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Host–guest chiral discrimination in incommensurate 2-hydroxyalkane/urea inclusion compounds: a computational study

Lily Yeo[a] and Kenneth D. M. Harris*[b]

[a] *School of Chemistry, University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom*
[b] *School of Chemistry, Cardiff University, P.O. Box 912, Cardiff CF10 3TB, United Kingdom.*
Fax: +44 2920 874 030; e-mail: HarrisKDM@cardiff.ac.uk

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Computational studies of the extent and nature of host–guest chiral discrimination in incommensurate 2-hydroxyalkane/urea inclusion compounds demonstrate a number of contrasting features between the 2-hydroxyalkane/urea inclusion compounds reported here and 2-bromoalkane/urea inclusion compounds reported previously.

There is currently much interest in understanding structural, dynamic and chemical properties of solid one-dimensional inclusion compounds, typified by urea inclusion compounds.[1–3] In conventional urea inclusion compounds, the host structure[4,5] comprises a hydrogen-bonded arrangement of urea molecules that contains linear, parallel tunnels. The diameter of the urea tunnel varies between *ca.* 5.5 and 5.8 Å as a function of position along the tunnel,[6] and guest molecules based on a sufficiently long *n*-alkane chain and with a sufficiently small degree of substitution can form these inclusion compounds with urea. This structure is stable only when the tunnels are filled with a dense packing of guest molecules. The space group of the host structure at ambient temperature is $P6_122$ or $P6_522$, with the tunnel constructed from a spiral arrangement of urea molecules. A given single crystal either has only right-handed spirals ($P6_122$) or only left-handed spirals ($P6_522$). The chirality of the tunnel structure is generated spontaneously during crystal growth. The potential to exploit the chiral nature of the urea tunnel structure clearly depends on the extent to which the interaction between a host tunnel of a given chirality (*e.g.*, $P6_122$) differs for the two enantiomers (*R* and *S*) of a chiral guest. In spite of the potential for exploiting the chirality of urea inclusion compounds, virtually all reported studies of urea inclusion compounds have focused on non-chiral guest molecules, although an important exception is the experimental work of Schlenk[7–11] (reviewed in ref. 12).

Conventional urea inclusion compounds have an incommensurate relationship[13] between the periodicity (c_h) of the host structure along the tunnel and the periodicity (c_g) of the guest molecules along the tunnel. Thus, there are no sufficiently small integers p and q for which $pc_g = qc_h$. As a consequence, each guest molecule within a given tunnel has a different environment with respect to the host structure, and all values of z-coordinate within the unit cell of the host structure are sampled with essentially equal probabilities by different guest molecules within the tunnel (z defines the position along the tunnel). Investigations of host–guest chiral discrimination, of the type presented in this paper, must therefore consider the host–guest interaction energy as a function of the position of the guest molecule along the host tunnel.

