

Characterization of Persistent Intramolecular C-H...X(N,O) Bonds in Solid State and Solution

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Abstract: The formation of intramolecular CH...X(N,O) bonds and their persistence in solution were studied by X-ray crystallography and NMR techniques in two different rotamers of a molecule containing the *ortho*-carborane cage, an amide group and a quinoline ring. Experimental data were confirmed by theoretical ab initio calculations.

From the resolved structure of the two forms of this potentially active drug for boron neutron capture therapy, accurate bonding and geometric parameters were extracted for this non-classic hydrogen interaction, and their strength was calculated. These findings provided new insight in the theory of CH...X bonds, which appear stronger and less rare than it was previously thought.

Keywords: ab initio calculations · BNCT · carborane · hydrogen bonds · NMR spectroscopy

Introduction

The existence, persistence in solution, and chemical properties of unusual hydrogen bonds have recently emerged as a subject of intense debate,^[1] reflecting the strong interest of this topic, both for the theory of chemical bonding and for its applications in several fields. Despite the fact that the complex between chloroform and acetone was explained by a Cl₃CH...OC(CH₃)₂ interaction since 1937,^[2] the first experimental observations of C-H...X (X=N,O,Cl) bonds in crystals, were proposed in the early 1960.^[3] In the same period Allerhand and co-workers,^[4] on the basis of spectroscopic evidences, stated that multiple withdrawing groups attached

to a sp³-hybridised carbon, should be the necessary condition to make the carbon atom a proton donor. At that time they also envisaged that the C-H group could have a wide range of proton-donor abilities, but despite their intriguing speculation, research in this field was neglected in the following years. One of the reasons for this fact could be the limited range of molecules in which such interaction was recognised.

Recently, a renewed interest in this topic arose, on the track of new horizons in structural chemistry,^[5] supramolecular chemistry,^[6] and biochemistry.^[7] Moreover, new experimental techniques and refinement of theoretical calculations allowed a more accurate description of this subtle interaction.^[8,9] Several X-ray diffraction studies on different kinds of molecules have shown a C-H donor group, which has been recognised to be involved in weak intermolecular C-H...X bonds in solid. Quantum mechanic ab initio methods were used to calculate bond energy and geometrical parameters and, recently, a few studies have reported that CH...O bonds can persist in solution, thus driving the structural properties of molecules with biological and pharmaceutical interest.^[10,11]

Another interesting feature of the CH...X interaction, which recently has polarised the attention of chemists, is that the C-H bond itself is strengthened by complexation. This phenomenon, which has been observed experimentally in several systems, is known as *blue-shifting* or *improper hydrogen bonding* and is the subject of widespread debate for its implication in the general bond theory.^[12]

In the present paper we describe the behaviour of a C-H donor included in the icosahedral cage of a 1,2-dicarba-

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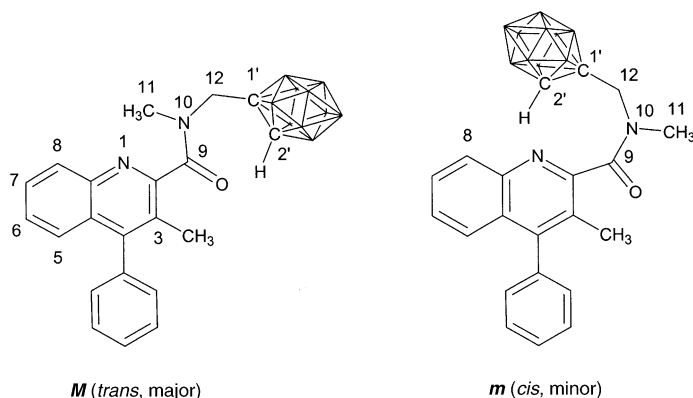
closo-dodecaboran-1-yl derivative, which could be considered as an element of a new generation of carborane compounds, designed to explore an alternative mechanism of action for boron neutron capture therapy (BNCT).^[13] In this molecule the CH enclosed in the cage (which presents H-donor behaviour) can form intramolecular C-H...O bond and C-H...N bonds, both of which surprisingly persist in solution. NMR data showed that the conformation with the C-H...O interaction was favoured, even if additional factors, such as steric hindrance, are co-responsible for this behaviour. X-ray crystallography, and ab initio calculations confirmed this finding.

In a very recent work by Fox and co-workers^[14] the persistence in solution of an intramolecular CH...N bond (closing a five-membered ring) has been proposed on the basis of ¹H NMR chemical shift measurement.

