



Clathrates of TETROL: Selective Inclusion of Methylcyclohexanones in their Energetically Unfavorable Axial Methyl Conformations

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COMMUNICATION

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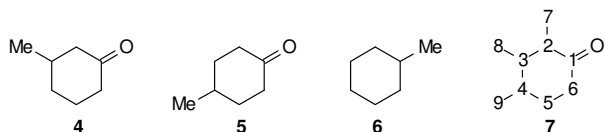
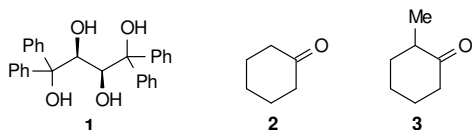
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3- and 4-Methylcyclohexanone have been isolated exclusively as their energetically disfavoured axial conformations in the host-guest complexes formed upon recrystallization of the novel optically pure host compound, (+)-(2*R*,3*R*)-1,1,4,4-tetraphenylbutane-1,2,3,4-tetraol (TETROL), from these cycloalkanones.

We are currently investigating applications of (+)-(2*R*,3*R*)-1,1,4,4-tetraphenylbutane-1,2,3,4-tetraol (TETROL) **1** as a novel chiral host compound in host-guest chemistry. We recently described a computational study on **1** which revealed that in its lowest energy structure, the butane chain adopts an *anti* conformation, with the four hydroxy groups in a *syn* arrangement with respect to the butane backbone, and stabilized through a pair of 1,3-hydrogen bonding interactions.¹ A single crystal X-ray diffraction analysis of **1** confirmed this geometry. Six independent molecules were located in the asymmetric unit of the crystal, forming three distinct dimeric motifs *via* intermolecular O-H...O hydrogen bonds. Association of the dimers into spiral arrays *via* additional O-H...O hydrogen bonds yielded an intricate crystal structure in the trigonal space group P3₁.



Recrystallization of **1** from pyridine and each of the three isomeric methylpyridines, respectively, led to the inclusion of pyridine in a 1:2 host:guest (H:G) ratio, and 4- and 3-methylpyridine, each in a 1:1 H:G ratio. 2-Methylpyridine was not included. In competition experiments with mixtures of the pyridines, TETROL was found to display significant inclusion selectivity.¹

As an optically pure chiral host compound, TETROL could potentially include racemic guest compounds enantioselectively, similarly to TADDOLs.²

We now report on the host-guest interactions of **1** with cyclohexanone **2** and the isomeric 2-, 3-, and 4-methylcyclohexanones **3-5**.

All four cyclohexanones were included by TETROL with 1:1 H:G ratios, as shown by ¹H-NMR analysis. Enantioselective inclusion of 2- and 3-methylcyclohexanone was assessed by distilling the guest compounds out of the crystal matrices under vacuum, followed by conversion of the distillates into diastereomeric acetals *via* reaction with optically pure (2*R*,3*R*)-(-)-butane-2,3-diol. Enantiomeric excesses were determined through integration of the appropriate twinned signals in their ¹³C-NMR spectra. In both cases some selectivity for the (*R*)-enantiomer was evident (13 % and 20 % e.e. for 2- and 3-methylcyclohexanone, respectively). Nassimbeni *et al*³ have employed a chiral diol host compound to attempt to resolve the enantiomers of 3-methylcyclohexanone but only partial resolution occurred (40% e.e.).

Crystals of all four host-guest complexes were analyzed by single crystal X-ray diffraction. In the case of 3- and 4-methylcyclohexanone⁴ (see Table S1, Supporting Information), the guest molecules were both found to occur as the axial methyl conformers. This result is surprising given the lower stabilities of axial methyl cyclohexanones compared to their equatorial analogues. Indeed, we are not aware of any precedents in the literature where selectivity for axial methyl cyclohexanones in host-guest complexes has been reported. Fig. 1 shows the 1:1 host-guest motifs in the asymmetric units of the crystals of TETROL-3-methylcyclohexanone **1·4** and TETROL-4-methylcyclohexanone **1·5**. While the host molecule maintains essentially the same conformation in the two structures, the guest molecule in **1·4** is disordered over two sites, the major component being the (*R*)-enantiomer [site-occupancy factor (s.o.f.) 0.78] and the minor the (*S*)-enantiomer (s.o.f. 0.22). The source of the selectivity during complexation is the formation of a very strong host-guest O-H...O=C hydrogen bond (O...O = 2.621(2) Å) involving the guest

(*R*)-enantiomer; instead, the H-bond linking the same host hydroxy group to the carbonyl oxygen of the (*S*)-enantiomer is very weak ($O\cdots O = 3.125(8)$ Å). In the crystal of **5**, the corresponding H-bond has comparable strength ($O\cdots O = 2.713(4)$ Å) to that of the shorter H-bond in the crystal of **1·4**.