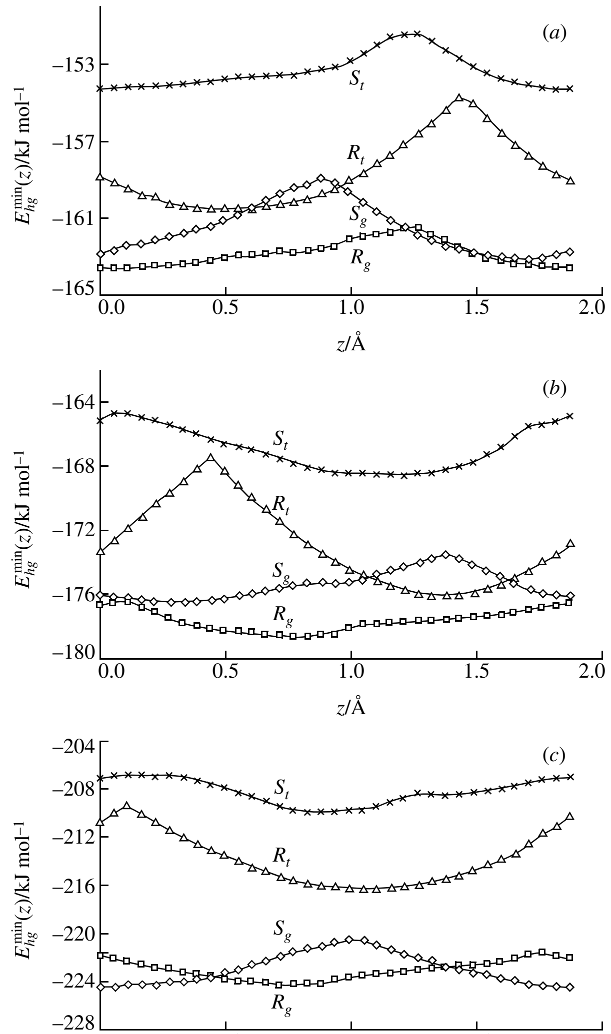

Figure 1 Graphs of $E_{hg}^{\min}(z)$ *versus* z (in the range $0 \le z < c_h/6$) for the four different combinations of chirality and end-group conformation of 2-hydroxyalkane guest molecules in the $P6_122$ urea tunnel structure: (*a*) 2-OHC$_9$/urea, (*b*) 2-OHC$_{10}$/urea and (*c*) 2-OHC$_{13}$/urea.

In this paper, we assess the extent and nature of host–guest chiral discrimination for chiral 2-hydroxyalkane guest molecules within the urea tunnel structure. For 2-hydroxyalkanes, the possibility that the guest molecules may participate in hydrogen-bonding interactions (both with urea molecules and with adjacent guest molecules) creates new opportunities for expressing chiral recognition that do not exist for 2-bromoalkane guest molecules, which we have studied previously[14] using a similar computational approach.

Our calculations of host–guest interaction in 2-hydroxyalkane/urea inclusion compounds considered a single guest molecule in the $P6_122$ urea tunnel structure.[5] All 2-hydroxyalkane/urea inclusion compounds that have been prepared experimentally are known[15] to have the conventional urea tunnel structure at ambient temperature. In our calculations of host–guest interaction, the host structure comprised 288 unit cells (6×6×8; with 8 unit cells along the tunnel axis) and the guest molecule was located in the central tunnel. Calculations were carried out for all members of the 2-hydroxyalkane series from 2-hydroxyoctane (denoted 2-OHC$_8$) to 2-hydroxypentadecane (denoted 2-OHC$_{15}$). Each guest molecule was constructed according to standard geometries, with the main alkane chain maintained in the all-*trans* conformation, as required to fit inside the tunnel. For each guest, both *R* and *S* enantiomers were considered, and for each enantiomer the following conformations of the OH-containing end-group were considered: (i) OH *trans*/Me *gauche* (denoted by subscript *t*); (ii) OH *gauche*/Me *trans* (denoted by subscript *g*).

In our model, six variables define the position (x, y, z) and orientation (θ, ϕ, γ) of the guest molecule within the tunnel [γ represents rotation about the tunnel axis (6_1 axis)], and one variable (μ) defines rotation of the H atom of the OH group about the C–OH bond. The host–guest interaction energy $E_{hg}(x, y, z, \theta, \phi, \gamma, \mu)$ was investigated as a function of the position (z) of the guest molecule along the host tunnel by considering specific (fixed) values of z on a grid of spacing $\Delta z = c_h/200 \approx 0.055$ Å. A standard potential energy parameterization[16] (validated in previous studies of urea inclusion compounds[17]) based on the atom–atom summation technique was used to compute $E_{hg}(x, y, z, \theta, \phi, \gamma, \mu)$. For each fixed value of z, the minimum value of $E_{hg}(x, y, z, \theta, \phi, \gamma, \mu)$ [denoted $E_{hg}^{\min}(z)$] was determined with respect to variation of x, y, θ, ϕ, γ and μ. For the $P6_122$ urea tunnel,