In this paper we were able to establish unambiguously that the intramolecular CH...N bond can persist in solution in a system where the hydrogen bond is enclosed in a eight-membered ring. In this case entropic factors are less effective. Our arguments were based on 1D- and 2D-NMR experiments, and on quantum mechanical calculations. The results thus obtained allowed to extract accurate geometrical parameters for the proposed conformations, and to calculate the energy involved in both the hydrogen bonds.

Experimental Section

Details on the synthesis of the carboranyl compound *N*-[1,2-dicarba-*closo*-dodecaboran(12)-1-ylmethyl]-*N*,3-dimethyl-4-phenylquinoline-2-carboxamide (DDQC, Scheme 1), are reported elsewhere.^[13]



Scheme 1. Structure and numbering for the two rotamers of DDQC. The carborane and aromatic protons were omitted for clarity, with the exception of H₂' which was relevant for discussion.

NMR methods: The NMR samples were prepared by dissolving DDQC in CDCl₃ (5 mm). NMR experiments were performed with a Bruker DRX-600 AVANCE spectrometer, equipped with a xyz gradient unit, operating at 600.13, 150.89, and 192.50 MHz for ¹H, ¹³C and ¹¹B, respectively. NOESY^[15] and DQF-COSY^[16] spectra were acquired with 2048 complex points for 256 experiments with 8 s recycle, and TPPI phase cycle.^[17] A squared-sine window function was obtained in both dimensions for every set of data and zero filling to 1024 points was applied along F1. ¹¹B decoupling was applied using a Waltz-16 sequence. For NOESY spectra,

mixing time of 200, 400 and 800 ms were used. NMR data were processed by using the NMRpipe^[18] software (version 3.3), and 2D spectra were analysed with the SPARKY software.^[19] Integration of the cross-peak volumes in the NOESY spectrum was carried out with the Gaussian-fitting algorithm of SPARKY. Calculation of inter-proton distances was done by using the isolated spin pair approximation under the assumption of a unique correlation time. For this calculation the intensities of the NOESY cross-peaks for both major and minor species were normalised to 100%.

Theoretical calculations: Standard ab initio calculations, were performed with the Gaussian98 package^[20] implemented on a parallel SGI ORIGIN 3000. For the *trans* starting model we used the coordinates of the crystal structure. The *cis* conformation was derived from the *trans* one by rotating the C₉-N₁₀ amide bond through 180° with the MacroModel 5.0 package.^[21] To shorten calculation time, both models were simplified by removing the pendent phenyl ring. Geometry optimisation was performed at RHF/6-31G** level. The optimised structure was used as a starting model for the torsional driving analysis of the C₁'-C₁₂ bond. The N₁₀-C₁₂-C₁'-C₂' dihedral angle was rotated through steps of 30° and single point energy calculations were performed after each rotation.

A single crystal of DDQC was submitted for X-ray data collection on a Siemens P4 four-circle diffractometer with graphite monochromated MoK_α radiation (λ = 0.71069 Å). The ω/2θ scan technique was used. The structures were solved by direct methods and refinements were carried out by full-matrix anisotropic least-squares of F² against all reflections. Hydrogen atoms were located on the Fourier difference maps, or placed in the calculated positions and included in the structure-factor calculations with isotropic temperature factor. Atomic scattering factors including f' and f'' were taken from ref. [22]. Structure solution was carried out by SHELXS-97^[23]. Structure refinement and molecular graphics were performed by SHELXL-97^[24] and the WinGX package, respectively. Crystallographic data of DDQC have been deposited to the Cambridge Crystallographic Data Centre.

CCDC-221809 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk).

Results and Discussion

The structure and numbering for the two rotamers of the molecule presented in this paper are reported in Scheme 1. With respect to a similar compound studied in previous works,^[9,10,14] the presence of an amide group in DDQC confers interesting stereochemical properties to this molecule. It also gives the possibility of studying the behaviour of the atoms involved in this biologically relevant group as C-H...X bond acceptors.

