Distinguishing hydrogen bonding networks in α-D-galactose using NMR experiments and first principles calculations

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Abstract
First principles calculations and solid-state NMR experiments are used to distinguish between possible hydrogen bonding networks in α-D-galactose. In contrast to 13C, the 1H chemical shift parameters show differences which are sufficient to allow the correct network to be identified by comparison with experiments which make use of modern homonuclear decoupling schemes. In addition, clear linear correlations are established between both 1H chemical shift and chemical shift anisotropy, and hydrogen bond length.

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1. Introduction
Solid-state nuclear magnetic resonance (NMR) is a sensitive probe of the local electronic environment in both crystalline and amorphous materials. The combination of experimental measurements of solid-state NMR parameters, such as chemical shifts and quadrupolar couplings, with first principles calculations provides a powerful method for structure elucidation. This approach can often provide complementary structural information to X-ray and neutron diffraction methods. Such a combined approach has been successfully applied to a variety of systems including organic molecular crystals [1–6], supramolecular assemblies [7], nanostructured materials [8,9], and both crystalline [10,11] and amorphous [12,13] inorganic materials.

In this Letter, a combination of solid-state NMR experiments and first principles calculations are used to elucidate the hydrogen bonding network in α-D-galactose. The X-ray structure of α-D-galactose was originally obtained independently by Sheldrick [14] and by Ohanessian and Gillier-Pandraud [15]. Despite similar unit cell dimensions and heavy atom co-ordinates, there were substantial discrepancies in the locations of hydrogen atoms which were calculated using electron density difference synthesis. Jeffrey and Shiono [16] established that these discrepancies result in the formation of quite different hydrogen bonding networks in the two structures. In the Sheldrick structure the network is a closed loop in which the longest hydrogen bond (2.13 Å) links the anomeric hydroxyl O1-H to O3 and the shortest (1.70 Å) links the primary alcohol O6-H to the anomeric oxygen O1. In contrast, the Ohanes- sian network consists of infinite chains in which the O1-H–O6 hydrogen bond is still the longest (2.02 Å), but O1 is not a hydrogen bond acceptor. Therefore, Jeffrey and Shiono favoured the latter on the grounds that anomeric hydroxyls in simple pyranoses are usually strong hydrogen bond donors, but very weak acceptors. Noting the unusually small O1-H–O6 bond angle (113.9°), they postulated a modified structure with a more linear arrangement of these three atoms and consequently the shorter hydrogen bond consistent with a strong donor. More recently, Kouwijzer et al. [17] published a third X-ray structure of α-D-galactose which is similar to that of Ohanessian, but with a more linear O1-H–O6 bond angle, making the O1–H–O6–O6 distance (1.69 Å) the shortest in the hydrogen bonding network as predicted by Jeffrey and Shiono.

We apply the fully periodic plane-wave pseudopotential formalism of density-functional theory to establish the NMR signatures for each proposed model of α-D-galactose. By comparison to solid-state NMR experiments we can unambiguously determine the correct structure. In addition, we establish which NMR parameters are most useful for making this assignment and comment on some general trends in the observed NMR parameters.

2. Experimental section

2.1. Sample
α-Galactose (99+%) was purchased from Across Organics and used without further purification. Only six resonances were present in the 13C CPMAS spectrum of D-galactose, demonstrating that the sample contains a single anomer with the observation of the anomeric carbon line at 92.4 ppm indicating the α anomer [18].
2.2. Solid-state NMR measurements

