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Evidences of Strong C−H····O Bond in an *o*-Carboranyl *β*-Lactoside in Solution

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The existence of short intermolecular C−H····O interactions has been established since the early 1960s for several molecules though IR[1] and X-ray crystallography.[2,3] Following these observations a variety of theoretical studies, based on semiempirical and ab initio molecular orbital approaches, have been reported for a series of C−H····X (X = O, N, Cl, F, P, S) hydrogen bonds.[4,5] Recently, a role for C−H····O bonds in stabilizing cohesive forces within biological macromolecules has been proposed.[6−8]

This unusual interaction has therefore a great interest. However, very few experimental evidences have been found for the presence of C−H····O bonds in solution.[9,10] In this study we found a strong intramolecular C−H····O bond in lactosyoxymethyl-*o*-carborane (LCOB, Chart 1),[11,12] a potential agent for boron neutron capture therapy (BNCT),[13] by using NMR spectroscopy. In particular, results showed that the interaction took place between the activated C_2−H of the carboranyl cage[14] and the anomeric oxygen of the glucose ring of lactose (O_1'). This hypothesis was confirmed by ab intio quantum mechanical calculations.

Chart 1. Structure and Numbering of Lactosyoxymethyl-*o*-carborane[15] and 1′-Deoxy-*o*-carboranyl *β*-C-glucoside

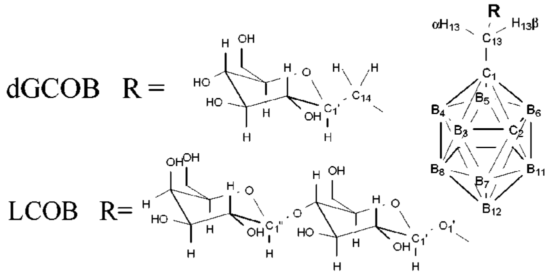

Figure 1 shows the $^1H\{^{11}B\}$ NOESY spectrum in the region containing the cross-peaks between $H_{13\alpha,\beta}$ and the protons linked to the boron atoms of the cage (H−B). From the analysis of the peak position and from their relative intensity, it was possible to establish an unexpected absence of isocronicity in the carborane cage. In particular, the large $H_{3/6}$ signal in the 1D projection shown on top of Figure 1, was the superposition of two different peaks, separated by about 10 Hz, and this allowed us to extract important structural information.

As it can be seen by the cross-peaks labeled with A and B, which are not aligned in the F_2 dimension, each of the two diastereotopic proton $H_{13\alpha}$ and $H_{13\beta}$ was connected only to one of the two partially superposed peaks $H_{3/6}$. This strongly indicated that the C_1−C_{13} bond did not freely rotate. Free rotation, should result in two broader cross-peaks, resonating at identical chemical shift, as it happened in the case of peak C. This peak showed an apparent symmetry because H_2 is bound to the C_2 carborane vertex, which is exactly in the middle between H_3 and H_6 (Figure 2). In addition, the lack of coupling between H_2 and $H_{13\alpha}$/$H_{13\beta}$ (Supporting Information) and the different intensity between peaks A and B, confirmed that the molecule was in a preferred conformation due to the restricted degree of freedom of the C_1−C_{13} bond.

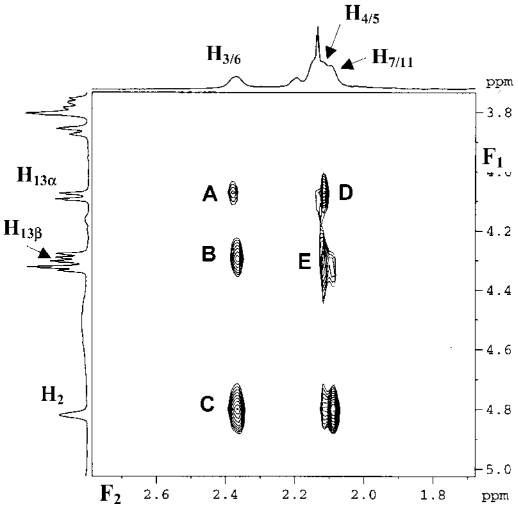

Figure 1. $^1H\{^{11}B\}$ NOESY spectrum of LCOB 2×10^{-2} M in C_2D_5OD, recorded at 600 MHz and 303 K. Region of the H−B to H_2, $H_{13\alpha}$, and $H_{13\beta}$ protons.