$$E_{hg}(x, y, z, \theta, \phi, \gamma, \mu) = E_{hg}(x, y, z + nc_h/6, \theta, \phi, \gamma + n\pi/3, \mu)$$

for any integer n, and so

$$E_{hg}^{\min}(z) = E_{hg}^{\min}(z + nc_h/6).$$

Thus, it is necessary to determine $E_{hg}^{\min}(z)$ only in the range $0 \le z < c_h/6$. The method employed to ensure that our calculations at each value of z locate the global minimum on the $E_{hg}(x, y, z, \theta, \phi, \gamma, \mu)$ surface, rather than a local minimum, has been described and tested rigorously elsewhere.[14] The average value (denoted $<E_{hg}^{\min}>$) of $E_{hg}^{\min}(z)$ is determined from

$$<E_{hg}^{\min}> = \frac{6}{c_h}\int_0^{c_h/6} E_{hg}^{\min}(z)\,\mathrm{d}z$$

and represents the average host–guest interaction energy for an incommensurate inclusion compound containing only the specified type of guest molecule. For each guest molecule considered, separate calculations were carried out for all four combinations of chirality and end-group conformation (*i.e.*, R_t, S_t, R_g or S_g).

Graphs of $E_{hg}^{\min}(z)$ versus z ($0 \le z < c_h/6$) for selected 2-hydroxyalkane/urea inclusion compounds are shown in Figure 1. For the longer guest molecules (2-OHC$_{11}$ to 2-OHC$_{15}$), $E_{hg}^{\min}(z)$ is lower for R_g and S_g than for R_t and S_t at all values of z [Figure 1(*c*)]. For the shorter guest molecules (2-OHC$_8$ to 2-OHC$_{10}$), $E_{hg}^{\min}(z)$ is lower for R_g and S_g than for R_t and S_t at most values of z, although there are some values of z for which the value of $E_{hg}^{\min}(z)$ for R_t drops below that for S_g [Figure 1(*a*)]. Thus, the graphs of $E_{hg}^{\min}(z)$ *versus* z show a clear overall preference for the OH *gauche* conformation of the guest molecules. The values of $<E_{hg}^{\min}>$ for each 'type' (*i.e.*, R_t, S_t, R_g or S_g) of guest molecule are given in Table 1. For all guest molecules and for both enantiomers R and S, the value of $<E_{hg}^{\min}>$ is lower for the OH *gauche* conformation than the OH *trans* conformation, with the difference ranging from *ca.* –3 to *ca.* –21 kJ mol^{-1}. The energetic preference for the OH *gauche* conformation generally increases as the guest molecule becomes longer.

Unlike the case for 2-bromoalkane guests,[14] for which the *gauche* Br atom protrudes further (and hence less favourably) into the urea tunnel wall compared with the *gauche* Me group, for 2-hydroxyalkane guest molecules, the C–OH bond length and the OH van der Waals radius are comparable to the C–Me bond length and the Me van der Waals radius, respectively. Thus, the size and shape compatibility between the guest molecule and the urea host tunnel is substantially similar for the OH *trans* and OH *gauche* conformations of a 2-hydroxyalkane guest molecule, and steric factors are therefore unlikely to be a major determinant of the preference for the OH *gauche* conformation. Instead, the preference for the OH *gauche* conformation reflects the capability of the gauche OH group to form specific hydrogen-bonding interactions with the urea molecules in the host tunnel, at least at certain positions z of the guest molecule along the tunnel.

