Imide-based Trezimide and Tennimide Macrocycles

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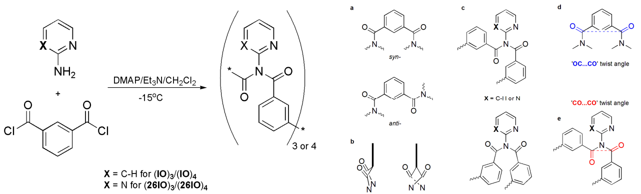
Targeted Therapeutics Theranostics

Introduction

Reaction of isophthaloyl dichloride (**I**) with 2-aminopyridine or 2-aminopyrimidine (**O**, **26O**) provides a facile entry into a new class of imide-based '3+3' macrocyclic trimer $(\mathbf{IO})_3$, $(\mathbf{26IO})_3$ (as **trezimides**), together with the known tetramer $(\mathbf{IO})_4$, $(\mathbf{26IO})_4$ (**tennimide**) scaffold.[1-5] **Trezimides** can adopt two asymmetric conformations, isolated as (**P**) in $(\mathbf{IO})_3$ and (**R**) in $(\mathbf{26IO})_3$.[2,4] The **tennimide** $(\mathbf{26IO})_4$ structure exhibits three discrete conformations as ***cc***/***oc***/***oo***, highlighting subtle geometric changes with the **tennimide** channel (pore) open (***o***) and/or closed (***c***). Macrocycle formation (competing with oligomer/polymer formation) relies on the *ortho*-pyr(im)idine *N* functionality and imide *hinge* ('**CO…CO**' twist) with the inherent flexibility of the isophthaloyl groups (Figures 1-5).

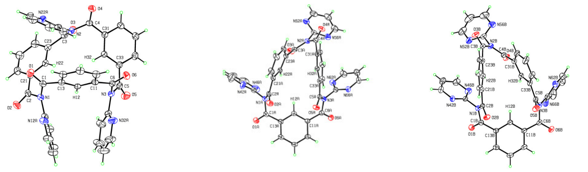


1 **2**

Scheme 1 Macrocyclic synthesis: the reaction route to $(\mathbf{IO})_{3/4}$ and $(\mathbf{26IO})_{3/4}$. **Scheme 2**. (a) *syn*- and *anti*-conformations of the isophthaloyl groups, (b) side-views of the isophthaloyl conformations, (c) imide conformations. (d) **OC…CO** isophthaloyl and (e) **CO…CO** imide hinge torsion angle (°).

Experimental methods

The reaction of isophthaloyl dichloride with 2-aminopyridine (or 2-aminopyrimidine) at −15°C in dry dichloromethane (CH_2Cl_2) with 3 equivalents of triethylamine (Et_3N) and a catalytic quantity of dimethylaminopyridine (DMAP) afforded a mixture of products (and oligomeric/polymeric material) (Scheme 1).[2-4] The single crystal X-ray data (Mo/Cu) were collected on an Oxford Diffraction Gemini S-Ultra diffractometer at 294(1) K: θ range typically from 2-26° (100% data coverage to 25°).



$(\mathbf{IO})_3$ **– P conformation** $(\mathbf{26IO})_3$ **– R conformation**

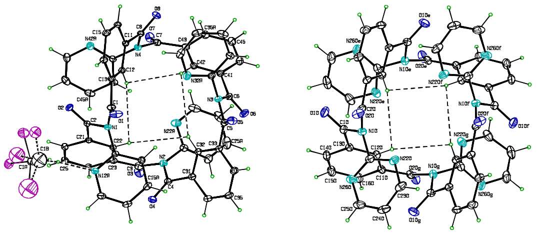


Figure 1: Views of the $(\mathbf{IO})_3$ and $(\mathbf{26IO})_3$ **trezimides** (top left/right) and the $(\mathbf{IO})_4$ and $(\mathbf{26IO})_4$ **tennimides** (bottom left/right) with displacement ellipsoids drawn at the 20% probability level.