CPMAS $^{13}\text{C}$ NMR spectra were recorded (Figure 1a) at a Larmor frequency of 75.46 MHz on samples packed into 4 mm rotors spinning in a double-resonance MAS probe. The MAS rate was 4 kHz, stabilised to ±5 Hz, resulting in spectra without spinning sidebands. $^1\text{H}$ decoupling at field strengths of up to 120 kHz was applied during the acquisition time which was 75 ms in duration. The contact time and the relaxation delay were optimised and set to 3 ms and 55 s, respectively. Isotropic $^{13}\text{C}$ chemical shifts were referenced externally to the high frequency line of adamantane which was assigned a shift of 37.8 ppm relative to the carbon in TMS. $^{13}\text{C}$ CSA amplification spectra were recorded as described previously [19] using two sequences of five $\pi$ pulses with timings chosen to achieve an amplification factor of 8. Two experiments were recorded with MAS rates of 4 and 4.8 kHz, resulting in effective rates of 500 and 600 Hz in the $\omega_1$ dimension. There were 16 values of $t_1$ with an increment corresponding to 1/16 of the MAS period, and 256 scans were acquired for each increment. The $^{13}\text{C}$ $\pi$ pulse was 5 ms. Other experimental parameters were identical to those used for standard CPMAS spectra, as described above. Sideband intensities were extracted from the $\omega_1$ dimension of CSA amplification spectra. The chemical shift anisotropy, $\zeta$, and asymmetry, $\eta$, were extracted using a least squares fitting procedure. This involves comparing the experimental sideband intensities to those simulated for a standard MAS spectrum at the effective MAS rate using the SIMPSON programme [20]. Powder averaging was performed with 31 $(\alpha,\beta)$ crystallite orientations distributed over an octant according to a Lebedev scheme [21]. The principal components of the chemical shift tensor $\delta_{xx}, \delta_{yy}$, and $\delta_{zz}$, ordered such that $|\delta_{zz} - \delta_{iso}| \geq |\delta_{xx} - \delta_{iso}| \geq |\delta_{yy} - \delta_{iso}|$, were calculated according to the definitions

$$\zeta = \frac{\delta_{zz} - \delta_{iso}}{\delta_{iso}},$$

(1)

$$\eta = \frac{\delta_{yy} - \delta_{iso}}{\zeta},$$

(2)

High resolution $^1\text{H}$ spectra were recorded (Figure 1b) at a Larmor frequency of 300.07 MHz with a MAS rate of 12 kHz using the same probe. DUMBO homonuclear decoupling [22] was employed between sampling points with $^1\text{H}$ field strength of 101.6 kHz and a cycle time of 29.4 $\mu$s. The relaxation delay was 55 s and 128 scans were acquired. The scaling factor for the $^1\text{H}$ chemical shifts was calibrated using a spectrum of alanine recorded under identical conditions.

3. Computational details

NMR shielding parameters and quadrupolar coupling constants were calculated using the gauge including projector augmented wave (GIPAW) [23] approach as implemented in the CASTEP [24,25] density-functional theory code. Wavefunctions were expanded in terms of plane-waves with kinetic energies lower than a maximum cutoff energy of 800 eV. Ultrasoft pseudopotentials [26] were used to represent the core electrons. The Brillouin zone was sampled using a Monkhorst–Pack [27] grid of $k$-points with a maximum spacing of 0.055 Å$^{-1}$. These parameters were chosen to converge isotropic shifts to within 0.1 ppm for all nuclei and $^2\text{H}$ and $^{17}\text{O}$ quadrupole coupling constants to within 1 kHz and 0.1 MHz, respectively.

Commonly used density-functionals such as LDA and GGAs are known to provide a poor description of the energetics of weak molecular bonds. Indeed, on performing an unconstrained geometry optimisation many molecular crystals will undergo a dramatic expansion of the unit cell, or even fall apart. However, if dispersion forces can be accounted for in some way and a good structural model obtained, then commonly used density-functionals have been shown to give NMR parameters in good agreement with experiment. For example, weak hydrogen bonding interactions were quantified in the saccharide maltose [6,28], the RNA base uracil [29], amino acids [2] and imidazole- and morpholine-based compounds [30]. In principle one might use a semi-empirical dispersion correction scheme such as presented in Ref. [31]. In molecular crystals a pragmatic alternative is to constrain the lattice parameter to the experimental values. This latter approach has been widely used [6,28–30] and we employ such an approach in this work.

Results were obtained with two generalised gradient approximations (GGA) to the exchange–correlation interaction: PBE [32] a non-empirical GGA functional which has been widely utilised to calculate a range of physical properties and KTD [33] a semi-empirical GGA functional which was specifically developed for the calculation of high-quality NMR shielding tensors for light main group nuclei. A recent benchmarking study [34] of density-functional theory predictions of isotropic NMR shielding constants

![Figure 1. Experimental isotropic (a) $^{13}\text{C}$ and (b) $^1\text{H}$ NMR spectra for x-o-galactose. Spectra was recorded at a Larmor frequency of 75.46 MHz on samples packed into 4 mm rotors spinning in a double-resonance MAS probe at a rate of 4 kHz for (a) and at Larmor frequency of 300.07 MHz with a MAS rate of 12 kHz using the same probe for (b).](image-url)
in hydrogen bonded systems demonstrated that KT3 outperforms hybrid functionals, such as B3LYP [35].

