Tetrahedron Letters 49 (2008) 5063–5066

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A pyridine-based macrocyclic host for urea and acetone

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ARTICLE INFO

Article history:
Received 17 April 2008
Revised 3 June 2008
Accepted 8 June 2008
Available online 12 June 2008

Keywords:
Acetone complex
Urea binding
Unconventional hydrogen bonds
Inclusion complex

ABSTRACT

A pyridine-based macrocycle with a polyether chain has been designed and synthesized. The macrocycle shows strong binding for acetone involving both conventional and unconventional hydrogen bonds. The acetone in the cavity is exchangeable in $CHCl_3$ by urea. This has been studied thoroughly by ^1H NMR, ^{13}C NMR, mass and X-ray analyses.

The application of hydrogen bonding as a design principle in the construction of host molecules for selective complexation of guest molecules is very important in biology, chemistry and material science.[1–4] Despite the relative weakness of hydrogen bonding interactions, both conventional and unconventional hydrogen bonds have been used extensively to control the supramolecular structure of solids, giving rise, for example, to linear ribbons, planar networks or helical structures.[5–11] In this respect, C–H---O and C–H---N unconventional hydrogen bonds play an important role in determining the supramolecular structures. Although short C–H---O contacts have been reported regularly in the crystallographic literature, it is only recently, notwithstanding Sutor's study, that their importance in organic structures has been accepted and their recognition as 'hydrogen bonds' been received without scepticism.[12] According to Taylor and Kennard, C–H---O contacts are not steric effects but distinct electrostatic phenomena and that the frequency with which they occur suggests that they play a significant role in determining the packing arrangements of some organic crystal structures.[13] It has also been suggested that these weak forces have an impact on the selectivity/ reactivity of chemical transformations.

As a part of our work in the area of molecular recognition, we report here the design, synthesis and hydrogen bonding properties of simple pyridine-based macrocycle **1**. The macrocycle **1** exhibits the unique property of inclusion of both acetone and urea.

Urea, the end product of nitrogen metabolism, is a toxic pollutant that causes serious biological disorders.[14,15] Various groups have addressed the recognition of urea using designed synthetic receptors. Crown ether-based receptors developed by Pedersen,[16] and the carboxylic acid-containing macrocyclic receptor of Reinhoudt[17] are known to bind urea. Reinhoudt et al. have also explored the concept of using an electrophilic centre to bind urea in the cavity of a crown ether.[18] Bell et al. reported the synthesis of naphthyridine fused polyaza heterocycles for urea recognition.[19] A recent report has shown that benzimidazole-containing cleft is able to form a complex with urea.[20] Goswami et al. reported the recognition of urea using a macrocyclic fluorescent receptor in chloroform based on their previous approach to a naphthyridine receptor for urea.[21]

In this study, our pyridine amide-based macrocyclic receptor **1** shows a strong propensity to form hydrogen-bonded complexes with carbonyl guests, especially with less polar acetone and more polar urea molecules. This is due to correct alignment of all the hydrogen bond donors and acceptors of **1** in the cavity as well as size/shape complementarity. The AM1 optimized geometry[22] of **1** in Figure 1a demonstrates that the cavity has enough room to accommodate small molecules with correct hydrogen bonding information. Figures 1b and 1c, in this connection, indicate the AM1 optimized geometries of complexes of **1** with acetone and urea, respectively.

The synthesis of macrocyclic receptor **1** is outlined in Scheme 1. Initially, the coupling of digol with 2-(*N*-pivaloyl)-6-bromethylpyridine afforded pyridine amide appended polyether **2**, which on alkaline hydrolysis gave the diamine **3** in 80% yield. High dilution coupling of diamine **3** with isophthaloyl diacid chloride in dry THF produced the macrocycle **1** in 18% yield.[23]

Characterization of the macrocycle **1** by ^1H NMR indicated all the expected signals but with an extra signal at δ 2.26 ppm. In the FTIR, a peak at 1673 cm^{-1} was observed along with the amide

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0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.06.030