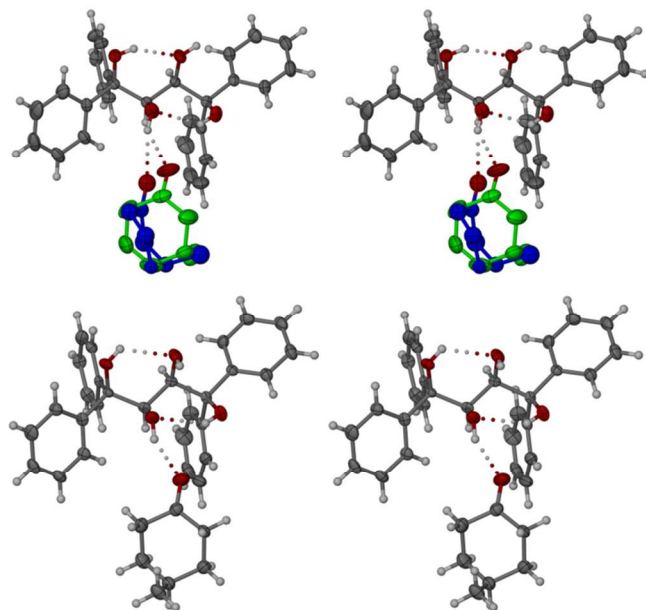


Figure 1. Stereoviews of the asymmetric units in the crystals of **1·4** (top) and **1·5** (bottom). For clarity, guest H atoms are omitted for **1·4** and the stereoisomers are distinguished by color [(*R*)-enantiomer in green; (*S*)-enantiomer blue].

Despite the difference in the crystal symmetries of **1·4** (monoclinic, $P2_1$) and **1·5** (triclinic, $P1$), both crystals pack with the equivalent of one guest molecule residing within an isolated chiral cavity formed by their respective host molecules (Fig. S1).

The consistent occurrence of *axial* methylcyclohexanone conformers in the inclusion crystals is of primary interest here and in order to rationalize this, the guest environments were studied in detail, with a focus on the possible existence of co-operative weaker stabilizing packing interactions. Inspection of short guest \cdots host contact distances in the crystal of **1·4** (as representative) revealed three intermolecular (guest) $C-H\cdots\pi$ interactions (1-3 in Fig. 2). These have short $H\cdots$ phenyl ring centroid distances in the range 2.75-2.87 Å (Table S2) and they contribute to the stabilization of the conformation of the (major) (*R*)-enantiomer of 3-methylcyclohexanone. In particular, the interaction labelled '1' involves the tertiary H atom at the chiral centre of the guest molecule as donor. There is an additional short intermolecular $H\cdots C_{ar}$ interaction (4) of length 2.76 Å between one of the guest methyl H atoms and a neighboring aromatic carbon atom.

The co-operative role that multiple 'soft' attractive interactions of this type may play in determining subtle aspects of crystal packing in supramolecular systems (e.g. enantiomeric selectivity, conformational preferences) is well known.⁵ We conclude here that the combination of these interactions with the anchoring role of the $C=O\cdots H-O$ hydrogen bond (Fig. 1) is evidently responsible for stabilizing the unusual *axial* conformation. The minor guest component in **1·4** (the (*S*)-enantiomer), also present as the *axial*

methyl conformer, engages in three $C-H\cdots\pi$ interactions and three weaker attractive contacts with $H\cdots C_{ar} \sim 3$ Å, one of these involving a methyl H atom (Table S2, Fig. S2). Given also that the (*S*)-enantiomer is encapsulated within a cavity of identical topology to that accommodating the (*R*)-enantiomer, spatial considerations suggest that the sterically more compact *axial* conformer of the former stereoisomer should also be favoured in this inclusion complex.