To assess the extent to which the host–guest interaction for 2-hydroxyalkanes is influenced by the *gauche* side-group, calculations were also carried out on dodecane (representing 2-OHC$_{12}$ in the OH *gauche* conformation with the OH group removed) and undecan-1-ol (representing 2-OHC$_{12}$ in the OH *trans* conformation with the *gauche* Me group removed). As shown in Figure 2, at all values of z, $E_{hg}^{\min}(z)$ is more negative for dodecane and undecan-1-ol than for the OH *trans* conformation of 2-OHC$_{12}$ (both S_t and R_t), but more positive than for the OH *gauche* conformation of 2-OHC$_{12}$ (both R_g and S_g). These results demonstrate that the *gauche* OH group makes an overall negative contribution (*ca.* –2.4 to –7.1 kJ mol^{-1} for S_g and *ca.* –5.6 to –8.2 kJ mol^{-1} for R_g) to the host–guest interaction energy, implying that there is a favourable local interaction (hydrogen-bonding) between the *gauche* OH group and the host tunnel. On the other hand, the fact that $E_{hg}^{\min}(z)$ is more positive for the OH *trans* conformation of 2-OHC$_{12}$ than for dodecane, undecan-1-ol and the OH *gauche* conformation of 2-OHC$_{12}$ suggests that the *trans* OH group is unable to form the same type of interaction and that the *gauche* Me group forms an unfavourable local interaction with the tunnel wall that makes an overall positive contribution to the host–guest interaction energy. The close similarity between the $E_{hg}^{\min}(z)$ *versus* z graphs for dodecane and undecan-1-ol suggests that the *trans* OH group does not form any specific interaction, such as hydrogen bonding, with the urea host tunnel.

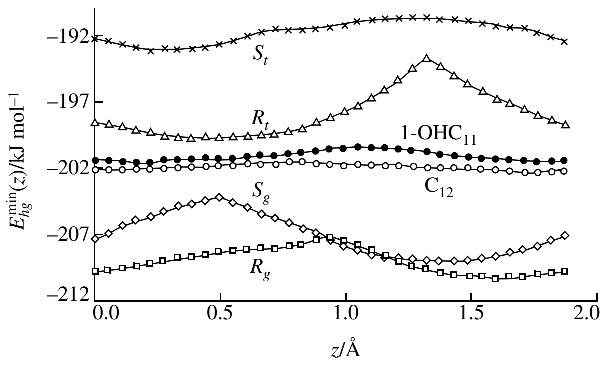

Figure 2 Graphs of $E_{hg}^{\min}(z)$ *versus* z (in the range $0 \le z < c_h/6$) for 2-OHC$_{12}$/urea (R_t, S_t, R_g and S_g guest molecules), undecan-1-ol/urea (denoted 1-OHC$_{11}$/urea) and dodecane/urea (denoted C$_{12}$/urea). All calculations refer to the $P6_122$ urea tunnel structure.

Ab initio calculations[18] with 3-21G* basis set (following local geometry optimization) for 2-hydroxyhexane [with the –(CH$_2$)$_3$Me chain in the all-*trans* conformation] suggest that, for the isolated molecule, the OH *gauche* conformation is lower in energy than the OH *trans* conformation by *ca.* 5.65 kJ mol^{-1}. Thus, both the intramolecular potential energy of the guest (established from the *ab initio* calculations) and the host–guest interaction energy (established from the force-field calculations above) contribute to promote the OH *gauche* conformation, and an overall preference for this conformation of 2-hydroxyalkane guest molecules within the urea tunnel structure is clearly predicted.

