10}H_{14}N_2O$ (**1**): $M = 178.\ 24$, monoclinic, $a = 15.480(3)$ Å, $b = 6.770(1)$ Å, $c = 11.060(3)$ Å, $\beta = 91.87(3)^\circ$, $V = 1786.9(5)$ Å^3, $T = 110$ K, space group $P\ 2/n$, $Z = 8$, μ(Mo-K) = 0.09 mm^{-1}, 4444 unique reflections. Least-squares refinement (G. M. Sheldrick, SHELX97, Program for the Refinement of Crystal Structures, University of Göttingen, Germany, 1997) on F^2 of 375 parameters converged to a final $R_1 = 0.041$ for 3709 $Fo > 4\ \sigma(Fo)$ (0.051 for all 4444 data) and a $wR_2 = 0.103$. Hydrogen atoms were treated isotropically. The final difference electron density map showed $\sigma_{max} = 0.35$ eÅ^{-3} and $\sigma_{min} = -0.20$ eÅ^{-3} values. The data of the fully occupied positions were chosen.
12. The forces involved in complexation are usually too weak to seriously change the geometry of rigid systems. See Ref. (20a).
13. The diazirine function proved to be very diffuse. The most probable maxima of residual electron densities show an N=N bond length of 1.28 Å and an N–C–N angle of 50.7°, these positions, however, cannot be refined reliably.
14. Crystal data for $C_{42}H_{70}O_{35}{\cdot}C_{10}H_{14}N_2O{\cdot}nH_2O$, $n = 10$–11 (**1@7-Cy**): $M = 1312.52$ (without crystal water), orthorhombic, $a = 19.144(2)$ Å, $b = 23.950(3)$ Å, $c = 32.670(3)$ Å, $V = 14979(3)$ Å^3, $T = 110$ K, space group $C222_1$, $Z = 8$, μ(Mo-K) = 0.119 mm^{-1}, 16776 unique reflections. The atomic arrangement of cyclodextrin was used as starting model in the refinement. The guest molecule was obtained by subsequent differential Fourier synthesis. Least-squares refinement (G. M. Sheldrick, SHELX97, Program for the Refinement of Crystal Structures, University of Göttingen, Germany, 1997) on F^2 of 893 parameters converged to a final $R_1 = 0.11$ for 10671 $Fo > 4\ \sigma(Fo)$ (0.16 for all 16776 data) and a $wR_2 = 0.31$. Hydrogen atoms were introduced using stereochemical restrictions. The hydrogen atoms of crystal water were not determined. The final difference electron density map showed $\sigma_{max} = 1.34$ eÅ^{-3} and $\sigma_{min} = -0.53$ eÅ^{-3} values.
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17. In addition, the weak crosspeaks between H_g and H_3 and H_5, respectively, give rise to the assumption that more than one arrangement is observed. One where the diazirine ring and the adamantyl OH are both located near the secondary OH groups on top of the wider rim, and one, though unlikely, where the OH group is located inside the cyclodextrin cavity. Both arrangements would put H_g in very close proximity to the inner cyclodextrin protons,

H-3 and H-5, and could account for the observed crosspeaks. However, the complete absence of a crosspeak between H_f and H-5, which should be observed if these structures were major contributors, suggests their unlikelihood.

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