Crystal structure of DDQC: The ORTEP^[25] drawing of the crystal structure of DDQC is shown in Figure 1. In the crystal only the DDQC_{*trans*} rotamer was observed. The pendent phenyl and amide groups were found to be almost perpendicular to the quinoline ring with dihedral angles of 78.1(1) and 74.6(1)°, respectively. This rather unusual orientation was due to the steric hindrance introduced by the *ortho*-methyl group. But the most interesting feature was the close contact between the C₂' and the O₉, which demonstrated the presence of a C-H...O bond between them, with consequent formation of a seven-membered ring. The experimental distances between the donor C₂' and the acceptor O₉ and between the H₂' and O₉ were 3.12 and 2.18 Å, respectively, with a bond angle (φ) of 139.4°. Following the notation of

Taylor and Kennard,^[26] the value of d , which is the difference between the sum of the van der Waals radii of H₂' and O₉ and the experimental distance between them, is 0.52 Å. For this calculation VdW radii for H and O atoms were considered 1.2 and 1.5 Å, respectively. The angle θ , which measures the displacement of H involved in the bond from the carbonyl plane, was found 41.6°. These geometrical features can be useful to define the directionality requirement, that is important to characterise the forces involved in this type of bond.

Intramolecular short contacts must be considered more carefully than intermolecular ones, because of possible internal constraints. In fact, all previous studies, based on the analysis of CH...X properties in crystals,^[21,22,27] mainly consider intermolecular contacts. It is also important to note that, notwithstanding the different frame in which inter- and intramolecular C-H...O bonds occur, the mechanism of their formation and the forces involved must be the same.

When dealing with molecules in solution, a more accurate investigation of intramolecular CH...X bond becomes mandatory. In fact, if for the crystal structures the limiting factor for a correct analysis is the occurrence of internal constraints, the presence of the solvent molecules in solution usually becomes an overwhelming barrier for the formation of weak CH...X intermolecular bonds. Moreover, solvents having hydrogen-acceptor capabilities may generate a competition toward the activated CH donor.

Taylor and Kennard and, later, Steiner, have performed thorough statistical analyses on a large number of crystal structures present in the Cambridge Crystallographic Data Centre. They found that inter- and intramolecular short contact C-H...O interactions are rather common in the solid state, most of them presenting d values in the range 0.35–0.45 Å. Only in three cases, distances shorter than 2.18 Å

are observed. Two of them are intermolecular contacts with bond angle (ϕ) approaching linearity (170.9 and 176.7°) while the third is an intramolecular contact with $\phi=155.7^\circ$. These values support the hypothesis of a predominant electrostatic mechanism, driving the geometry of the hydrogen bond in such short contacts. In fact, the shorter is the CH...O distance, the higher the tendency to assume a linear configuration in order to minimize electrostatic repulsions between the donor and the acceptor atoms of the H-bond (which are both negatively charged). For longer distances, the ϕ angle tends to be lower. As proposed by Kollman^[28] in his theory of hydrogen-bond directionality, the deviation from linearity could be due to the charge-transfer contribution. In this quantum mechanical attraction both the geometry and phase of the interacting molecules molecular orbitals^[29] affect the geometry of the hydrogen bond.

Comparing these geometrical parameters with the values obtained for DDQC, it can be outlined that the intramolecular C-H...O contact found in the present study is significantly short, especially if considering the large values of ϕ and θ angles. This means that the hydrogen bond is particularly strong (as it was confirmed by experimental evidences showing its persistence in solution, see next section), and that electrostatic repulsion was not predominant in determining the geometry. Both ϕ and θ angles, could be affected by the steric effects due to the formation of a seven-membered ring but, in principle, the two rotatable bonds N₁₀–C₁₂ and C₁₂–C₁' should be sufficiently unrestricted to accommodate the destabilizing effect of electrostatic repulsion forces. In this case the charge-transfer mechanisms seems to be relevant for the geometry of this interaction in which an amidic oxygen is involved, but additional contribution (i.e., exchange repulsion, polarization or dispersion) can not be excluded.

