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Secondary Bonding-Directed Self-Assembly of Amino Acid Derived Benziodazoles: Synthesis and Structure of Novel Hypervalent Iodine Macrocycles

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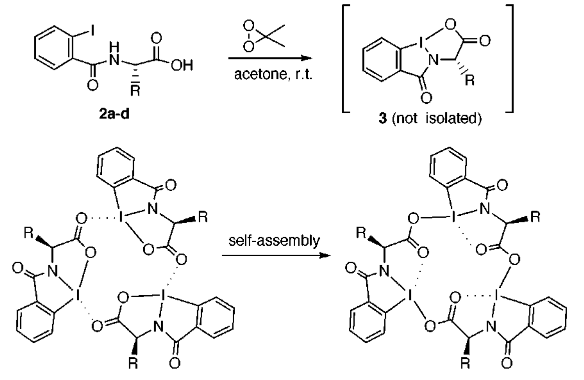
Self-assembly of molecular subunits into supramolecular structures via hydrogen bonding or a transition-metal coordination is a well-documented phenomenon of exceptional significance.[1] Secondary bonding between heavier main-group atoms has also been recognized as an important noncovalent interaction that can be exploited for the rational design of supramolecular structures.[2] Secondary I•••O bonds represent an essential feature of structural chemistry of hypervalent iodine.[3] Recently, such secondary bond interactions have been utilized to construct new soluble derivatives of (tosyliminoiodo)benzene and iodosylbenzene.[4] In the present communication, we describe a novel self-assembly of organoiodine(III) molecules into chiral and optically pure hypervalent iodine macrocycles (**1**, Scheme 1), which is directed by secondary bonding between hypervalent iodine and oxygen atoms of the amino acid fragment.

Macrocyclic products **1** were prepared by oxidation of the corresponding *N*-(2-iodobenzoyl) amino acids **2** with dimethyldioxirane in 76−90% yield (Scheme 1).[5] We assume that the initial products in this reaction are monomeric *N*-substituted benziodazoles **3**, subsequent trimerization of which affords the final products **1**.[6]

Scheme 1. Preparation of Hypervalent Iodine Macrocycles **1**



1a-d (76-90%)
a, R = H; **b**, R = Me; **c**, R = *i*-Pr, **d**, R = *i*-Bu

Macrocycles **1** were characterized by elemental analysis, spectroscopic data,[5] and single-crystal X-ray analyses for **1c** and **1d**.[7] Single crystals of **1c** suitable for X-ray crystallographic analysis were obtained from $CHCl_3$ or $C_2H_2Cl_4$ and were analyzed as the respective solvates; crystals of **1d** were grown from chloroform.[7] Molecular diagrams of all three products (**1c**•$CHCl_3$, **1c**•$C_2H_2Cl_4$, and **1d**•$CHCl_3$) are quite similar with only slight variations in the geometry and planarity. The ORTEP of **1c**•$CHCl_3$ (one of the two crystallographically independent molecules) from two different perspective views is shown in Figure 1.

Molecule **1c**•$CHCl_3$ consists of a slightly distorted planar macrocyclic system with three oxygens of the amino acid carboxyls (O3, O3′, and O3″) inside the ring and all three alkyl groups above the plane (Figure 1). The incorporated $CHCl_3$ solvent molecule is situated above the macrocycle on the 3-fold axis such that the H is directed toward the center of the macrocycle with a H•••O(3) distance of ca. 2.6 Å. Each iodine atom is covalently bonded to carbon [I−C1 = 2.092(12) Å] and nitrogen [I−N = 2.064(11) Å] and has three longer intramolecular contacts with oxygen atoms [I−O2 = 2.368(9) Å, I−O3 = 2.524(9) Å, and I−O3′ = 2.877(9) Å]. With the consideration of primary and secondary bonds, iodine atoms in **1** have the pentagonal-planar geometry, which is analogous to that found in the solid state for $PhI(OAc)_2$.[8] Secondary bonding between iodine and oxygen atoms of the neighboring molecular subunits provides the driving force for self-assembly of monomeric benziodazoles **3** into macrocyclic molecules **1**. The effects of secondary interactions between carboxylate oxygens and the electron-deficient iodine centers are evidenced by the small disparity between carboxylate C−O bond lengths. Averaging the values for the two independent molecules in **1c**•$CHCl_3$ shows that C9−O3 at 1.251 Å is only slightly shorter than C9−O2 at 1.287 Å. The internuclear distance between oxygen atoms directed toward the center of the macrocycle **1c**•$CHCl_3$ (O3, O3′, and O3″) is 3.31 Å, and ranges from 3.31 to