The outputs from the calculations are the absolute shielding tensor $\sigma$ and the electric field gradient (EFG) tensor [36] $\mathbf{V}$. The principal components of the shielding tensor were obtained by diagonalising the symmetric part and the isotropic average was calculated according to

$$\sigma_{iso} = \frac{1}{3} (\sigma_{xx} + \sigma_{yy} + \sigma_{zz}). \quad (3)$$

Chemical shifts are measured relative to a reference frequency such that their direction is the opposite of the shielding, so the isotropic chemical shift was obtained from the isotropic average of the shielding tensor according to

$$\delta_{iso} = - (\sigma_{iso} - \sigma_{ref}). \quad (4)$$

The principal components of the chemical shift tensor were calculated from those of the shielding tensor in a similar fashion.

For $I > 1/2$ nucleus the quadrupolar coupling constant $C_Q$ measures the magnitude of the interaction between the nuclear quadrupole moment $Q$ and the EFG at the nucleus. Values of $C_Q$ were calculated according to

$$C_Q = \frac{e Q_{zz}}{h}, \quad (5)$$

where $Q_{zz}$ is the largest eigenvalue of the EFG tensor. The quadrupole moment $Q$ for $^{17}$O and $^2$H were taken [37] as $-2.56 \times 10^{-30}$ and $0.286 \times 10^{-30}$ m$^2$, respectively.

4. Results and discussion

4.1. Geometry optimisation

The X-ray structures for $\alpha$-$\beta$-galactose were obtained from the Chemical Database Service [38]. Initially, the calculated forces on the hydrogen and the heavier atoms were up to 30 eV/Å and 6 eV/Å, respectively. Therefore, a partial geometry optimisation in which only the hydrogen atom co-ordinates were altered was carried out prior to calculating the NMR parameters. After this procedure hydrogen atoms in the Kouwijzer and Ohanessian structures had relaxed into indistinguishable positions, so that the older Ohanessian structure is no longer considered here. Full geometry optimisations were also carried out but these did not affect the hydrogen bond networks and the small changes in atomic positions were found to have only a small effect on the NMR parameters, in particular the errors with respect to experiment were not changed. The partially optimised Kouwijzer and Sheldrick structures are shown in Figure 2 where the labelling scheme of Ref. [17] has been adopted for both structures for consistency. Partial optimisation reduced the mean residual force on all atoms to a more acceptable 0.2 eV/Å for the Kouwijzer structure and 0.5 eV/Å for the Sheldrick structure. For consistency with the NMR calculations, partial geometry optimisations were carried out using both PBE and KT3 exchange–correlation functionals, but these resulted in almost identical hydrogen bond lengths and angles, as shown in Table 1. Note that Figure 2 shows optimised structures obtained using the PBE functional.

The hydrogen atoms in the optimised structures are generally only slightly displaced from their original locations and the essential features of the hydrogen bonding networks identified by Jeffrey and Shiono are preserved. The main disparity between the two remains the positions of three hydroxyl hydrogen atoms O1-H8, O2-H9 and O6-H12 which are hydrogen bonded to different acceptors in the two networks. In the optimised Kouwijzer structure the anomeric hydroxyl hydrogen O1-H8 is involved in the shortest hydrogen bond (1.66 Å) as expected for a strong donor. However, in the optimised

![Figure 2](image)

Table 1

Summary of the hydrogen bonding networks in terms of the distance $d_{O-H}$ (in Å) and the angle $\angle_{O-H-O}$ for the Kouwijzer and Sheldrick galactose structures with optimised hydrogen atom positions using PBE and KT3 exchange–correlation functionals.

<table>
<thead>
<tr>
<th></th>
<th>PBE $d_{O-H}$</th>
<th>$\angle_{O-H-O}$</th>
<th>KT3 $d_{O-H}$</th>
<th>$\angle_{O-H-O}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kouwijzer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O1-H8</td>
<td>0.66</td>
<td>173.4</td>
<td>1.67</td>
<td>173.8</td>
</tr>
<tr>
<td>O2-H9</td>
<td>0.69</td>
<td>173.2</td>
<td>1.71</td>
<td>172.6</td>
</tr>
<tr>
<td>O3-H10</td>
<td>0.89</td>
<td>174.3</td>
<td>1.91</td>
<td>174.8</td>
</tr>
<tr>
<td>O4-H11</td>
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<td>163.0</td>
<td>1.89</td>
<td>162.0</td>
</tr>
<tr>
<td>O6-H12</td>
<td>0.79</td>
<td>156.9</td>
<td>1.82</td>
<td>155.7</td>
</tr>
<tr>
<td>Sheldrick</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O1-H8</td>
<td>0.66</td>
<td>173.4</td>
<td>1.67</td>
<td>173.8</td>
</tr>
<tr>
<td>O2-H9</td>
<td>0.69</td>
<td>173.2</td>
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<tr>
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<td>0.79</td>
<td>156.9</td>
<td>1.82</td>
<td>155.7</td>
</tr>
</tbody>
</table>
4.2. $^{13}$C chemical shift parameters and comparison with experiment

