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Conformational Chiral Recognition in a Simple Urea

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Urea 4 was unexpectedly isolated from the reaction of benzylamine with tosylate ester 1. Crystallisation of an inseparable mixture of hemiaminal 3 and 4 from ethanol provided crystals of 4 suitable for single crystal X-ray diffraction ($C_{15}H_{16}N_2O$, monoclinic, space group *Ia*, $a = 22.9800(16)$, $b = 4.618(9)$, $c = 24.059(10)$ Å, $\beta = 99.91(3)°$, $D_c = 1.269\ \mathrm{g\,cm^{-3}}$, $Z = 8$ and 2703 observed reflections. Refinement terminated with $R_1 = 0.0876$, $wR_2 = 0.1953$ $(I > 2\sigma I)$ and $R_1 = 0.2154$, $wR_2 = 0.2445$ (all data). These revealed that the unit cell contained only two of the possible three conformers of 4. Both the predictable achiral conformer 4a and the unexpected chiral conformer 4b appear to be independent of one another. Each conformer is linked into an independent *polymeric* chain via an array of hydrogen bonds between the Lewis basic oxygen lone pairs and N–H donors of the urea.

Keywords: Molecular recognition; Induced chirality; Chiral amplification; Hydrogen bonding

INTRODUCTION

The understanding of the process of molecular recognition involving non-covalent interactions is paramount [1–5]. Recently, significant interest has been devoted to the recognition, and analyses of such interactions present in nature [6] in an attempt to aid future design of polyfunctional molecular assemblies, e.g. molecular separation [7,8], gears [9–11], drug–receptor interactions [12] and crystal engineering [13–18]. These molecular, and in many cases, chiral recognition processes are also central to life. The ability of one molecule to recognise another and subsequently alter its conformation, is important if recognition processes are to occur. Such interactions are well known [19,20] and reasonably understood but their origins are somewhat overlooked or speculative. In particular chirality arising from conformational change in molecules that would normally be considered to be achiral, has largely been ignored [21]. Clearly at some stage during the evolutionary pathway such recognition processes occurred and were amplified to generate the chiral building blocks of life that are used today.

During our investigations into the synthesis of unsymmetrically substituted azamacrocycles [22,23], we attempted to synthesise **2** by adding benzylamine to a stirred solution of **1** in DMF (Fig. 1). These attempts resulted in the serendipitous crystallisation of a simple urea **4**, which was revealed to have significant chiral recognition present in the unit cell by single crystal X-ray diffraction.

RESULTS

Only crystals of **4** suitable for single crystal X-ray diffraction could be isolated by crystallisation (in ethanol) of an inseparable mixture of **3** and **4** isolated by column chromatography. The formation of **4** appears to have occurred as a result of the addition of benzylamine to carbon dioxide derived from the carbonate base. Similar reactions have previously been reported [24–27], as have numerous reports of **4** [28], although to the best of our knowledge, no reports of its single crystal X-ray structure have been reported. The unit cell revealed that two independent and unique conformations of **4** were present, Fig. 2. The first was the predictable achiral conformer **4a**, whereas the other chiral conformer **4b** was unexpected, Fig. 3. It appears that both conformers **4a** and **4b** are needed in the unit cell, both of which form elaborate and systematic hydrogen bonded

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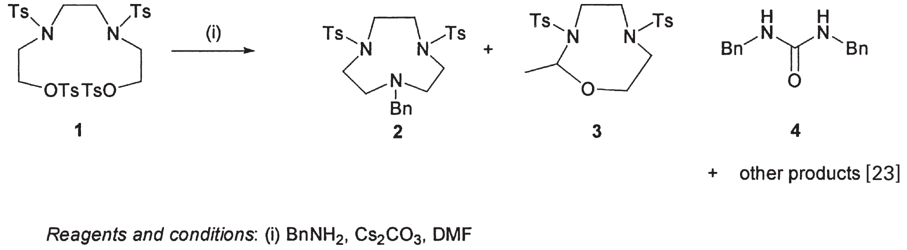

FIGURE 1 Reagents and conditions: (i) $BnNH_2$, Cs_2CO_3, DMF.