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(5) **Representative procedure**: A freshly prepared 0.1 M solution of dimethyldioxirane in acetone (40 mL, 4 mmol) was added to a stirred mixture of *N*-(2-iodobenzoyl) leucine **2d** (0.18 g, 0.5 mmol) in 5 mL of dry methylene chloride at 0 °C. The color of the solution immediately changed from colorless to light yellow. The reaction mixture was stirred at room temperature for an additional 8 h, then the resulting white precipitate was collected by filtration, washed with ether and methylene chloride, and dried in a vacuum to afford 0.14 g (78%) of product **1d**, mp 155−156 °C dec. IR (KBr): 3082, 2958, 2366, 1716, 1643, 1560, 1280 cm^{-1}. ^1H NMR (DMSO-d_6): δ 8.28 (d, 1H), 8.18 (d, 1H), 7.82 (t, 1H), 7.68 (t, 1H), 5.08 (m, 1H), 2.17 (t, 2H), 1.86 (m, 1H), 1.14 (d, 3H), 0.98 (d, 3H). ^{13}C NMR ($CDCl_3$): δ 179.2, 167.4, 134.9, 133.6, 131.2, 130.8, 130.3, 120.0, 62.6, 39.4, 27.6, 15.1, 12.4. Anal. Calcd for $C_{39}H_{42}I_3N_3O_9$: C, 43.47; H, 3.93; N, 3.90. Found: C, 43.37; H, 4.06; N, 3.71. ESI MS: *m/z* (%) 1100 (100), $[M + Na]^+$. Additional synthetic and characterization details are provided as Supporting Information.

(6) The preparation and structure of several monomeric benziodazoles have previously been reported in the literature, see: (a) Zhdankin, V. V.; Arbit, R. M.; McSherry, M.; Mismash, B.; Young, V. G., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 7408. Zhdankin, V. V.; Arbit, R. M.; Lynch, B. J.; Kiprof, P.; Young, V. G., Jr. *J. Org. Chem.* **1998**, *63*, 6590. Zhdankin, V. V.; Smart, J. T.; Zhao, P.; Kiprof, P. *Tetrahedron Lett.* **2000**, *41*, 5299. (b) Barber, H. J.; Henderson, M. A. *J. Chem. Soc. (C)* **1970**, 862. (c) Balthazar, T. M.; Godaz, D. E.; Stults, B. R. *J. Org. Chem.* **1979**, *44*, 1447. Naae, D. G.; Gougoutas, J. Z. *J. Org. Chem.* **1975**, *40*, 2129.

(7) Compound **1c**•$CHCl_3$ ($C_{37}H_{37}Cl_3I_3N_3O_9$; formula weight 1154.75) crystallized in the trigonal space group *P*3 (no. 143) with a = 16.8651(12) Å, c = 9.6356(11) Å; V = 2373.5(4) Å^3, Z = 2; R = 0.0498 (3230 reflections with $F_o^2 \geq 2\sigma(F_o^2)$), R_w = 0.1339 for 4079 unique reflections with $F_o^2 \geq -3\sigma(F_o^2)$. Compound **1c**•$0.75C_2H_2Cl_4$ ($C_{37.5}H_{34.5}Cl_3I_3N_3O_9$; formula weight 1158.23) crystallized in the orthorhombic space group $P2_12_12_1$ (no. 19) with a = 10.9591(12) Å, b = 14.6367(17) Å, c = 52.962(6) Å; V = 8495.3(17) Å^3, Z = 8; R = 0.0578 (14777 reflections with $F_o^2 \geq 2\sigma(F_o^2)$), R_w = 0.1462 for 17413 unique reflections with $F_o^2 \geq -3\sigma(F_o^2)$. Compound **1d**•$CHCl_3$ ($C_{40}H_{43}Cl_3I_3N_3O_9$; formula weight 1196.82) crystallized in the monoclinic space group $P2_1$ (no. 4) with a = 11.0940(6) Å, b = 17.3082(10) Å, c = 12.0815(7) Å; β = 105.3626(10)°; V = 2237.0(2) Å^3, Z = 2; R = 0.0260 (8412 reflections with $F_o^2 \geq 2\sigma(F_o^2)$), R_w = 0.0617 for 8866 unique reflections with $F_o^2 \geq -3\sigma(F_o^2)$.

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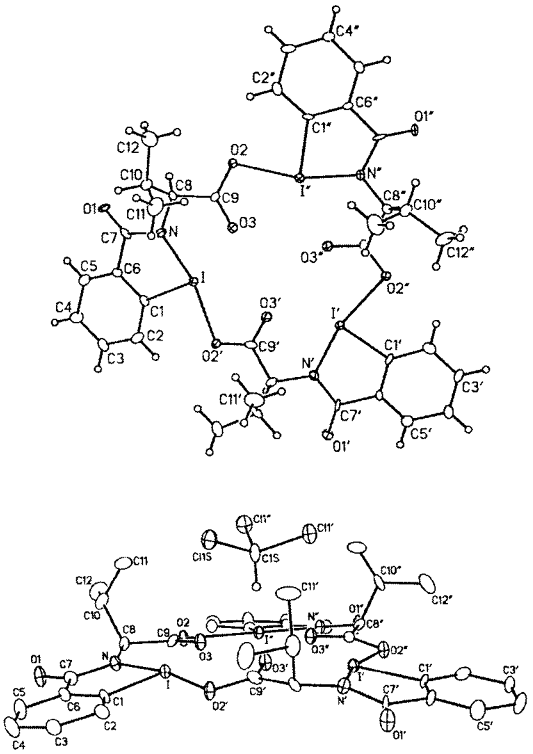