Calculated $^{13}$C isotropic shifts and shift anisotropies for the two partially optimised $\alpha$-$\omega$-galactose structures are compared with experimental values in Table 2. Following standard practice [39] the $^{13}$C reference shielding was optimised for each structure and each exchange–correlation functional by fitting the calculated isotropic shift from Eq. (4) to the experimental values with $\sigma_{\text{ref}}$ as a variable parameter. Isotropic shifts calculated with PBE and KT3 functionals agree equally well with experiment, since the mean absolute error obtained with PBE is slightly lower, but the maximum absolute error is smaller for KT3. Regardless of the functional used, the isotropic shifts calculated for the Kouwijzer structure are significantly closer to the experimental values with a PBE mean absolute error of 0.9 ppm compared to 1.4 ppm for the Sheldrick structure and a KT3 maximum absolute error of 2.1 ppm compared to 3.7 ppm.

In common with previous work, including a study of $^{13}$C chemical shift tensors in disaccharides [3], the magnitude of the calculated $\zeta$ was found to be consistently too large. Hence, the calculated tensor span

$$\Omega = \delta_{a2} - \delta_{a3}$$

was scaled by a constant factor for each structure and each exchange–correlation functional to facilitate comparison with experiment. The values of the isotropic shift and the asymmetry were not adjusted during this scaling procedure. Calculated shift anisotropies required scaling factors of between 0.73 and 0.77 in good agreement with the mean value of 0.77 taken from previous work on a series of disaccharides [3]. There was no significant divergence between scaling factors required for different functionals. Once again the mean absolute error between parameters calculated from the Kouwijzer structure and the experimental values is smaller than that for the Sheldrick structure.

The calculated shift parameters which show the largest divergence between the two structures are the anisotropies for carbon sites C1 and C6. These carbon atoms are both attached to hydroxyl groups which are hydrogen bonded to different acceptors in the two possible networks. This indicates that the $^{13}$C shift anisotropy is more sensitive to the hydrogen bonding at an attached hydroxyl group than the isotropic shift alone. However, the effect is not significant enough in this case to allow resolution of the correct structure, since the calculated differences are generally less than 1 ppm.

Overall, the better agreement with experiment suggests that the Kouwijzer structure best describes the hydrogen bonding network. However, for $\alpha$-$\omega$-galactose the carbon atoms are only peripherally involved in hydrogen bonding, suggesting that $^{17}$O or $^1$H NMR parameters might be more useful for distinguishing between the structures.

4.3. $^{17}$O Chemical shift parameters and quadrupolar couplings

For $^{17}$O I = 5/2, and so in this case the quadrupolar coupling provides an additional experimental NMR parameter with which to probe the local electronic environment. Calculated $^{17}$O isotropic shifts, shift anisotropies and quadrupolar couplings for the two partially optimised $\alpha$-$\omega$-galactose structures are given in Table 3. In the absence of experimental data for comparison, $\sigma_{\text{ref}}$ for $^{17}$O was set to 265 and 280 ppm for PBE and KT3 calculations, respectively. These reference shieldings were obtained by following Ref. [10] and repeating calculations on coesite SiO$_2$ using ultrasoft pseudopotentials with PBE and KT3 exchange–correlation functionals, resulting in reference shieldings of good agreement used in previous works [10,40,11,41,12]. Calculations with PBE and KT3 exchange–correlation functionals produced similar isotropic shift parameters. However, the quadrupolar coupling constant was consistently larger in magnitude and the shift anisotropy consistently smaller for KT3, with a maximum difference of 0.6 MHz and 5.8 ppm, respectively.