We now consider the host–guest chiral discrimination, focusing on the two enantiomers (R_g and S_g) of the preferred OH *gauche* conformation of the 2-hydroxyalkane guest molecules. From graphs of $E_{hg}^{\min}(z)$ *versus* z, the 2-hydroxyalkanes can be classified broadly into three categories: (i) 2-OHC$_9$, 2-OHC$_{12}$ and 2-OHC$_{15}$: $E_{hg}^{\min}(z)$ is lower for R_g than S_g at most values of z, but is lower for S_g than R_g at some values of z [Figure 1(*a*)]; (ii) 2-OHC$_{10}$: $E_{hg}^{\min}(z)$ is lower for R_g than S_g at all values of z [Figure 1(*b*)]; and (iii) 2-OHC$_8$, 2-OHC$_{11}$, 2-OHC$_{13}$ and 2-OHC$_{14}$: $E_{hg}^{\min}(z)$ is lower for R_g than S_g over about half the region of z, and lower for S_g than R_g at the other values of z [Figure 1(*c*)]. Clearly, a higher degree of chiral discrimination is expected for guest molecules in classes (i) and (ii) than those in class (iii). These observations are reflected by the differences in $<E_{hg}^{\min}>$ between R_g and S_g shown in Table 1. Thus, for all 2-hydroxyalkanes except 2-OHC$_{11}$, $<E_{hg}^{\min}>$ is lower for R_g than S_g in the $P6_122$ tunnel structure, although the differences in $<E_{hg}^{\min}>$ are comparatively small (less than *ca.* 2.3 kJ mol^{-1}). For 2-OHC$_{11}$, $<E_{hg}^{\min}>$ is lower (by 0.2 kJ mol^{-1}) for S_g than R_g. For all 2-hydroxyalkanes studied, the differences in $<E_{hg}^{\min}>$ between the R_g and S_g enantiomers are substantially smaller than those found previously[14] for 2-bromoalkane/urea inclusion compounds, for which the difference in $<E_{hg}^{\min}>$ between the R and S enantiomers in the preferred conformation ranges from 2.8 to 8.1 kJ mol^{-1}.

As suggested above, the host–guest interaction for 2-hydroxyalkane guest molecules depends significantly on the ability to establish hydrogen-bonding interactions with urea molecules in the host tunnel. The fact that, in the OH gauche conformation, both the R and S enantiomers are able to form hydrogen bonding interactions with the urea host tunnel (albeit with dif-

Table 1 Values of $<E_{hg}^{\min}>$ for the four different combinations (denoted R_t, S_t, R_g or S_g) of chirality and end-group conformation of 2-hydroxyalkane guest molecules in the $P6_122$ urea tunnel structure. The differences between the values of $<E_{hg}^{\min}>$ for the two conformations of a given enantiomer and the difference between the values of $<E_{hg}^{\min}>$ for the two enantiomers in the same conformation are also shown.

Guest molecule	$<E_{hg}^{\min}>$/kJ mol^{-1}				Differences in $<E_{hg}^{\min}>$/kJ mol^{-1}			
	S_g	R_g	S_t	R_t	$S_g - S_t$	$R_g - R_t$	$R_g - S_g$	$R_t - S_t$
2-OCH$_8$	–144.9	–145.0	–138.2	–141.5	–6.7	–3.5	–0.1	–3.3
2-OCH$_9$	–161.5	–162.9	–153.4	–158.6	–8.1	–4.3	–1.4	–5.2
2-OCH$_{10}$	–175.4	–177.7	–166.9	–172.9	–8.5	–4.8	–2.3	–6.0
2-OCH$_{11}$	–193.3	–193.1	–183.1	–186.8	–10.2	–6.3	+0.2	–3.7
2-OCH$_{12}$	–207.1	–209.0	–191.7	–197.8	–15.4	–11.2	–1.9	–6.1
2-OCH$_{13}$	–222.9	–223.1	–208.3	–213.8	–14.6	–9.3	–0.2	–5.5
2-OCH$_{14}$	–239.0	–239.6	–218.6	–222.8	–20.4	–16.8	–0.6	–4.2
2-OCH$_{15}$	–253.4	–255.2	–234.6	–239.2	–18.8	–16.0	–1.8	–4.6

ferent optimum positions and orientations with respect to the tunnel) underlies our finding that there is no substantial energetic discrimination between the *R* and *S* enantiomers in 2-hydroxyalkane/urea inclusion compounds.

While the investigations reported here have focused on the crucial interaction (*i.e.*, host–guest interaction) responsible for chiral recognition in these solids, we note that other factors may also influence the exact proportions of the two enantiomers of a chiral guest molecule within the host tunnel. These factors include the guest–guest interaction, which may be expected to exert some influence when the orientations of adjacent guest molecules are such that their chiral head-groups come together, and structural relaxation of the host framework (recalling that the calculations presented here were within the approximation of a rigid host structure). Future computational studies of host–guest chiral recognition in urea inclusion compounds will include consideration of these additional aspects.

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