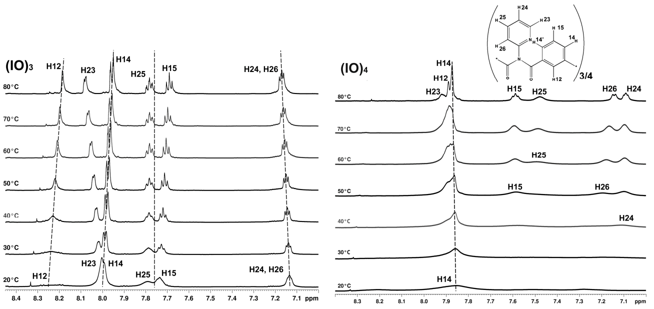


Figure 2: Variable temperature ^{1}H NMR studies (from 20°C to 80°C, 600 MHz, d_6-DMSO) for $(\mathbf{IO})_3$ and $(\mathbf{IO})_4$. Dashed lines indicate the displacement of resonances.[2,4]

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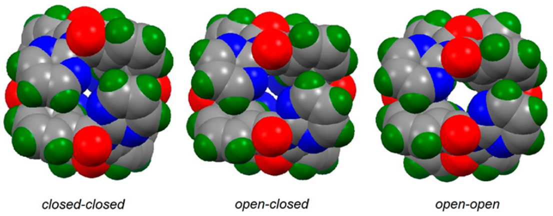
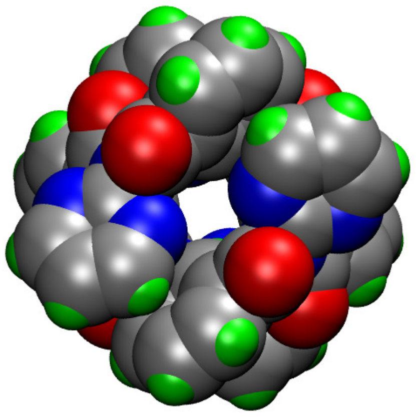


Figure 3. CPK views of the three discrete ***cc*** ↔ ***oc*** ↔ ***oo*** conformational states of $(\mathbf{26IO})_4$.[2]



Scan to view animations

Figure 4. CPK view of the $(\mathbf{26IO})_4$ molecule (molecule "O" in the ***oo*** conformation).[2]

Halogen bonding directed supramolecular assembly[5]

Brominated macrocycles aggregate *via* C–Br…O=C$_{carbonyl}$ and/or C–Br…N$_{aromatic}$ halogen bonds (with $N_c \leq 0.90$) and often augmented by longer C–Br…H/π(arene) contacts. The brominated **trezimides** and **tennimides** (each with 3 or 4 Br atoms) lack classical strong hydrogen bonding donors (*i.e.* N–H, O–H), but contain many acceptors (*i.e.* N$_{aromatic}$, C=O, arene) participating in a myriad of halogen and weaker hydrogen bonding interactions.[5] The C–Br groups promote overall molecular aggregation linking macrocycles into 1–D halogen bonded chains. $(\mathbf{BrIO})_3$ exhibits three different types of Br…O=C/π(arene) halogen and Br...H hydrogen bonds, with C–H…O contacts whereas $(\mathbf{26BrIO})_3$ contains Br…O=C halogen bonds (Figure 5).[5]

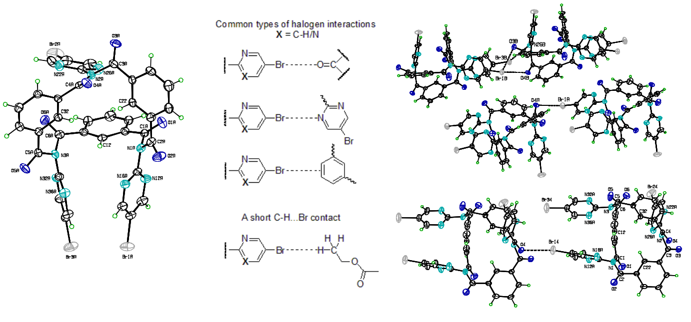


Figure 5: ORTEP diagram of $(\mathbf{26BrIO})_3$ and types of halogen/hydrogen bond interactions in $(\mathbf{26BrIO})_3$

Results and Conclusions

The one-step formation of **trezimides** and **tennimides** is achieved in modest yields from readily available starting materials [*i.e.* isophthaloyl dichloride and (un)substituted 2-aminopyr(im)idines]. Macrocycle formation depends on the asymmetric imide *hinge* (*i.e.* the **O=C…C=O** twist angle – Scheme 2e) and inherent flexibility of the isophthaloyl groups to twist and bend on macrocyclisation. Two distinct **trezimide** conformations (**P**) and (**R**) have been structurally characterised. The macrocyclic scaffold and core has been isolated in three different conformational states in the $(\mathbf{26IO})_4$ **tennimide**. The internal macrocyclic cavity is large to accommodate a small atom/ion. Future work is being directed towards the synthesis of larger macrocycles, coordination chemistry and halogen bonding applications.[5]

References:

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