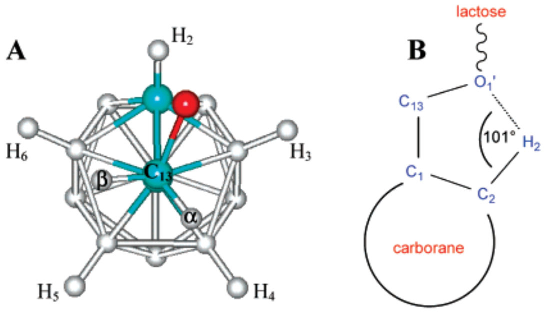

Figure 2. (A) View of carboranyl cage along C_{13}−C_1 bond of GCOB model optimized by ab initio calculation. Protons $H_{13\alpha}$ and $H_{13\beta}$ are indicated as α and *β*, respectively. Glucosyl portion is omitted for clarity. (B) Sketch of five member ring in which the proposed H-bond is involved.

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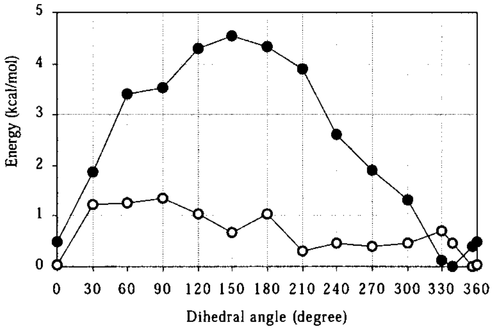

Figure 3. Torsional energy profile of C_1-C_{13} bond for GCOB (filled circles) and dGCOB (unfilled circles).

A similar behavior was observed for the NOESY cross-peaks between $H_{13\alpha,\beta}$ and the $H_{4/5}$ protons (peaks D and E in Figure 1).

All of the above observations could not be explained on the sole basis of steric hindrance due to the cage substituents, and it was necessary to assume the formation of a strong H-bond between the activated C_2H and the O_1' atoms. To verify this hypothesis we performed comparative NMR experiments on the 1′-deoxy-*o*-carboranyl *β*-C-glucoside (dGCOB) (Supporting Information). The substantial difference between LCOB and dGCOB, in the interesting portion of the molecule, is the substitution of O_1' with CH_2. The two molecules show very similar structures, but obviously, they have different electronic properties in the acceptor group of the H-bond.

With these experiments we found: (i) the chemical shift of the H_2 resonating at 0.26 ppm upfield with respect to the same proton of a LCOB. A comparative analysis of H_2 high-field shift with the one of the cage H−B protons (0.04−0.06 ppm), strongly suggests that a major contribution of the deshielding of H_2 in LCOB was caused by the formation of a specific intramolecular CH−O interaction; (ii) the NOESY spectrum of dGCOB clearly showed two equivalent cross-peaks ($H_2-H_{13\alpha}$ and $H_2-H_{13\beta}$) that were absent for the LCOB. This indicated that, contrary to LCOB, the two H_{13} diastereotopic protons experienced a close contact with H_2 and suggested that in the dGCOB molecule the O1′ atom was not forced in the CH····O bond orientation.

The fact of having observed a C−H····O bond in solution at temperature as high as 303 K implies that this intramolecular interaction should be remarkably strong. To verify its strength we performed ab initio quantum mechanical calculations on two different simplified models. One was the glucosyl-carborane (GCOB) which differs from LCOB by the lack of the distal sugar (galactose), and the other was the dGCOB.

Torsional driving analysis was performed first by optimizing the molecule at B3LYP/6-31G** level, and then calculating the single-point energy, by rotating the $C_2-C_1-C_{13}-O_1'$ dihedral angle ($C_2-C_1-C_{13}-C_{14}$ in the deoxy molecule) trough steps of 30°.[16] In Figure 3 the two torsional energy profiles, for GCOB and dGCOB are reported. These curves demonstrated that the C−H····O interaction gave a major contribute to the structure rigidity. The highest energy value was calculated for a dihedral angle (150°) in which the C_2-H pointed toward the opposite side with respect to O_1'. The theoretical value of the C−H····O bond strength could be obtained by the difference between the energy calculated for GCOB and dGCOB at 150°. This operation allowed us to remove all contributions to the total energy due to steric hindrance. The value obtained, 3.87 kcal/mol, is among the highest calculated for this kind of interaction,[5] is well above the value of about 1−2 kcal/mol which is generally accepted,[17] and could explain its persistence in solution.