The variation in the calculated $^{17}$O chemical shift parameters between the two structures is more significant than for $^{13}$C with differences of up to 12.8 ppm and 14.1 ppm for the isotropic shift and the magnitude of the shift anisotropy, respectively. Note that for the oxygen O4 site neither the shift nor the quadrupolar parameters vary significantly between the two structures. This oxygen atom is the only one which occupies an identical position in the two hydrogen bonding networks, acting as an acceptor for O3–H in both cases. In contrast, large variations in the calculated parameters are observed for O1, O3 and O6 which occupy very different

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**Table 2**

Comparison of the experimental and calculated $^{13}$C isotropic shifts and shift anisotropies in ppm for the partially optimised Kouwijzer and Sheldrick $\alpha$-$\omega$-galactose structures using PBE and KT3 exchange–correlation functionals. The mean absolute error (mae) and maximum absolute error (max ae) in the isotropic shift and shift anisotropy are also reported. The calculated shift anisotropies were scaled by a constant factor according to procedures described in the text.

<table>
<thead>
<tr>
<th>Site</th>
<th>Experiment</th>
<th>Kouwijzer PBE</th>
<th>Sheldrick PBE</th>
<th>Kouwijzer KT3</th>
<th>Sheldrick KT3</th>
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</thead>
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<tr>
<td></td>
<td>$\delta_{\text{iso}}$</td>
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<td>$\delta_{a3}$</td>
<td>$\delta_{\text{iso}}$</td>
<td>$\delta_{a2}$</td>
</tr>
<tr>
<td>C1</td>
<td>92.4</td>
<td>21.3</td>
<td>95.0</td>
<td>23.9</td>
<td>96.5</td>
</tr>
<tr>
<td>C2</td>
<td>70.4</td>
<td>19.7</td>
<td>70.3</td>
<td>19.0</td>
<td>69.2</td>
</tr>
<tr>
<td>C3</td>
<td>70.6</td>
<td>20.1</td>
<td>70.0</td>
<td>20.3</td>
<td>69.5</td>
</tr>
<tr>
<td>C4</td>
<td>70.1</td>
<td>22.8</td>
<td>70.4</td>
<td>23.6</td>
<td>70.0</td>
</tr>
<tr>
<td>C5</td>
<td>68.8</td>
<td>20.2</td>
<td>68.0</td>
<td>21.2</td>
<td>68.9</td>
</tr>
<tr>
<td>C6</td>
<td>58.8</td>
<td>36.4</td>
<td>57.6</td>
<td>34.6</td>
<td>56.9</td>
</tr>
<tr>
<td>mae</td>
<td></td>
<td></td>
<td>0.9</td>
<td>1.1</td>
<td>1.4</td>
</tr>
<tr>
<td>max ae</td>
<td></td>
<td></td>
<td>2.5</td>
<td>2.5</td>
<td>4.1</td>
</tr>
</tbody>
</table>

a: $\sigma_{\text{ref}} = 168.2$ ppm.
b: Anisotropy scaling factor = 0.73.
c: $\sigma_{\text{ref}} = 167.2$ ppm.
d: Anisotropy scaling factor = 0.76.
e: $\sigma_{\text{ref}} = 178.5$ ppm.
f: Anisotropy scaling factor = 0.74.
g: $\sigma_{\text{ref}} = 177.7$ ppm.
h: Anisotropy scaling factor = 0.77.
positions in the two networks. This suggests that NMR chemical shifts and quadrupolar couplings can be used in principle to distinguish between the different structures. Note, however, that in this case there is no correlation between hydrogen bond distance and any of the three calculated parameters.

Although $^{17}$O NMR is now routine [42], a combination of high magnetic field, isotopic enrichment and methods to reduce the second-order quadrupolar broadening [43,44] are required in order to acquire good quality high resolution spectra. The stereoselective synthesis of $^{17}$O labeled saccharides is possible [45], but this approach has not been pursued further here.

