Trimeric Cyclamers: Hierarchical High Z′ Crystal Engineering Based on Guest Structure and Basicity

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Supplementary information

Synthesis of 5-ureidosalicylic acid (1).
A suspension of 5-aminosalicylic acid (3.00 g, 19.6 mmol) in acetonitrile (300 mL) was treated with 96% ethanol (4.5 mL) and trimethylamine (6 mL) under a dynamic nitrogen atmosphere. After stirring for 30 min at room temperature sodium cyanate (1.274 g, 19.6 mmol) was added and the mixture stirred at 95 °C for 48 h. The resulting pale precipitate was isolated by filtration and immediately added to aqueous hydrochloric acid (5 M). The suspension was sonicated for 25 min filtered to yield an off white precipitate. This material was air dried for 3 days and then further dried under vacuum at 110 °C to yield the product as an off white powder (1.72 g, 8.77 mmol, 57 %). 1H NMR (400 MHz, DMSO-d6): 13.81 (1H, br, S, COOH), 10.85 (1H, s, ArOH), 8.70 (1H, s, ArNH), 7.89 (1H, d, J=2.8 Hz, ArH), 7.47 (1H, dd, J = 8.8 & 2.8 Hz, ArH), 6.84 (1H, d, J = 8.8, ArH), 5.85 (2H, s, NH2). 13C{1H} NMR (101 MHz, DMSO-d6): 172.4, 156.7, 156.2, 133.0, 126.9, 119.3, 117.4, 112.8. IR (solid, ν / cm⁻¹): 3460w (OH), 3323w, 3146w (NH), 1664s, 1654s (C=O), 1632m, 1560m (NH), 1493m (C=C), 1235m (CO). Anal. Calc. for C₈H₈N₂O₄·1.5H₂O: C, 42.93; H 4.05; N, 12.87 %. Found: C, 43.05; H, 4.97; N, 12.55 %.

Crystallographic data
Crystal data for 1: C₈H₈N₂O₄, M =196.16 , colourless plate, 0.099 × 0.077 × 0.043 mm³, triclinic, space group (No. 2), a = 4.7242(12), b = 12.369(3), c = 13.831(3) Å, α = 90, β = 82.466(8), γ = 90°, V = 801.2(3) Å³, Z = 4, Dc = 1.626 g/cm³, F(000) = 408, Bruker D8 Venture, MoKα radiation, λ = 0.71073 Å, T = 173(2)K, 2θmax = 46.6°, 6579 reflections collected, 1154 unique (Rint = 0.1669). Final Goof = 1.146, RI = 0.1138, wR2 = 0.1711, R indices
based on 719 reflections applied with I > 2σ(I) (refinement on F²), parameters, restraints. Lp and absorption corrections applied, μ = 0.133 mm⁻¹. Poor precision and low resolution is because of the extremely small crystal size and hence weak diffraction.

Crystal data for 1·THF: C₁₂H₁₆N₂O₅, M = 268.27, colourless block, 0.30 × 0.25 × 0.10 mm³, monoclinic, space group P2₁/c (No. 14), a = 22.3090(19), b = 19.1478(16), c = 9.0100(8) Å, β = 91.398(3)°, V = 3847.6(6) Å³, Z = 12, Dc = 1.389 g/cm³, F₀₀₀ = 1704, Bruker D8 Venture, MoKα radiation, λ = 0.71073 Å, T = 120(2)K, 2θmax = 49.7°, 43079 reflections collected, 6619 unique (Rint = 0.0930). Final GoOF = 0.989, R1 = 0.0605, wR2 = 0.1375, R indices based on 4236 reflections with I >2σ(I) (refinement on F²), 514 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.109 mm⁻¹.

Crystal data for 1·MeCN: C₁₀H₁₁N₃O₄, M = 237.22, Colourless Block, 0.38 × 0.32 × 0.12 mm³, triclinic, space group P-1 (No. 2), a = 13.3689(18), b = 15.143(2), c = 18.786(3) Å, α = 77.079(3), β = 74.563(4), γ = 63.839(3)°, V = 3265.4(8) Å³, Z = 12, Dc = 1.448 g/cm³, F₀₀₀ = 1488, Bruker D8 Venture, MoKα radiation, λ = 0.71073 Å, T = 120(2)K, 2θmax = 46.7°, 26914 reflections collected, 9285 unique (Rint = 0.1028). Final GoOF = 1.034, R1 = 0.0892, wR2 = 0.2027, R indices based on 5891 reflections with I >2σ(I) (refinement on F²), 925 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.114 mm⁻¹.