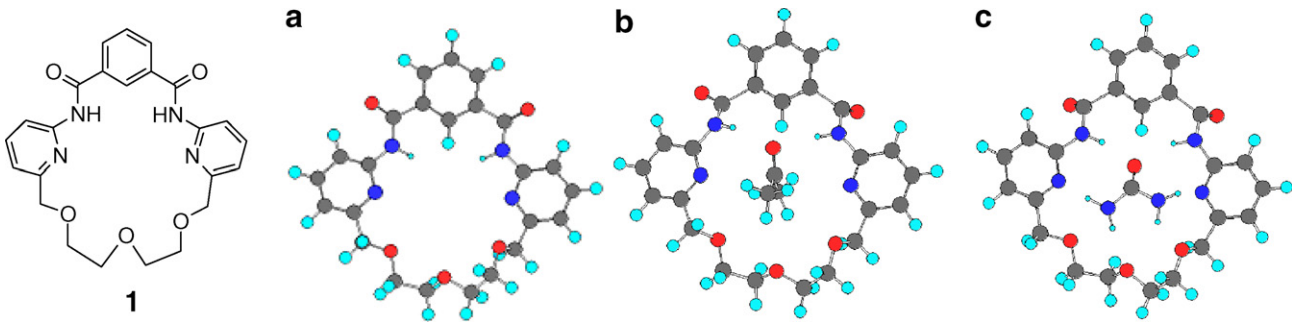
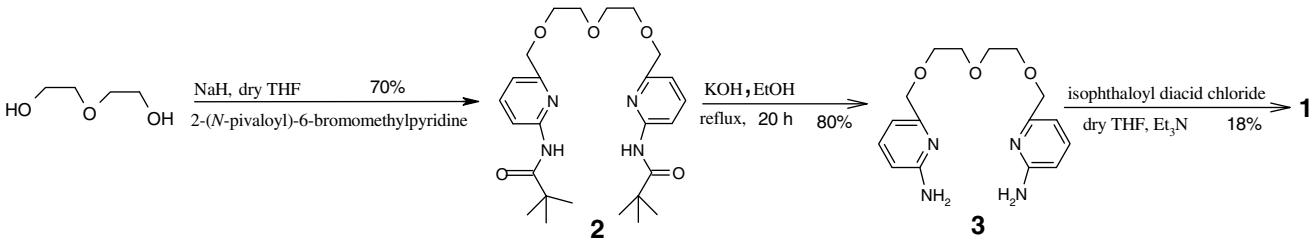


Figure 1. AM1 optimized geometries of (a) **1** (heat of formation = −56.39 kcal); (b) **1**·acetone complex (heat of formation = −48.14 kcal) and (c) **1**·urea complex (heat of formation = −8.03 kcal).



Scheme 1. Synthesis of receptor **1**.

carbonyl stretch at 1682 cm^{-1}. These findings led us to suspect the presence of a carbonyl compound with a $–COCH_3$ group in the cavity. In the ^{13}C NMR spectrum, signals at 178.7 ppm and 21.7 ppm further supported the presence of a carbonyl carbon and methyl carbon, respectively. In the ESI mass spectra, the ion peak at 449.3 confirmed the $(M+H)^+$ ion and HRMS analysis showed the same result indicating no inclusion of any molecule in the cavity.

To solve this problem, single crystals of **1** were obtained by slow evaporation from a chloroform/methanol mixture (2:1). The crystallographic information is listed in Table 1. The macrocycle **1** yields a 1:1 inclusion compound with acetone (melting point = 226 °C), which crystallizes in the orthorhombic space group, *Pnma* (No.62) (see Table 1). As can be seen from Figure 2 the macrocycle **1** shows strong inclusion of acetone involving

Table 1
Crystallographic and structure refinement data for the inclusion compounds of **1**[a]

Empirical formula	$C_{24}H_{24}N_4O_5·C_3H_6O$	$(C_{24}H_{24}N_4O_5)_2·CH_4N_2O·CHCl_3$
Formula weight	506.55	1076.37
Temperature (K)	198(2)	223(2)
Wavelength (Å)	0.71073	1.54178
Crystal system, space group	Orthorhombic, *Pnma* (No.62)	Monoclinic, $P2_1/n$ (No.14)
Unit cell dimensions		
a (Å)	7.401(1)	15.766(1)
b (Å)	20.858(1)	13.163(1)
c (Å)	15.904 (1)	25.448(1)
β (°)		104.15 (1)
Volume (Å^3)	2455.1(4)	5120.9(5)
Z, calculated density (Mg/m^3)	4, 1.370	4, 1.396
Absorption coefficient (mm^{-1})	0.098	2.212
F(000)	1072	2248
Crystal size (mm)	0.20 × 0.20 × 0.20	0.35 × 0.30 × 0.20
Theta range for data collection (°)	1.95–28.21	4.43–67.70
Limiting indices	$-9 \leqslant h \leqslant 9$, $-27 \leqslant k \leqslant 27$ $-20 \leqslant l \leqslant 20$	$-18 \leqslant h \leqslant 18$, $-14 \leqslant k \leqslant 15$, $-30 \leqslant l \leqslant 29$
Reflections collected/unique (R_{int})	21,090/3074 (0.059)	47,127/9068 (0.04)
Completeness to theta = 28.21	99.0%	97.8%
Max. and min. transmission	0.981 and 0.981	0.666 and 0.512
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	3074/0/180	9068/30/736
Goodness-of-fit on F^2	1.025	1.027
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.060$, $wR_2 = 0.164$	$R_1 = 0.054$, $wR_2 = 0.132$
R indices (all data)	$R_1 = 0.098$, $wR_2 = 0.185$	$R_1 = 0.061$, $wR_2 = 0.138$
Extinction coefficient	0.0070(19)	
Largest diff. peak and hole (e Å^{-3})	0.58 and −0.36	1.10 and −0.38
CCDC	679748	679747