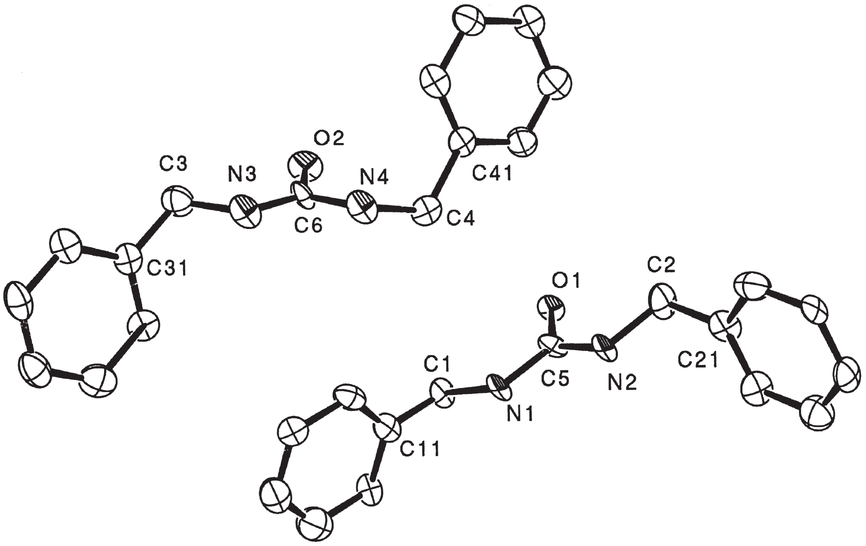

FIGURE 2 The two conformers of **4** in the asymmetric unit.

pairs between Lewis basic oxygen lone pairs and N–H donors, Fig. 4.

DISCUSSION

The single crystal X-ray structure of **4** was far more complicated than might initially be anticipated from its simple classical achiral representation. Of the three conformers of **4** that can exist only two were present in the asymmetric unit, Fig. 2. One of these was the achiral conformer **4a**, in which the phenyl rings are related by a C_2-axis. The other, **4b**, was one, of a possible two, conformational enantiomers. However, even in the apparently achiral conformer **4a**, asymmetry occurs, as illustrated by the single amide bond lengths of N(1)–C(5) = 1.37 Å and N(2)–C(5) = 1.30 Å and the dihedral angles C(21)–C(2)–N(2)–C(5) = −166.8° and C(11)–C(1)–N(1)–C(5)= −165.4°. It is worthy of note that one of the nitrogen lone pairs appears to be donating into the carbon–oxygen π^* orbital slightly more efficiently than the other, which is evident by the slight twist in the dihedral angle C(2)–N(2)–C(5)–O(1) of 4.6° *c.f.* C(1)–N(1)–C(5)–O(1) of 2.3°. In the chiral conformer the asymmetry in the amide N–C bond lengths is significantly less pronounced N(3)–C(6) = 1.31 Å and N(4)–C(6) = 1.34 Å, although the overall magnitude of the dihedral angles are comparable with **4a** (C(4)–N(4)–C(6)–O(2) = −23.8° and C(3)–N(3)–C(6)–O(2) = 5.0°). It is clear that both phenyl groups in **4b** have a different orientation as judged by the following dihedral angles C(31)–C(3)–N(3)–C(6) = 143.7° and C(41)–C(4)–N(4)–C(6)=86.9°. Other selected bond lengths and angles are given, Table I.

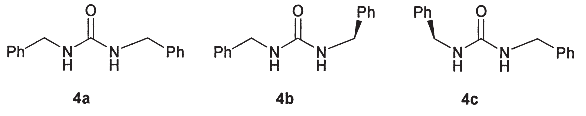

FIGURE 3 Possible conformations of **4**.

In the unit cell the two conformers are completely independent of one another and are linked into *polymeric* chains via a hydrogen bonded network, Fig. 4. This appears to indicate that the crystal packing forces play a minor role in the conformational preference of this urea. There are however, considerable differences between the lengths of the