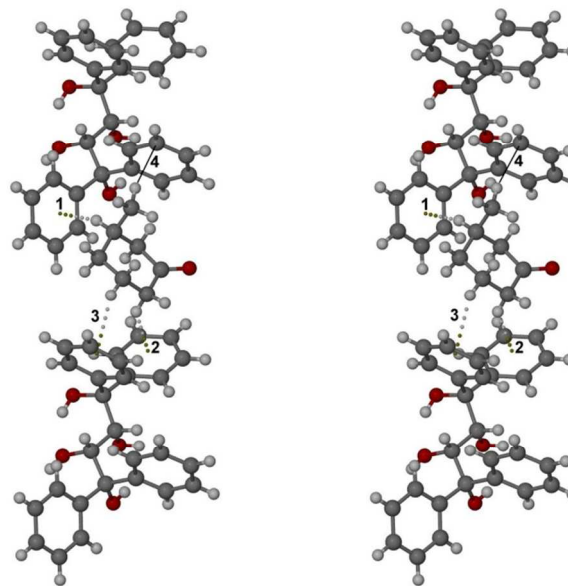


Figure 2. Stereoview illustrating $C-H\cdots\pi$ type interactions 1-4 that stabilize the conformation of the (*R*)-enantiomer of the guest molecule in the crystal of **1·4**.

In the case of **1·5**, the complex containing 4-methylcyclohexanone as the *axial* conformer, analogous host-guest stabilizing interactions include two (guest) $C-H\cdots\pi$ interactions and four $H\cdots C_{ar}$ interactions (Table S2, Fig. S3). The methyl group orientation is symmetrical with respect to the ring, the two CH_3/H 1,3-diaxial interactions being almost equal ($H\cdots H$ 2.3 and 2.4 Å).

The conformational equilibria for mono-alkyl cyclohexanes are invariably biased in favor of the equatorial alkyl chair conformers. While this is also the case for cyclohexanones, the conformational free energy difference is significantly smaller for 2-alkyl- and especially 3-alkyl-cyclohexanones, leading to an increase in the relative amount of the *axial* conformer. The '3-alkylketone effect'⁶ has been attributed to the loss of one of the destabilising 1,3-diaxial alkyl-hydrogen van der Waals repulsions, resulting from replacement of a tetrahedral 3-methylene carbon with the trigonal planar carbon of the carbonyl group. Consequently, the equatorial-*axial* enthalpy difference has been estimated to be about 2.5 kJ mol⁻¹ smaller.⁷

However, we note that for the (*R*)-enantiomer of 3-methylcyclohexanone in the crystal of **1·4**, the remaining 1,3-diaxial repulsive interaction is not significant since the methyl group orientation (Fig. 2) is such that its two closest H atoms are sufficiently far from the synaxial methylene H atom (distances 2.4 and 2.8 Å). Stabilization of the *axial* conformer is attributed to an attractive intramolecular $CH/\pi(C=O)$ interaction involving the closest methyl H atom ($H\cdots C$ distance 2.65 Å). Takahashi *et al*⁸

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have concluded from *ab initio* MO calculations carried out at the MP2/6-311++G(d,p)//MP2/6-311G(d,p) level, that the 'alkylketone effect' in axial 2- and 3-alkyl-cyclohexanones arises from a stabilizing interaction of this kind.

We have likewise calculated the energies of the axial and equatorial conformers for the methylcyclohexanones **3-5** and methylcyclohexane **6** using the G3(MP2) composite method⁹ (Table 1). Similar trends to those reported by Takahashi and coworkers were observed, with a general preference for the equatorial conformers, and confirmation of a significant 3-alkylketone effect for 3-methylcyclohexanone **4**.

Table 1. Computed energies^[a] (kJ mol⁻¹) and conformer Boltzmann distributions for methylcyclohexanones **3-5 and methylcyclohexane **6**.**

	3	4	5	6
ΔH_{eq}	-257.21 (0.36) ^[b]	-257.57 (0.00)	-256.95 (0.62)	-151.85 –
ΔH_{ax}	-249.88 (7.69)	-253.37 (4.20)	-250.83 (6.74)	-144.41 –
$\Delta H_{\text{ax}} - \Delta H_{\text{eq}}$	7.32	4.20	6.11	7.44
Boltzmann distributions				
equatorial	95.0	84.5	92.2	95.3
axial	5.0	15.5	7.8	4.7
Alkylketone effect ^[c]	0.12	3.25	1.33	–

[a] G3(MP2) composite method.⁹

[b] Relative to the most stable conformer (**4eq**).

[c] $(\Delta H_{\text{ax}} - \Delta H_{\text{eq}})_{\text{methylcyclohexane}} - (\Delta H_{\text{ax}} - \Delta H_{\text{eq}})_{\text{methylcyclohexanone}}$

The structures of the three methyl cyclohexanone conformers found in the host-guest complexes were compared with the corresponding computed geometries (Fig. 3, Table S3). Close correspondence was found for equatorial 2-methylcyclohexanone **3eq** where a root mean square deviation (RMSD) of 0.029 Å was calculated for differences between only the heavy atom pairs in the two structures. In contrast, the axial 3- and 4-methylcyclohexanones **4ax** and **5ax** showed significantly greater geometric variations between their crystal and theoretical structures (RMSD 0.093 Å and 0.072 Å, respectively).