4.4. $^1$H chemical shift parameters, $^2$H quadrupolar couplings and comparison with experiment

Table 4 shows $^1$H isotropic shifts, shift anisotropies and $^2$H quadrupolar couplings calculated for the partially optimised Kouwijzer and Sheldrick $\alpha$-D-galactose structures using both the PBE and KT3 exchange–correlation functionals. $^1$H reference shielding $\sigma_{ref}$ was set to 30.22 ppm and 30.61 ppm for PBE and KT3 calculations, respectively. The reference shieldings were obtained by following Ref. [6] and repeating calculations on $\beta$-maltose monohydrate using ultra-soft pseudopotentials with PBE and KT3 exchange–correlation functionals and comparing to experimental data recorded at temperature of 298 K. The carbon-bound hydrogen atoms (H1–H7) have almost identical positions in the two structures and therefore show similar $^1$H isotropic shifts. However, the isotropic shifts of the hydroxyl hydrogen atoms (H8–H12) vary considerably between the two structures, as expected given the different hydrogen bonding networks. As noted previously [46,47] the $^1$H isotropic shift is correlated with the O–H···O bond length with stronger and shorter hydrogen bonds resulting in more deshielding. Since the hydrogen bonds are shorter on average in the Kouwijzer structure compared to the Sheldrick structure, the average H8–H12 shift is over 1 ppm greater in the former. The correlation between $^1$H shift and hydrogen bond length for $\alpha$-D-galactose is demonstrated in Figure 3a where the correlation coefficient is −0.77, and the slope and intercept of the best fit straight line are −7.98 ppm Å$^{-1}$ and 20.0 ppm, respectively. Note, however, that the hydrogen bonds fall into two separate groups depending on the O–H···O bond angle. If this angle is greater than 167° the proton is more shielded than expected from the correlation, if less than 167° the proton is more deshielded. The correlation between $\delta_{sh}$ and $d_{sh,\alpha-O}$ is better when these two groups of protons are considered separately with correlation coefficients of −0.97 and −0.94 for $\angle$O–H···O > 167° and $\angle$O–H···O < 167°, respectively. A further linear correlation with a coefficient of 0.98 was found between the shift anisotropies and their O–H···O bond length for which the best fit straight line has slope 16.86 ppm Å$^{-1}$ and intercept −48.76 ppm. A similar correlation was observed by Jeffrey and Yeon [46], but their definition of the anisotropy is scaled by the isotropic shift and therefore does not provide as good a linear fit.

The three hydrogen atoms H8, H9 and H12 occupy the most significantly different positions in the hydrogen bonding networks of the two structures. The variation in the calculated shift parameters for these sites can be fully explained in terms of the changes in the corresponding O–H···O bond length and angle between the structures. For example, both the 3.9 ppm increase in $\delta_{sh}$ and the 9 ppm increase in the magnitude of $\zeta$ for the H8 site in the Kouwijzer structure relative to the Sheldrick structure arise because of the corresponding 0.48 Å decrease in bond length. Note that this hydrogen atom is involved in hydrogen bonds with similar O–H···O bond angles of 173.4° and 171.9°, in the Kouwijzer and Sheldrick structures, respectively.

Table 3

Comparison of calculated $^{17}$O chemical shift parameters in ppm and quadrupolar coupling constants in MHz for the partially optimised Kouwijzer and Sheldrick $\alpha$-galactose structures using both PBE and KT3 exchange–correlation functionals.

<table>
<thead>
<tr>
<th>Site</th>
<th>Kouwijzer PBE</th>
<th>Sheldrick PBE</th>
<th>Kouwijzer KT3</th>
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<tbody>
<tr>
<td></td>
<td>$\delta_{sh}$</td>
<td>$\zeta$</td>
<td>$C_Q$</td>
<td>$\delta_{sh}$</td>
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<tr>
<td>O1</td>
<td>37.1</td>
<td>−35.0</td>
<td>9.2</td>
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<tr>
<td>O2</td>
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<td>−38.7</td>
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<tr>
<td>O5</td>
<td>55.6</td>
<td>−56.6</td>
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<tr>
<td>O6</td>
<td>−14.8</td>
<td>−58.8</td>
<td>10.0</td>
<td>−10.3</td>
</tr>
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</table>

Note: $\sigma_{ref} = 265$ ppm.

Table 4

Comparison of calculated $^1$H isotropic shifts and shift anisotropies and $^2$H quadrupolar coupling constants in kHz from the partially optimised Kouwijzer and Sheldrick $\alpha$-galactose structures using PBE and KT3 exchange–correlation functionals.