TABLE I Selected bond lengths(Å) and angles (°) for **4**

C(1)–C(11)	1.458(13)
C(1)–N(1)	1.431(15)
C(2)–N(2)	1.466(16)
C(2)–C(21)	1.530(13)
C(3)–N(3)	1.466(15)
C(3)–C(31)	1.517(14)
C(4)–N(4)	1.443(15)
C(4)–C(41)	1.560(14)
C(5)–O(1)	1.263(9)
C(5)–N(2)	1.295(16)
C(5)–N(1)	1.371(16)
C(6)–O(2)	1.241(11)
C(6)–N(3)	1.311(14)
C(6)–N(4)	1.344(15)
C(11)–C(1)–N(1)	111.0(10)
N(2)–C(2)–C(21)	109.2(11)
N(3)–C(3)–C(31)	110.7(10)
N(4)–C(4)–C(41)	114.6(10)
O(1)–C(5)–N(2)	123.0(13)
O(1)–C(5)–N(1)	118.4(13)
N(2)–C(5)–N(1)	118.6(7)
O(2)–C(6)–N(3)	124.5(12)
O(2)–C(6)–N(4)	119.0(11)
N(3)–C(6)–N(4)	116.3(9)
C(5)–N(1)–C(1)	125.7(10)
C(5)–N(2)–C(2)	121.0(10)
C(6)–N(3)–C(3)	122.6(10)
C(6)–N(4)–C(4)	121.8(10)
C(12)–C(11)–C(1)	119.2(9)
C(16)–C(11)–C(1)	120.8(9)
C(22)–C(21)–C(2)	118.9(9)
C(26)–C(21)–C(2)	121.1(9)
C(32)–C(31)–C(3)	120.4(8)
C(36)–C(31)–C(3)	119.6(8)
C(42)–C(41)–C(4)	118.2(7)
C(46)–C(41)–C(4)	121.8(7)

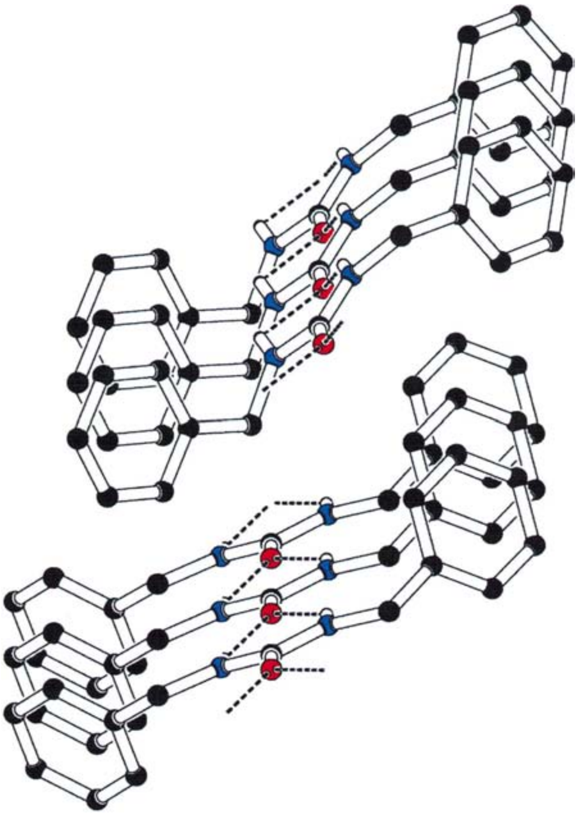

FIGURE 4 The polymeric hydrogen bonded array.

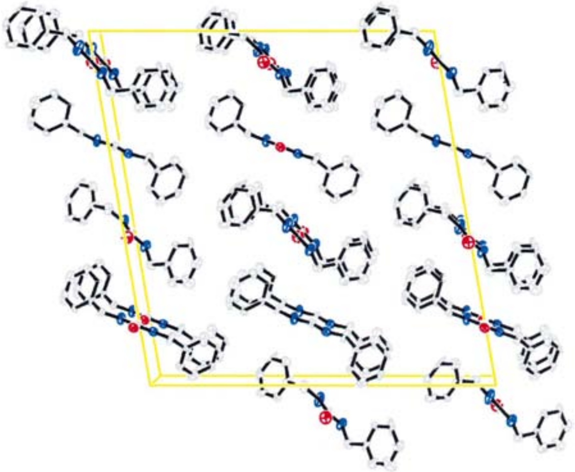

FIGURE 5 A perspective view along the *b*-axis of the unit cell.

hydrogen-bonded interactions. In conformer **4a** which contains a pseudo C_2-rotation axis, these interactions are fairly similar O(1)···N(1) 2.96 Å and O(1)···N(2) 2.87 Å. In contrast, the chiral conformer shows considerable asymmetry in these interactions O(2)···N(3) 2.84 Å and O(2)···N(4) 3.02 Å. These differences do not result from variations in the efficiency of π–π interactions between the aryl rings of the two conformers, as the ring centre-ring centre distance is the same for both conformers and equal to 4.618 Å viz. the *b*-axis of the unit cell. Since the average of these hydrogen bonding distances are approximately identical for each conformer it suggests that the asymmetry in the chiral conformer induces asymmetric hydrogen-bonding between like conformers.