Figure 1. Top: Perspective view of one of two crystallographically independent molecules of **1c**·$CHCl_3$ ($CHCl_3$ removed for clarity). Selected distances [Å] and angles [deg]: I−N 2.064(11), I−C1 2.092(12), I−O2 2.368(9), I−O3 2.524(9), I−O3′ 2.877(9); O2−I−N 164.6(4), O2−I−C1 85.0(4). Bottom: Edge-on view of **1c** showing orientations of the isopropyl groups and the $CHCl_3$ solvent molecule. Hydrogen atoms are omitted.

3.42 Å in **1c**·$C_2H_2Cl_4$ and **1d**·$CHCl_3$. These three oxygens therefore circumscribe a relatively small cavity within the macrocycle. The secondary bonding I−O3 interactions likely dissipate a fair amount of charge density from the oxygens such that electrostatic repulsions are diminished. It is still somewhat surprising, however, that the formation of macrocycle **1** is favored over that of the monomer **3** or a polymer species,[4] situations in which any negative electrostatic interactions could be reduced or eliminated.

As a result of the central oxygens, the electron-rich cavity of macrocycles **1** should be suitable for complexation of cations in a manner similar to that observed for the slightly larger guanosine quartet.[9,10] ESI-MS analyses of macrocyclic compounds **1** provide information about their structure in solution and offer empirical evidence as to their selective cation binding.[11] The ESI-MS spectrum for **1d** from a nitromethane solution is shown in Figure 2 and is typical of that observed for the macrocycles. The most significant peak in is that of the trimeric species **1d** complexed with a single sodium cation at *m*/*z* 1100.[12] Smaller signals for $[M + K]^+$ and $[M + H]^+$ are also observed. Less intense patterns are present for H^+, Na^+, and K^+ complexes of the oligomers of **3d**, including the tetrameric, dimeric, and monomeric species.

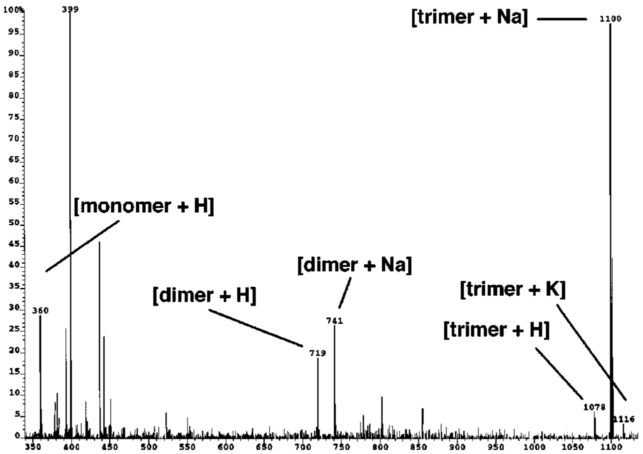

Figure 2. ESI-MS for macrocycle **1d** comparing complexation with H^+, Na^+, and K^+ (nitromethane solvent).

Addition of both NaCl and KCl to a nitromethane solution of **1d** followed by MS analysis shows an increased signal for $[$**1d** $+ K]^+$ at the expense of $[$**1d** $+ Na]^+$, and this change is concurrent with increased signals for the dimeric and monomeric species. Analysis of solutions of **1d** following addition of either LiCl or $Pb(ClO_4)_2$ showed no evidence of complexation with these cations. Addition of AgOTf under similar conditions afforded weak signals for both $[$**1d** $+ Ag]^+$ and $[\text{dimer} + Ag]^+$.

In conclusion, we have reported the first example of self-assembly of organoiodine(III) molecules into a hypervalent iodine macrocycle, which is directed by secondary bonding between trivalent iodine and oxygen. X-ray data on macrocycles **1** clarify the structure of these synthetically useful benziodazoles.[6] Furthermore, these novel hypervalent iodine macrocycles **1** are potentially useful ligands for selective binding of metal cations.

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Supporting Information Available: Synthetic and characterization data for all new compounds, ^1H and ^{13}C spectra for compounds **1b** and **1c**, ESI MS for compounds **1c** and **1d**, and X-ray crystallographic details for compounds **1c**·$CHCl_3$, **1c**·$C_2H_2Cl_4$, and **1d**·$CHCl_3$ (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The signal at *m*/*z* 399 is not well understood. This peak shows with relatively low intensity at low sampling cone/skimmer lens voltages, increasing as the voltages are increased to better tune signals at higher *m*/*z* values. Exact mass measurement provides a good match for the addition of ammonia to the monomer **1d**, $[M + Na + NH_3]^+$, although the presence of ammonia in the sample is yet to be explained. Similar behavior is observed for compound **1c**.