Crystal data for 1-(CH₃)₂CO: C₁₁H₁₄N₂O₄, M = 254.24, colourless block, 0.33 × 0.11 × 0.07 mm³, monoclinic, space group P2₁/n (No. 14), a = 14.6759(9), b = 31.2850(19), c = 15.9269(10) Å, β = 99.324(2)°, V = 7216.0(8) Å³, Z = 24, Dc = 1.404 g/cm³, F₀₀₀ = 3216, Bruker D8 Venture, MoKα radiation, λ = 0.71073 Å, T = 120(2)K, 2θmax = 44.14°, 63443 reflections collected, 8899 unique (Rint = 0.1104). Final GoOF = 1.055, R1 = 0.0790, wR2 = 0.1799, R indices based on 5728 reflections with I >2σ(I) (refinement on F²), 985 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.112 mm⁻¹.

Crystal data for 1·0.7C₆H₄NO₂: C₁₂₂H₁₄₅N₂₇O₅₄, M =282.34, yellow needle, 0.100 × 0.010 × 0.001 mm³, tetragonal, space group P-42₁c (No. 114), V = 2311.8(7) Å³, Z = 8, Dc = 1.622 g/cm³, F₀₀₀ = 1174, Diamond I19, Synchrotron radiation, λ = 0.6889 Å, T = 296(2)K, 2θmax = 54.6°, 22865 reflections collected, 2853 unique (Rint = 0.0559). Final GoOF = 1.030, R1 = 0.0749, wR2 = 0.1999, R indices based on 2613 reflections with I > 2σ(I) (refinement on F²), 129 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.122 mm⁻¹. Absolute structure parameter is 0.7(3).

Crystal data for 1·(4-picoline)₂: C₂₀H₂₂N₄O₄, M = 382.42, colourless block, 1.15 × 0.07 × 0.07 mm³, triclinic, space group P-1 (No. 2), a = 4.5668(4), b = 20.5310(16), c = 20.9090(16) Å, α = 76.149(2), β = 88.228(3), γ = 88.156(3)°, V = 1901.2(3) Å³, Z = 4, Dc = 1.336 g/cm³, F₀₀₀ = 808, Bruker D8 Venture, MoKα radiation, λ = 0.71073 Å, T = 120(2)K, 2θmax = 49.6°, 21149 reflections collected, 6528 unique (Rint = 0.0829). Final GoOF = 0.996, R1 = 0.0653, wR2 = 0.1367, R indices based on 4312 reflections with I >2σ(I) (refinement on F²), 509 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.095 mm⁻¹.

Crystal data for 1·H₂O: C₅H₁₀N₂O₅, M = 214.18, colourless plate, 0.184 × 0.103 × 0.054 mm³, orthorhombic, space group P2₁2₁2₁ (No. 19), a = 4.5426(19), b = 10.729(5), c = 18.692(8) Å, V = 911.0(7) Å³, Z = 4, Dc = 1.562 g/cm³, F₀₀₀ = 448, Bruker D8 Venture, MoKα radiation, λ = 0.71073 Å, T = 153(2)K, 2θmax = 49.7°, 9640 reflections collected,
1573 unique \((R_{\text{int}} = 0.1211)\). Final \(GooF = 1.042, R1 = 0.0555, wR2 = 0.1122\), \(R\) indices based on 1138 reflections with \(I > 2\sigma(I)\) (refinement on \(F^2\)), 165 parameters, 0 restraints. \(Lp\) and absorption corrections applied, \(\mu = 0.132\) mm\(^{-1}\). Absolute structure parameter = 1.6(10).