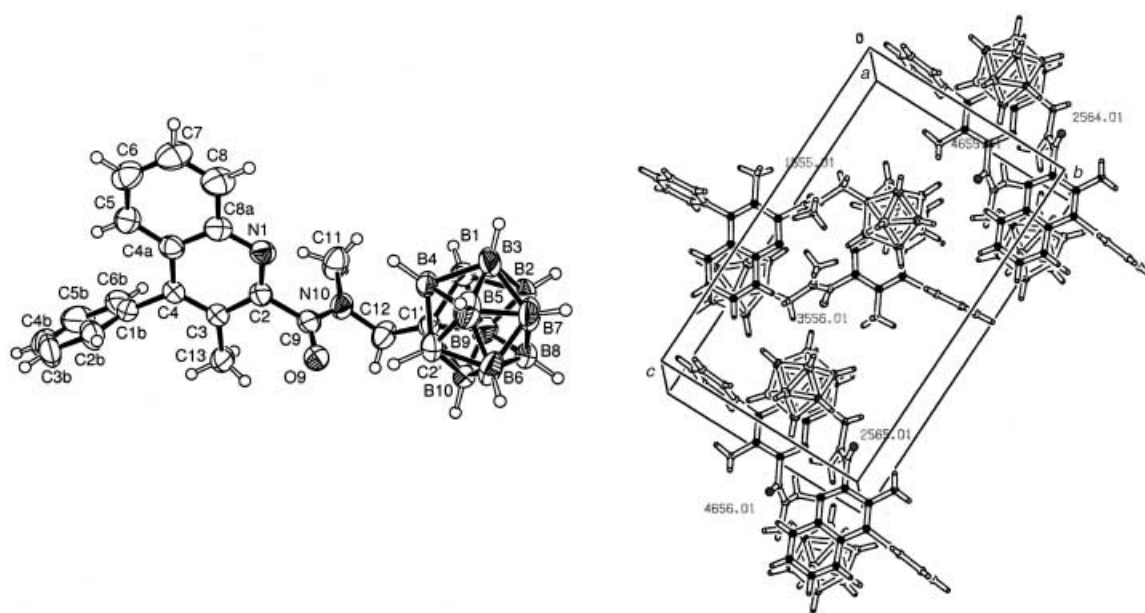


Figure 1. ORTEP drawing of the crystal structure and crystal packing diagram of DDQC. Symmetry code: [1555.01] = x, y, z ; [3556.01] = $\frac{1}{2}+x, \frac{1}{2}-y, 1-z$; [2565.01] = $\frac{1}{2}-x, 1-y, \frac{1}{2}+z$; [2564.01] = $\frac{1}{2}-x, 1-y, -\frac{1}{2}+z$; [4656.01] = $1-x, \frac{1}{2}+y, \frac{3}{2}-z$; [4655.01] = $1-x, \frac{1}{2}+y, \frac{1}{2}-z$.

Structure of DDQC in solution: The analysis of the DDQC structure in solution was performed by using ^1H NMR spectroscopy.

The $^1\text{H}\{^{11}\text{B}\}$ spectrum of DDQC, reported in Figure 2, clearly showed the presence of two rotamers in solution, in slow exchange with each other through rotation around the amide bond. The relative abundance of the two rotamers, as measured from the relative intensities of the corresponding peaks, was found to be 80% (major, *M*) and 20% (minor, *m*). Spectra recorded at different concentrations did not show meaningful chemical shift variation, thus ruling out the possibility of intermolecular interaction in solution.

The complete assignment of both the major and minor species peaks, which clearly showed well separated networks of correlation, was done by using 2D $^1\text{H}\{^{11}\text{B}\}$ -COSY and $^1\text{H}\{^{11}\text{B}\}$ -NOESY and is reported in Figure 2 for the most relevant peaks.

The analysis of the relative peak shifts in the one-dimensional $^1\text{H}\{^{11}\text{B}\}$ NMR spectrum and the analysis of 2D spectra provided evidence that the minor species, which is the less stable in solution, was associated to the *cis* rotamer. Moreover, from 1D spectrum we could draw important considerations about the conformation of both rotamers in solution.

The most important difference between the spectra of the two species was recorded for the H_2' (carborane cage). In this case the shift between the major and the minor peaks was 1.32 ppm. The position of the $\text{H}_2'_{(M)}$ peak (4.45 ppm) was considerably low-field shifted with respect to the common values found for carbaborane (C)H, included in molecules which do not contain a hydrogen acceptor, in the same solvent (about 3.5–3.6 ppm)^[30]. The value we measured was thus consistent with the formation of a stable $\text{CH}\cdots\text{O}$ interaction in solution. This evidence, coupled with the unambiguous X-ray structure and ab initio calculations,

was a robust confirmation of the ability of activated CH groups to form strong H-bonds, driving conformational properties in solution as well as in the solid state. The persistence of the intramolecular $\text{CH}\cdots\text{O}$ interaction in solution has been recently demonstrated for another carboranyl derivative.^[9] In that case, the acceptor atom was a glycosidic (ether) oxygen.

In the light of these considerations, the strong low-field shift of the H_2' observed for the minor species was unexpected. The only explanation for this was that the $\text{H}_2'_{(m)}$ atom should be fixed in the close proximity of the quinoline ring deshielding cone, with the molecule assuming a rigid conformation along the two rotatable bonds $\text{N}_{10}\text{--C}_{12}$, and $\text{C}_{12}\text{--C}'_1$. We interpreted this important feature of the molecule as a consequence of a strong $\text{C}_2'\text{H}\cdots\text{N}_1$ (quinoline) bond, the sole interaction able to constrain the molecule in this geometry.