[a] Structure solution and refinement were performed using SHELXS-97 and SHELXL-97.

CH---O [2.34 Å, 159° (C20–H20C---O4) and 2.42 Å, 124° (C18–H18---O21)], CH---N [2.45 Å, 115° (C20–H20A---N7)] and NH---O [2.21 Å, 174° (N12–H12---O21)] interactions. Acetone is found to interact from the top of the macrocycle and the carbonyl oxygen is bonded to two amide NHs through two coplanar hydrogen bonds. Two hydrogens of each methyl group form unconventional C–H---O and C–H---N hydrogen bonds which result in a seven-membered hydrogen bonded ring. The angled molecules lead to corrugated packing. The acetone molecule and the centre of the macrocycle are packed in the [1 0 0] direction. This inclusion of acetone was due to contamination of the solvent used either during work up or during purification of the macrocycle **1**. This was proved by repeating the synthesis, isolation and purification of **1** using acetone-free solvents. Characterization was achieved by ^{1}H NMR, ^{13}C NMR and mass spectroscopies, which revealed that the structure **1** was free from acetone. The inclusion of acetone into the cavity of macrocycle **1** was further tested using the same crystallizing solvent, contaminated with acetone which gave the same result. To determine the robustness of the acetone complex of **1**, thermal analysis was performed and the weight losses at different temperatures are shown in Figure 3. The weight loss between 152 °C and 233 °C is presumably due to loss of acetone.

To remove acetone from the cavity of **1**, urea dust was added to its chloroform solution and the solution was sonicated thoroughly for 15 min. The excess urea was filtered off and the solvent was evaporated to dryness. The solid mass obtained was redissolved in dry $CDCl_3$ and a ^{1}H NMR was taken. A smaller downfield shift of the amide protons ($\Delta\delta$ = 0.45 ppm) of **1** was observed but no signal for the urea NH was found in the ^{1}H NMR. Even the signal at 2.15 ppm for the $-CH_3$ of acetone was present. On keeping the same solution for 10 days, a signal at 5.65 ppm for the urea NHs was observed along with the absence of the peak at 2.15 ppm for the $-CH_3$ of complexed acetone. The integration ratio of urea protons to receptor protons showed a clear 2:1 (**1**: urea)

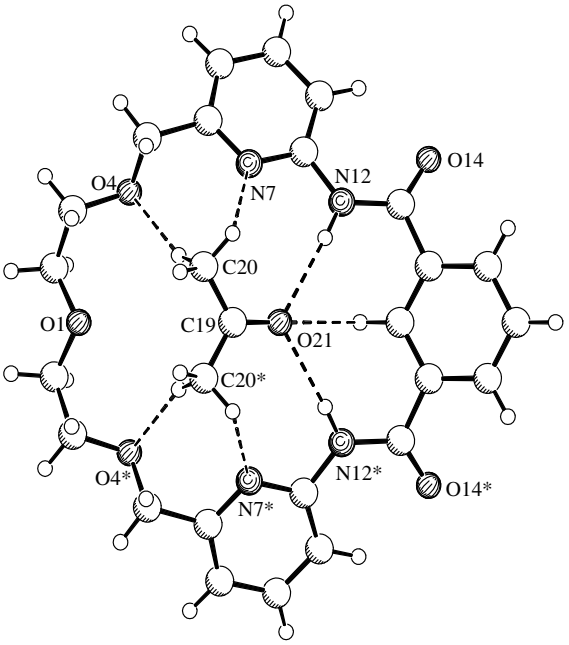


Figure 2. SCHAKAL plot with hydrogen binding network of **1**·C_3H_6O with numbering scheme for the hetero atoms.