The unit cell presents a further interesting feature when viewed along the *b*-axis, Fig. 5. When the cell is viewed in this way, *polymeric* chains of conformer **4b** are present in which the orientation of the polar carbonyl group alternates along the *a*-axis. These rows are interspersed with rows of the achiral

TABLE II Crystal data and structure refinement for **4**

Formula	$C_{15}H_{16}N_2O$
M	240.30
T (K)	180(2)
Crystal system	Monoclinic
Space group	*Ia*
a(Å)	22.9800(16)
b(Å)	4.618(9)
c(Å)	24.059(10)
β(°)	99.91(3)
U(Å^3)	2515(5)
ρ(g Å^{-3})	1.269
Z	8
μ(Mo-Kα)(mm^{-1})	0.081
F(000)	1024
Reflections collected	4891
Independent reflections	2703
R_{int}	0.3113
Final R_1, $wR_2[I > 2\sigma(I)]$	0.0876, 0.1953

conformer **4a**, again with analogous alternating dipole moments. In contrast the view along the *c*-axis of the cell reveals that the orientations are different and the dipole moments of adjacent chiral and achiral conformers align, this synergistic polarity is then opposed by an equivalent, but oppositely aligned pair such that this axis can be described as having a 2:2 repeat unit of **4a** and **4b**.

CONCLUSIONS

We have been able to show that a simple achiral molecule can exist in one of two possible chiral conformers, as a result of intimate and simple hydrogen bonded networks. The mirror image of this conformer is not present in the unit cell. Therefore interaction of other simple molecules that are capable of exhibiting conformational chirality, or indeed chiral molecules, with this crystal would be expected to result in chiral amplification through crystallisation [29]. We believe that such interactions are important and could have implications in the origins of life.

MATERIALS AND METHODS

A solution of **1** (1.0 g, 1.30 mmol), benzylamine (157 μl, 1.43 mmol) and cesium carbonate (940 mg, 2.86 mmol) in dry DMF (15 cm^3) was stirred at 100°C in an atmosphere of nitrogen for 6 days. After cooling to room temperature, the inorganic salts were removed by filtration and the filtrate evaporated under reduced pressure to leave a yellow solid which was purified by column chromatography on silica gel (petroleum spirit 40/60-ethyl acetate, 3:1) to give a range of products. Hemiaminal **3** and urea **4** were isolated as an inseparable mixture (90 mg). Slow evaporation of an ethanolic solution of this inseparable mixture yielded crystals suitable for single crystal X-ray diffraction. A crystal of dimensions $0.65 \times 0.10 \times 0.10\,\text{mm}^3$ was selected and mounted on a glass fibre. Data collection and structure refinement parameters are given in Table II. Intensity data were collected on an Enraf-Nonius CAD-4 diffractometer using Mo-Kα radiation ($\lambda = 0.71073$ Å) with ω–2θ scans at 180(2) K. The structure was solved by direct methods using the SHELXS 97 program [30] and developed by Fourier difference techniques with subsequent refinement on F^2 by full matrix least squares using SHELXL 97 [30]. Absorption correction was initially carried out by ψ-scans [31] and later using the program DIFABS [32] to give an improved absorption correction considering the crystal morphology. The positions of all H-atoms were calculated geometrically and refined using an atom riding model. A restrained refinement of anisotropic thermal parameters was carried out for all non-hydrogen atoms. Due to the relatively poor scattering of this crystal R_{int} and R factors are relatively high. Publication material was prepared using WINGX [33] and molecular graphics using ORTEP-3 [34] and PLATON[†] [35,36].

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[†] Crystallographic data (excluding structure factors) have been deposited with the Cambridge crystallographic data Centre as supplementary publication number CCDC 169257. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-0-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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