In principle, the mobility around the two mentioned rotatable bonds should not be strongly affected by steric hindrance and in particular, the rotation along the $\text{C}_{12}\text{--C}'_1$ bond should be almost completely insensitive to the relative position of (C)H, with respect to the four isoplanar (B)H. A remnant of this mobility, could be found observing the line-width of the H_{12} peaks. The broadening of both these peaks, for the major and minor species, could in fact be due to the libration of the methylene group, which is gated in the seven-membered ring, closed by the $\text{C}_2'\text{H}\cdots\text{O}$, bond for the *trans* rotamer and in the eight-membered ring, closed by the $\text{C}_2'\text{H}\cdots\text{N}_1$ bond, for the *cis* rotamer.

The broad peak H_{12} was shifted up-field by 0.3 ppm, whereas the $(\text{N}_{10})\text{CH}_3$ peak was 0.2 ppm shifted to lower field. This indicated that, in the minor species, the $(\text{N}_{10})\text{CH}_3$ was closer to the deshielding anisotropy region of the carbonyl group. On the contrary the methylene, pointing far from the carbonyl, was shifted to higher field.

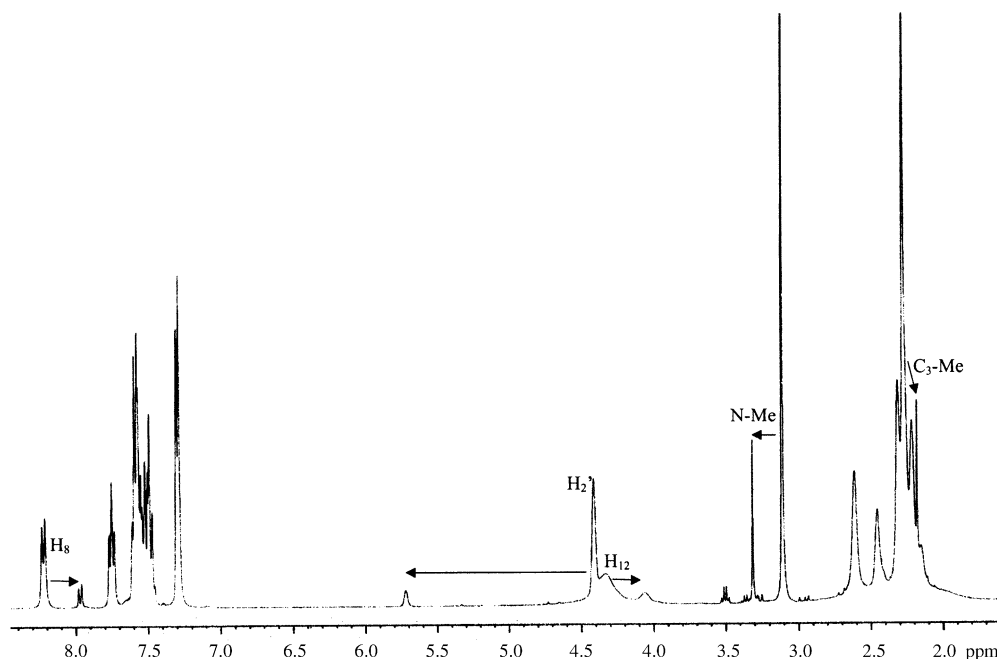


Figure 2. $^1\text{H}\{^{11}\text{B}\}$ NMR spectrum of DDQC in CDCl_3 solution. Assignments of the relevant resonances are reported for the major rotamer. Arrows indicate the magnitude and direction of the frequency shift for the minor rotamer peaks.

The $(C_3)CH_3$ group and H_8 are both shifted high-field. These shifts could be due either to electronic or to anisotropic effects. In both cases it is difficult to determine the effective contribution of each.

The proposed arrangement for both rotamers in solution and the persistence of the two intramolecular $CH\cdots X(N,O)$ bonds, was confirmed by the presence of diagnostic cross-peaks in the $^1H\{^{11}B\}$ 2D-NOESY spectra. In Figure 3a a portion of $^1H\{^{11}B\}$ -NOESY spectra is reported, showing the cross-peaks between the $H_{8(M)}$ ($F2$, 8.22 ppm) and $(N_{10})CH_{3(M)}$ ($F1$, 3.10 ppm). Figure 3b shows the cross-peak between $H_{8(m)}$ ($F2$, 7.96 ppm) and $H_{2'(m)}$ ($F1$, 5.53 ppm).