**DOSY NMR**

The DOSY NMR spectrum of compound 1 in acetone-\(d_6\) at 25°C in the presence of \(o\)-xylene as an internal reference is shown in Figure S1. This experiment yielded the following diffusion coefficients \((D)\):

<table>
<thead>
<tr>
<th>Compound</th>
<th>(D) (m(^2)s(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound 1</td>
<td>15.64 ± 0.06</td>
</tr>
<tr>
<td>(o)-xylene</td>
<td>32.0 ± 0.2</td>
</tr>
<tr>
<td>Acetone</td>
<td>41.7 ± 0.3</td>
</tr>
</tbody>
</table>

A value of 41.5 m\(^2\)s\(^{-1}\) has been reported by M. Holz, X. a. Mao, D. Seiferling and A. Sacco in *J. Chem. Phys.*, 1996, **104**, 669.


Based on this data the method of Morris and coworkers (R. Evans, Z. Deng, A. K. Rogerson, A. S. McLachlan, J. J. Richards, M. Nilsson and G. A. Morris, *Angew. Chem., Int. Ed.*, 2013, **52**, 3199.) was used to calculate the approximate molecular mass (MW) of each species in this medium using the equation given below. In addition to experimental \(D\) values this method requires knowledge of effective molecular density \((\rho_{\text{eff}})\), solvent viscosity \((\eta)\) and temperature \((T)\). MW\(_s\) is the molar mass of the solvent.

\[
D = \frac{k_B T \left( \frac{3\alpha}{2} + \frac{1}{1 + \alpha} \right)}{6\pi\eta\sqrt{\frac{3\text{MW}_{\text{S}}}{4\pi\rho_{\text{eff}}N_A}}} \quad \text{where} \quad \alpha = \sqrt[3]{\frac{\text{MW}_{\text{S}}}{\text{MW}}}
\]

The viscosity of acetone-\(d_6\) at 25 °C (0.326 cP) was taken from M. Holz, X. a. Mao, D. Seiferling and A. Sacco in *J. Chem. Phys.*, 1996, **104**, 669.

The density of acetone-\(d_6\) (0.872 g/mL) was obtained from the manufacturer, Sigma-Aldrich http://www.sigmaaldrich.com/catalog/product/aldrich/444855?lang=en&region=GB

This method yielded molecular masses of 55.5 – 57.0 g mol\(^{-1}\), for acetone, 91.0 – 93.2 g mol\(^{-1}\) for \(o\)-xylene, and 385.4 – 391.8 g mol\(^{-1}\) for compound 1. The molecular mass of the dimer is 392.4 g mol\(^{-1}\) and that of the trimer is 588.6 g mol\(^{-1}\).

These values compare to the actual molecular weight of acetone-\(d_6\): 64.1 g mol\(^{-1}\), acetone-\(d_4\) (the species actually observed in the NMR experiment): 62.1 g mol\(^{-1}\) and \(o\)-xylene: 106 g mol\(^{-1}\) implying an underestimation by a factor of 1.15. Correcting for this systematic under-estimation in the acetone and \(o\)-xylene masses would give an average value of 446.9 g mol\(^{-1}\) for 1.

Both the measured and corrected values for 1 are closer to a dimer than a trimer but far from the mass of a monomer. This data can be interpreted as meaning that 1 is in essentially 100% dimer form in acetone at 25 °C. However this would imply a very high dimerization constant for 1 and would not explain the very broad nature of the OH and
NH protons in acetone (see Figure S2), which then sharpen on addition of DMSO. We interpret the observed molecular mass and other data results as implying that 1 is an equilibrating mixture of monomer, dimer and trimer under these conditions.

Figure S1. DOSY NMR spectrum of 1 in acetone-$d_6$. 
Figure S2. Addition of DMSO to an acetone-$d_6$ solution of 1 showing the gradual appearance of the NH and OH resonances.

**ESI-MS**

![ESI mass spectrum](image)

**Figure S2** ESI mass spectrum of 1 (197 M+H+) showing a peak at $m/z$ 392.7 assigned to a dimer of 1 2M+H+. 
**Figure S3.** The picoline capped urea α-tape in 1·2(picoline). Selected hydrogen bond distances (Å): N1···N46 2.973(4), N1···O1 2.843(3), O2···O3 2.544(3), N3···O1 2.868(3), O4···N39 2.546(3).

**Figure S4.** Crystal packing in the monohydrate 1·H2O. Selected intermolecular interactions (Å): N3···O1 2.812(6), N1···O3 2.925(7), N1···O1 2.938(6), O1S···O1S 2.881(5), O1S··O1 2.757(6), O2···O3 2.610(5), O4···O1S 2.660(6).