With this conformation the $H_{13\alpha}-H_3$ (r_A) and $H_{13\beta}-H_6$ (r_B) distances were found to be 3.15 and 2.60 Å, respectively. These values were consistent with the different intensities, I_A and I_B, of the corresponding NOESY cross-peaks (peaks A and B in Figure 1).[18] In this optimized model, the C_2····O_1' distance was found to be 2.81 Å (H_2····O_1' distance = 2.43 Å), that is well below the sum of the respective VdW radii (3.30 Å) and in perfect agreement with the hypothesis of a H-bond formation.

The geometry of the five-member $H_2-C_2-C_1-C_{13}-O_{1'}$ ring is illustrated in Figure 2b. The bent C_2-H····$O_{1'}$ angle (101°) is to be considered rather unusual for these types of interactions, that are known to exhibit some directional requirements. However, in some cases geometrical arrangements similar to the one found for LCOB in the present study have been reported.[19] For instance, a five-member cycle containing an intramolecular CHO bond was proposed in the gas phase.[20] It is important to note that almost all the cases reported in the literature deal with intermolecular interactions in the solid state. In the present case, in which an intramolecular interaction occurs, entropic factors may be also critical to induce the formation of a hydrogen bond which appreciably deviates from the linear arrangement.

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Supporting Information Available: (1) $^1H\{^{11}B\}$ NOESY spectrum of LCOB in C_2D_5OD. Region of the H_2 to $H_{13\alpha}$ and $H_{13\beta}$ protons. (2) Models used for ab intio calculations. (3) Torsional energy profile of the C_1-C_{13} bond for 2-Methyl-GCOB. (4) Superposition of $^1H\{^{11}B\}$ spectra of LCOB and dGCOB. (5) ^1H NOESY spectrum of dGCOB in C_2D_5OD. Region of the H_2 to $H_{13\alpha}$ and $H_{13\beta}$ protons. (6) Superposition of $^1H\{^{11}B\}$ spectra of GCOB and dGCOB in $CDCl_3$ (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Allerhand, A.; von Ragué Schleyer, P. *J. Am. Chem. Soc.* **1963**, *85*, 1715.
(2) Sutor, D. J. *J. Chem. Soc.* **1963**, 1105.
(3) Berkovitch-Yellin; Leiserowitz, L. *Acta Crystallogr. B* **1984**, *40*, 159.
(4) Hartmann, M.; Wetmore, D. S.; Radom, L. *J. Phys. Chem. A* **2001**, *105*, 4470.
(5) Gu, Y.; Kar, T.; Scheiner, S. *J. Am. Chem. Soc.* **1999**, *121*, 9411.
(6) Musah, R. A.; Jensen, G. M.; Rosenfeld, R. J.; McRee, D. E.; Goodin, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 9083.
(7) Wahl, M. C.; Rao, S. T.; Jundaoahngam, M. *Nat. Struct. Biol.* **1996**, *3*, 24.
(8) Leroy, J.-L.; Snoussi, K.; Guéron, M. *Magn. Reson. Chem.* **2001**, *39*, 171.
(9) Mizuno, K.; Ochi, T.; Shindo, Y. *J. Chem. Phys.* **1998**, *109*, 9502.
(10) De Jong, P. H. K.; Wilson, J. E.; Nailson, G. N.; Buckingham, A. D. *Mol. Phys.* **1997**, *91*, 99.
(11) Tietze, L. F.; Bothe, U. *Chem. Eur. J.* **1998**, *4*, 1179−1183.
(12) Giovenzana, G. B.; Lay, L.; Monti, D.; Palmisano, G.; Panza, L. *Tetrahedron* **1999**, *55*, 14123.
(13) Tietze, L. F.; Bothe, U.; Griesbach, U.; Nakaichi, M.; Hasegawa, T.; Nakamura, H.; Yamamoto, Y. *Bioorg. Med. Chem.* **2001,** *9*, 1747.
(14) Godfrey, P. D.; Grigsby, W. J.; Nichols, P. J.; Raston, C. L. *J. Am. Chem. Soc.* **1997**, *119*, 9283.
(15) For the sake of clarity, labels are reported only for anomeric carbons and O_1' of lactose. Protons of the carboranil cage are omitted.
(16) Ab initio calculations were carried out using: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.
(17) Steiner, T. *Chem. Commun.* **1997**, 727.
(18) The NOESY cross-peak intensities were obtained by using SPARKY program: T. D. Goddard and D. G. Kneller, *SPARKY 3*, University of California, San Francisco, 2001.
(19) Steiner, T.; Saenger, W. *J. Am. Chem. Soc.* **1992**, *114*, 10146.
(20) Fujii, A.; Fujiimaki, E.; Ebata, T.; Mikami, N. *J. Am. Chem. Soc.* **1998**, *120*, 13256.

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