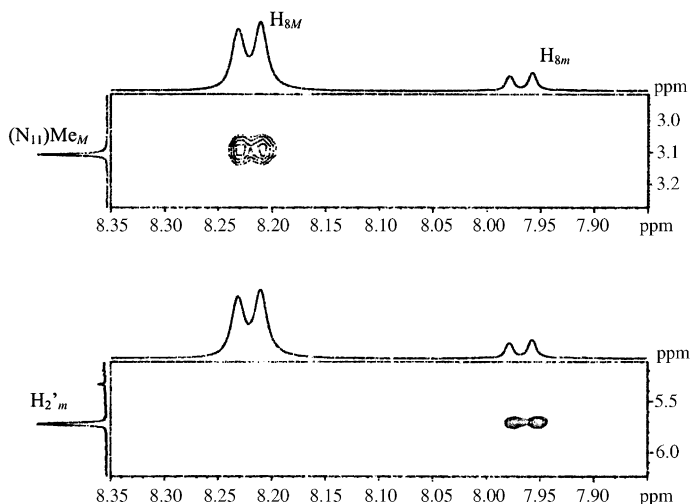


Figure 3. Portion of the $^1H\{^{11}B\}$ NOESY spectrum of DDQC in $CDCl_3$, acquired at 400 MHz, reporting the diagnostic cross-peaks for this work (see text). Assignment is also reported. Capital M and lower case m indicate peaks relative to the major and minor rotamers, respectively.

In the major species, the presence of a weak cross-peak between H_8 of the quinoline ring and the $(N_{10})Me$ is in good agreement with the *trans* structure obtained by X-ray crystallography.

For the minor rotamer, the high relative intensity of the NOE contact between $H_{2'}$ and H_8 was unexpected, considering that this species is only 20% populated. It demonstrated that the distance between these two protons is considerably short and that the $C_2'H\cdots N_1$ bond is sufficiently strong to persist in solution. The experimental distance, calculated by using normalised $H_{2'}-H_8$ NOESY cross-peak, was 2.88 Å which is in good agreement with the theoretical distance of 2.59 Å obtained by ab initio calculations (see next section).

Theoretical calculations: In order to confirm experimental data, ab initio calculations were performed by using the

Gaussian 98 package^[17] on a slightly simplified model of the two rotamers, in which the pendant phenyl ring was removed to reduce calculation time.

Both species were optimised at the RHF/6-31G** level, using the X-ray structure as a starting model for the *trans* rotamer and an X-ray derived model for the *cis* one (as outlined in the Experimental Section).

The geometry of DDQC_{trans} optimised model did not present significant differences with respect to the X-ray structure, consequently, we will refer to Figure 1 for discussion. The optimised structure of DDQC_{cis} is reported in Figure 4. As for the *trans* rotamer, it is possible to observe a close proximity between the C-H donor and the N_1 acceptor. The calculated distance for the atoms involved in the $CH\cdots N$ bond were found to be 3.25 and 2.36 Å for the $C_2'\cdots N_1$ and $H_2'\cdots N_1$ pairs, respectively ($d=0.39$ Å). Angles ϕ and θ were found to be 140.7 and 10.2° (similarly to the $CH\cdots O$ case, θ is considered as the displacement of H from the sp^2 nitrogen plane). With respect to the $CH\cdots O$, the H_2' presents a better alignment with the nitrogen sp^2 lone-pair.

To obtain further details on the strength of the $CH\cdots X(N,O)$ interaction in both DDQC_{trans} and DDQC_{cis}, a torsional driving analysis around $C_{12}-C_1'$ bond was performed, by calculating single point energy at the RHF/6-31G** level, with rotation of the $N_{10}-C_{12}-C_1'-C_2'$ torsion angle through steps of 30°. This angle variation induced a mere rotation of the carbaborane cage, which presented approximately the same steric hindrance every 72°, without affecting the global conformation of the molecule. This consideration suggested that the measured energy difference should be largely due to bonding and electrostatic interactions.