<table>
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<th>Kouwijzer KT3</th>
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<tr>
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<td>$\delta_{is}$</td>
<td>$\zeta$</td>
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<td>−5.4</td>
<td>172</td>
<td>4.2</td>
</tr>
<tr>
<td>H7</td>
<td>3.8</td>
<td>5.3</td>
<td>172</td>
<td>3.2</td>
</tr>
<tr>
<td>H8</td>
<td>7.9</td>
<td>−21.7</td>
<td>192</td>
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</tr>
<tr>
<td>H9</td>
<td>7.7</td>
<td>−19.9</td>
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</tr>
<tr>
<td>H10</td>
<td>5.7</td>
<td>−16.6</td>
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<td>4.0</td>
</tr>
<tr>
<td>H11</td>
<td>4.1</td>
<td>−17.0</td>
<td>227</td>
<td>3.8</td>
</tr>
<tr>
<td>H12</td>
<td>5.1</td>
<td>−19.1</td>
<td>226</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Note: $\sigma_{ref} = 30.22$ ppm.

Note: $\sigma_{ref} = 30.61$ ppm.
$^1$H NMR spectra with satisfactory resolution can be obtained even at relatively low magnetic field by a combination of moderate MAS and multi-pulse homonuclear decoupling schemes. The large differences between the calculated shift parameters for sites H8, H9 and H12 suggests that even fairly low resolution will be sufficient to distinguish between the two possible hydrogen bonding networks in $\alpha$-D-galactose. To test this hypothesis simulated $^1$H spectra for the two structures were constructed by convolving the 12 isotropic shifts with a lineshape function. These are shown in Figure 4 using isotropic shifts calculated with (a) PBE and (b) KT3 exchange–correlation functionals. A Lorentzian lineshape with a width (FWHH) of 200 Hz was assumed and other parameters matched those in the experimental section.

This procedure results in a $^1$H spectrum for the Kouwijzer structure (short blue dashes) which shows a resolved peak at 7.8 ppm due to the deshielded H8 and H9 protons which are involved in the shortest hydrogen bonds in the network. On the other hand, the spectrum for the Sheldrick structure (long red dashes) lacks any resolution, since the hydrogen bonding network involves generally longer bonds in this case. Note that two simulated spectra are similar, regardless of the exchange–correlation functional used. Therefore, even a low field $^1$H spectrum has the potential to distinguish between the two possible hydrogen bonding networks in $\alpha$-d-galactose. The experimental $^1$H spectrum recorded as described above is plotted (black line) for comparison with the simulated spectra in both panels of the figure. This clearly shows the resolved peak at high ppm expected for the Kouwijzer hydrogen bonding network, indicating that this is the correct structure. Both functionals do not agree with the separation of 3.2 ppm between the two peaks measured by the experiment. PBE overestimates the separation at 3.7 ppm, while KT3 underestimates the separation at 2.9 ppm. This is in contrast to the $^{13}$C case where PBE and KT3 gave similar agreement with experiment. The resolution in the measured $^1$H spectrum could have been enhanced through a combination of higher field, faster MAS, and sophisticated pulse sequences, but this is not necessary in order to distinguish between the two structures.

The $^2$H quadrupolar coupling constants calculated for the two structures were identical to within 1 kHz for most of the hydrogen sites. As expected the most significant differences of 60 and 15 kHz were found for hydrogen atoms H8 and H9, respectively. Once again the KT3 functional resulted in consistently larger quadrupole coupling constants than PBE. The calculations suggest the possibility of using experimental measurements of $^2$H quadrupolar...
isotopic enrichment, the use of $^{17}$O NMR to differentiate the structures was not examined experimentally. Correlations were established between calculated hydroxyl $^1$H isotropic shifts and shift values with experiment. For $^{17}$O, calculated NMR parameters showed large variations between the two possible structures, but no correlation with O–H distance. Given the necessity for selective deuteration this approach has not been pursued experimentally here.

5. Conclusions

The three different hydrogen bonding networks obtained from published X-ray structures of $\alpha$-D-galactose have been reduced to two possibilities through geometry optimisation of the hydrogen atom positions. $^{13}$C NMR shift parameters were not sufficiently sensitive to the hydrogen bonding in $\alpha$-D-galactose to allow the two structures to be differentiated by a comparison of calculated shifts with experiment. For $^{17}$O, calculated NMR parameters were used to distinguish even by a low field $^1$H spectrum, and in this way the Kouwijzer structure for $\alpha$-D-galactose was found to be correct. A relatively new semi-empirical GGA exchange–correlation functional specifically developed for the calculation of high-quality NMR parameters was tested. It was found that, although the calculated $^{13}$C parameters were not significantly changed by the choice of the functional, the $^1$H isotropic shifts obtained with KT3 gave less shielded results than the PBE functional.

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References