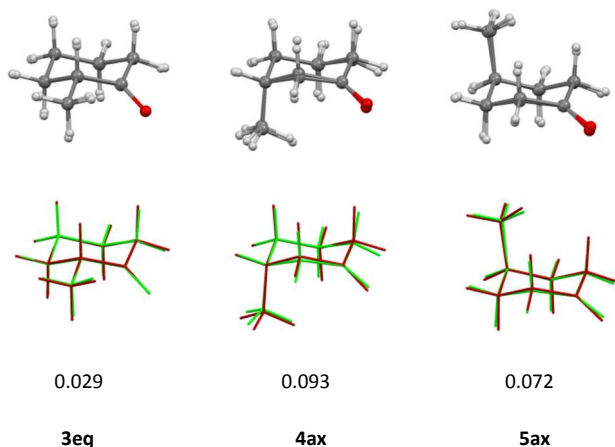


Figure 3. Overlaid crystal and computed structures for equatorial 2-methylcyclohexanone (3eq**), axial 3-methylcyclohexanone (**4ax**), and axial 4-methylcyclohexanone (**5ax**) distinguished by color [crystal structure in green; theoretical structure in red] with RMSD values (Å) for C and O atom pairs.**

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In the case of **4ax**, the intra-annular torsion angle $C_5-C_6-C_1-C_2$ (the numbering sequence used is defined in structure **7**), as well as those terminating in the carbonyl group, $O-C_1-C_2-C_3$ and $C_5-C_6-C_1-O$, differ by -11.4° , 13.4° and -13.6° , respectively, in the crystal structure compared to the computed values. Furthermore, the methyl group is rotated by about 12° from the ideal staggered conformation with respect to the underlying ring carbon atoms in the crystal structure.

While the theoretical structure of the axial conformer **5ax** of 4-methylcyclohexanone is symmetrical about the OC_1C_4 plane, the crystal structure is slightly asymmetrically distorted. Indicative of this is the $C_2-C_3-C_5-C_6$ torsion angle of approximately 2° found for the crystal structure, compared to 0° in the computed geometry. However, the most significant difference is evident in a partial flattening of the carbonyl terminus of the ring in the crystal structure, hence increasing the C_1 -(centroid $C_2 C_6$)-(centroid $C_3 C_5$) angle by more than 5° . In contrast, the $C_3-C_4-C_5$ plane is tilted more acutely by about 1° . Consequently, in the crystal structure the methyl group is located about 0.1 Å closer to the carbonyl carbon.

A CSD search¹⁰ for compounds containing 3- and 4-methylcyclohexanone yielded eight crystal structures containing the former guest and two the latter, with equatorial conformers featuring consistently. Our observation of solely axial conformers is thus exceptional. Furthermore, their occurrence has a different origin from that proposed *e.g.* for the isolation of the axial conformer of chlorocyclohexane in the crystal of an inclusion compound, which instead is partly attributed to *attractive* $Cl \cdots H$ 1,3-diaxial interactions,¹¹ a situation very different from that in our host complexes.

Conclusions

3- and 4-Methylcyclohexanone have been isolated as their energetically disfavoured axial conformations in crystalline complexes with the novel host compound, TETROL. This observation is unprecedented in the literature, and demonstrates the profound and extraordinary effect that subtle host-guest interactions can have in determining the favoured geometries of guest molecules.

Notes and references

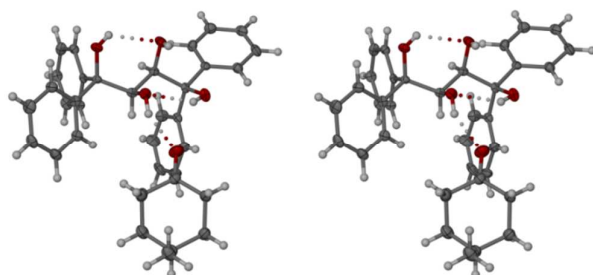
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Electronic Supplementary Information (ESI) available: [Experimental, additional X-ray diffraction and computational data are contained in the Supplementary Information provided with this manuscript]. See DOI: 10.1039/c000000x/

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Graphical Abstract

TETROL, surprisingly, includes 3- and 4-methylcyclohexanone exclusively in their energetically disfavoured axial conformations.