The result of the torsional driving analysis for DDQC_{trans} is reported in Figure 5. The lowest energy was found at 90°,

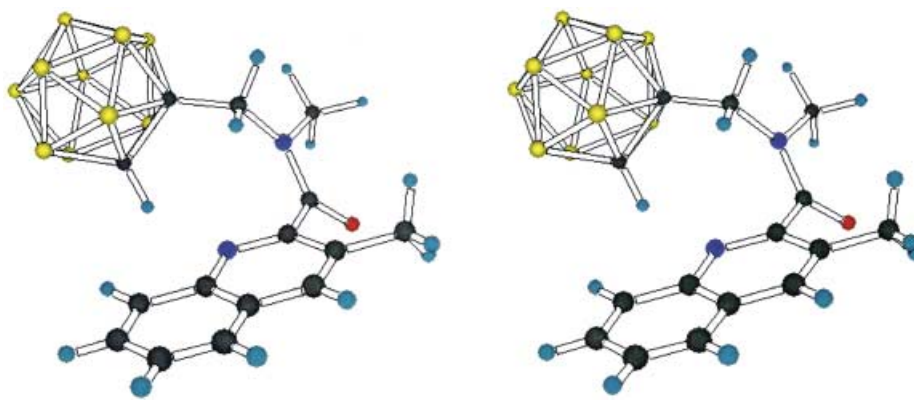


Figure 4. Stereoview of DDQC_{cis} model optimised by ab initio calculations at RHF/6-31G** level. Boron bonded hydrogens were omitted for clarity.

with a very small difference with respect to the value obtained at 60° ($\Delta E=0.14$ kcal mol⁻¹). The torsion angle in the optimised model was found at 77.2°, with an energy stabilization of 0.64 kcal mol⁻¹ with respect to the 90° value. The energy maximum was found at 270°, with a relative value of 10.14 kcal mol⁻¹. In this conformation the $C_2'H$ pointed toward the opposite side with respect to O_9 . The $H_2'-O_9$ dis-

tance measured at 90 and 270° was 2.18 to 5.16 Å, respectively. The correlation between the C₂H...O₉ H-bond formation and the torsional energy profile was confirmed by measuring the H₂'-O₉ distance for each rotation angle. The results of this measurement are also reported in Figure 5. These data confirmed that the energy was essentially modulated by the distance, with two important exceptions at 60 and 240°, where the energy and distance curves were “de-phased” by 30°. In fact, at these torsion angles the lowest and the highest distances, respectively, were observed, but not the corresponding minimum and maximum energy values. This meant that a minor steric contribution to the energy was also present, which could be estimated as 2.0–2.5 kcal mol⁻¹ from the difference between the values at 240 and 270°. It follows that the energy of the C₂H...O₉ interaction was in the range of 7–8 kcal mol⁻¹, that is far beyond the values reported in the literature for this kind of interaction (≤ 2.5 kcal mol⁻¹)^[24] and it is in good agreement with the experimental evidence of its persistence in solution.

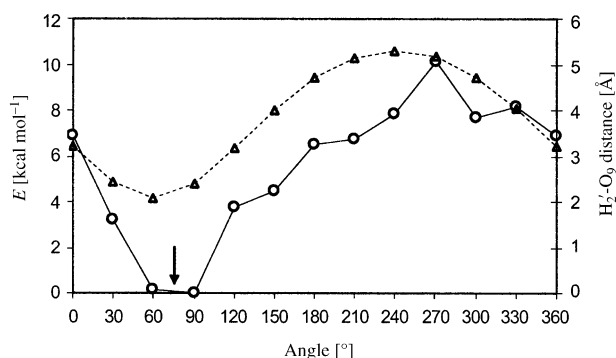


Figure 5. Torsional energy profile of the C₁'-C₁₂ bond for DQCC_{trans} rotamer (○), together with the internuclear H₂'-O₉ distance (▲). The arrow indicates the torsion angle for the optimised model (77.2°) in which the calculated energy was 0.64 kcal mol⁻¹ lower than in the 90° conformer. Distance units are reported on the right vertical axis.

The result of the torsional driving analysis for DDQC_{cis} is reported in Figure 6. The lowest energy value was found at 60°, which is very close to the value found for the optimised model (61.8°). The C₂H is pointing in the N₁ direction, confirming the presence of a CH...N interaction. Two additional local minima were found at 180 and 330°, which corresponded to the *anti* and right-*gauche* conformations of the C₂H with respect to amide nitrogen (N₁₀). In the 330° conformation (Figure 6c), the energy local minimum is considerably lower than the minimum at 180° (Figure 6b), probably because of the electrostatic interactions between H₂' and the amide nitrogen (N₁₀). From the calculations, the residual Mulliken charge could be extracted for all the atoms of the optimised model. The most relevant atoms showed the following values: C₂' = -0.76, H₂' = 0.34, N₁₁ = -0.86, N₁ = -0.65, O₁₀ = -0.60. This is an important issue, because we must take account of this interaction when calculating the energy involved in the C₂H...N₁ bond. In fact, also in the case of the 60° conformation (left-*gauche*, Figure 6a), a very similar H₂'-N₁₀ electrostatic interaction took place, and con-