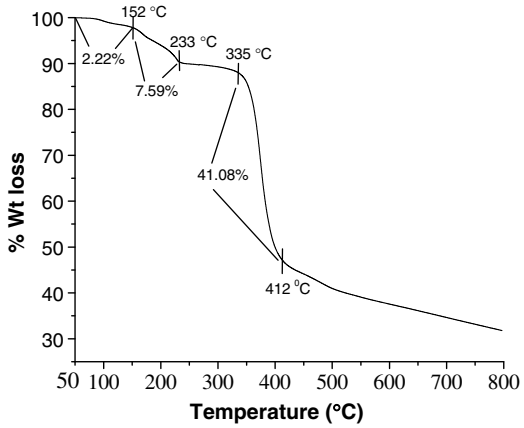


Figure 3. Thermo gravimetric analysis (TGA) plot showing the (%) weight loss of compound **1**·C_3H_6O on increasing the temperature.

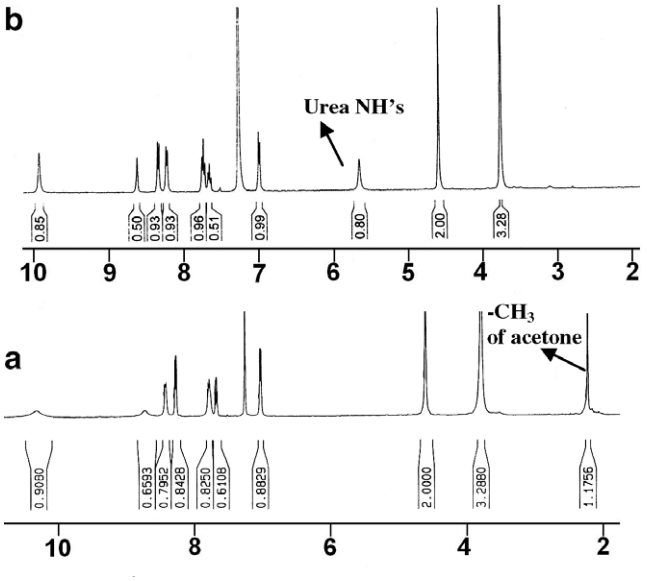


Figure 4. ^{1}H NMR spectra of the acetone complex of **1** (a) and urea complex of **1** (b) in $CDCl_3$ (400 MHz).

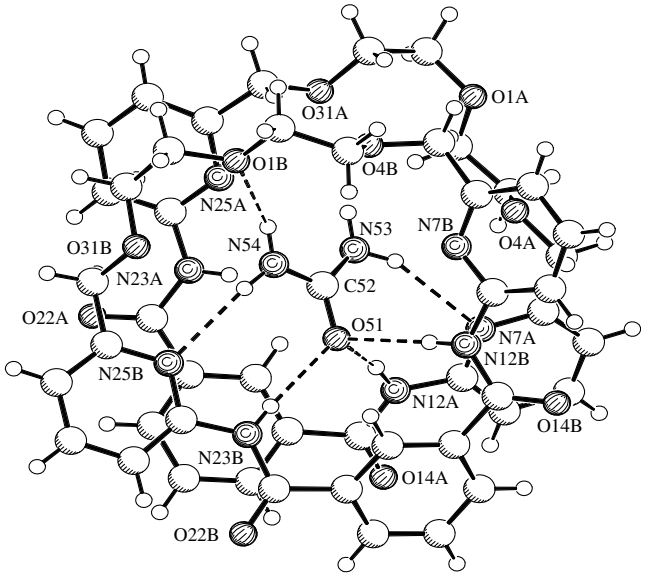


Figure 5. SCHAKAL plot with hydrogen binding network of (**1**)$_2$·CH_4N_2O with numbering scheme for the hetero atoms (adhered $CHCl_3$ has been omitted).

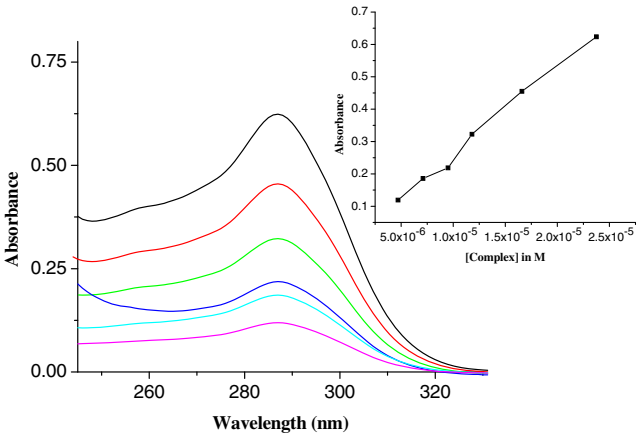


Figure 6. UV–vis spectra of the acetone complex of **1** on dilution with $CHCl_3$; inset—change in absorbance with concentration of acetone complex **1** at 287 nm.

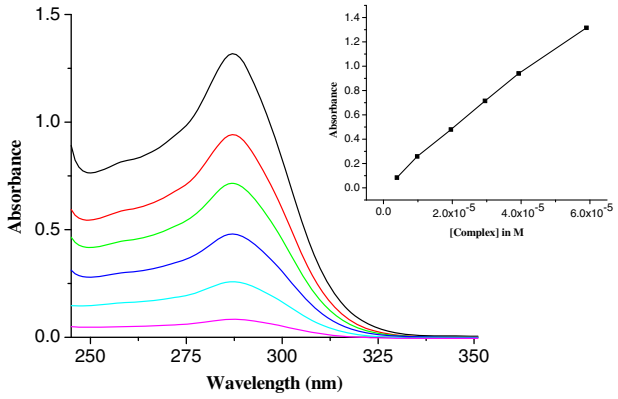


Figure 7. UV–vis spectra of the urea complex of **1** on dilution with $CHCl_3$; inset—change in absorbance with concentration of urea complex **1** at 287 nm.

stoichiometry. These experimental observations indicate that acetone is slowly replaced by urea from the macrocyclic cavity which was present in the colloidal form in the $CHCl_3$ solution.

The ^1H NMR spectra of **1** in the presence of both acetone and urea are shown in Figure 4. Crystallization of **1** from $CHCl_3$ in the presence of urea further confirmed the mode of interaction. The macrocycle **1**/urea 2:1 inclusion compound (melting point = 200 °C) crystallizes in the monoclinic space group $P2_1/n$ (No.14) (see Table 1). Due to the greater number of 'traditional' hydrogen-bond acceptor groups present no unconventional hydrogen bonds are formed (Fig. 5). Two independent molecules of macrocycle **1** show strong inclusion for urea involving NH---O [2.03 Å, 161° (N12A–H12A---O51), 2.18 Å, 174° (N12B–H12B---O51), 2.22 Å, 171° (N23B–H23B---O51), and 2.18 Å, 141° (N54–H54B---O1B)] and NH–N [2.32 Å, 159° (N54–H54A---N25B), and 2.49 Å, 155° (N53–H53B---N7A)] interactions. The urea molecule is located between two flat macrocycles and the molecules are flat packed, again the urea molecule and the centres of the macrocycles are packed in the [100] direction.

To establish the spectral properties of the inclusion complexes of acetone and urea, UV–vis spectra were taken in $CHCl_3$. The acetone complex of **1** in $CHCl_3$ ($c = 2.37 \times 10^{-5}$ M) showed an absorbance peak at 287 nm which on dilution with $CHCl_3$ exhibited a sharp change in absorbance (Fig. 6). The urea complex of **1** ($c = 5.90 \times 10^{-5}$ M) was similarly diluted in $CHCl_3$ and Figure 7 (inset) shows a linear change in absorbance at 287 nm with complex concentration. The binding constants were not estimated and compared due to the different stoichiometries of the complexes of acetone and urea with the macrocyclic receptor **1**.

In conclusion, we have shown that the synergy of both conventional and unconventional hydrogen bonds in simple macrocycle, **1**, plays an important role for effective binding of acetone, which can have practical application in complexation of a chiral ketone by a chiral receptor. Additionally, the biologically important metabolite, urea, can also be complexed by the same macrocycle with a moderate binding constant value involving conventional hydrogen bonds only. To the best of our knowledge this example is unknown in the literature. Further modification of **1** is under progress in our laboratory.

Acknowledgement

We thank CSIR, New Delhi, for financial support.

Supplementary data

^1H NMR and ^{13}C NMR spectra of the macrocycle **1**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.030.

References and notes

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22. Semi-empirical AM1 calculations were performed using CS Chem 3D version 8.0.
23. Macrocycle **1**: Mp 150 °C, ^1H NMR (400 MHz, $CDCl_3$, δ in ppm) 9.63 (2H, –CONH–, s), 8.77 (1H, s), 8.35–8.30 (4H, m), 7.76–7.67 (3H, m), 6.99 (2H, d, $J = 8$ Hz), 4.63 (4H, s), 3.77 (s, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) 164.3, 155.5, 151.6, 139.2, 133.9, 132.4, 129.9, 124.2, 118.0, 112.8, 73.3, 71.1, 69.9; HRMS calcd for $C_{24}H_{24}N_4O_5$: 448.1747. Found: 449.1806 $(M+1)^+$, 471.1476 $(M+Na)^+$, FTIR (ν cm^{-1}, KBr) 3387, 2921, 2850, 1686, 1579, 1544, 1458.