tributed to lower the energy of the whole molecule. Thus, two main contributors gave rise to the global minimum at 60°, the H₂'-N₁₀ electrostatic interaction (that is symmetric to the interaction occurring at the right-*gauche* conformation, at 330°), and the C₂H...N₁ bond.

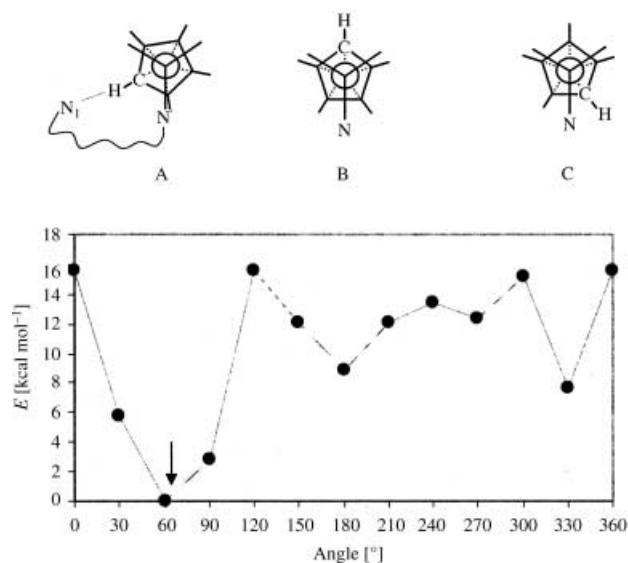


Figure 6. Torsional energy profile of the C₁'-C₁₂ bond for DQCC_{cis} rotamer. The arrow indicates the torsion angle for the optimised model (61.8°) in which the calculated energy was found 2.58 kcal mol⁻¹ lower than 60° conformer. The Newman structures indicate the approximate arrangement of the cage with respect to the amide nitrogen and N₁, along the C₁₂-C₁'.

From both CH...O and CH...N torsional driving calculations it was possible to establish that the B_n-H...X(O,N) interaction was negligible and did not affect the local molecular conformation. This was probably due to the almost vanishing Mulliken charge on the B-H groups of the cage.

Consequently, even if an accurate determination was not possible from this analysis, we can speculate that the observed stabilizing effect, which is given by the difference between the calculated energies at 330 and 60° (7.8 kcal mol⁻¹), was largely due to the CH...N bond formation. In other words, following this interpretation we can conclude that, in our case, the energy of this non-classic H-bond was significantly higher than the values currently reported in the literature.^[24] The value obtained was very close to the upper limit of the energy range for the classic NH...X and OH...X bonds (3–8 kcal mol⁻¹)^[24] which, as mentioned above, could well explain its persistence in solution.

Conclusion

In the present paper the occurrence and persistence in solution of CH...X(N,O) bonds was demonstrated for the two rotamers of a carbaboranyl derivative of potential pharmaceutical interest. The activated CH group of the carborane cage can thus be considered an important probe for the evaluation of the chemical behaviour in this non-classic in-

teraction, especially when groups of biological interest such as the amide are involved. Crystallographic studies demonstrated that the amide oxygen was involved in the bond as hydrogen acceptor. This allowed the accurate determination of geometric parameters, from which it was possible to extract information on the forces involved in the hydrogen bond. Moreover, this intramolecular CH...O interaction was demonstrated to persist in solution, showing its importance in driving conformational properties of bio-macromolecules and supramolecular complexes.

The occurrence of a CH...N bond in solution was also demonstrated by NMR studies and was confirmed by ab initio calculations. The strength of both these interactions and their geometrical parameters were found to be in the same range of classical hydrogen bonds. In particular, in the case of the CH...N for the *cis* rotamer, the H atom directly pointed toward the nitrogen sp² lone-pair, whereas in the case of the CH...O bond for the *trans* rotamer a higher deviation from planarity was observed ($\theta = 10.2$ and $\theta = 41.2^\circ$, respectively). However, for the CH...O bond we should consider that a seven-membered ring was formed, in which geometrical constraints were more effective.

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