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Synthesis and Clathrates of Oligomeric 2-*O*-Naphthoide Macrocycles

Tayel A. AlHujran, Louise N. Dawe, Julie Collins, and Paris E. Georghiou*

Department of Chemistry, Memorial University of Newfoundland, St. John's, Newfoundland and Labrador, A1B3X7, Canada

parisg@mun.ca

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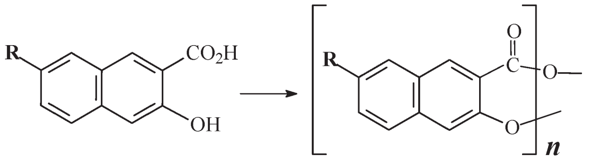
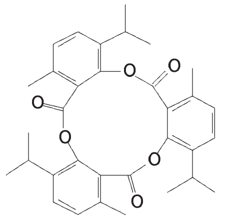


4: R = H; *n* = 4. **5: R** = *t*-Bu; ***n* = 3.**
6: R = *t*-Bu; ***n* = 6.**

New macrocyclic *O*-naphthoides **4**−**6** were synthesized from dehydration reactions of 3-hydroxy- and 7-*tert*-butyl-3-hydroxy-2-naphthoic acids, respectively. Their X-ray structures were determined and their clathrate inclusion properties were investigated. Hexamer **6** formed an inclusion clathrate with four chloroform molecules. The trimer **5**, by analogy with tri-*o*-thymotide, was studied for its potential optical resolution effects.

There has been much research devoted to the study of clathrate inclusion compounds since they have been shown to have many potential applications.[1] Clathrates form as a result of initial favorable van der Waals interactions between a "host" and a "guest" while they are in solution, and then associate to form stable crystalline lattices. The properties of clathrates are generally different from those of their individual components. Tri-*o*-thymotide ("TOT") (**1**), the trimeric lactone derived from *o*-thymotic acid, is one of the best known and studied host molecules.[2] First reported in 1865, it was only in 1952 that Baker established its correct structure and that unlike closely related compounds, it formed stable clathrate inclusion compounds, which are either channel- or cage-type, when crystallized from various organic solvents.[3] Powell reported different enantiomorphous crystal clathrates produced from TOT and different solvents and that TOT therefore was capable of spontaneous optical resolution upon clathrate formation.[4] In its crystalline phase, TOT exists in C_3-symmetrical propeller-shaped conformations that are either *P* or *M*. These permit discrimination between enantiomers of chiral guest molecules during crystallization.[5]



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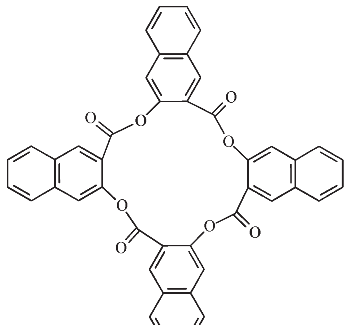
The recent report by Tanaka and co-workers[6] on the inclusion properties of novel salicylide macrocycles prompts us to report on our own work on the synthesis and properties of the oligomeric macrocyles derived from 3-hydroxy-2-naphthoic acid (**2**) and its 7-*tert*-butylated derivative **3**. Under certain conditions, these compounds form the respective calix[4]naphthalenes,[7] which are analogous to the better-known calixarenes. However, under reflux conditions with $POCl_3$ in toluene solution **2** forms the tetra-*O*-naphthoide **4**. Under the same conditions, the *tert*-butylated derivative **3** forms the tri- and hexa-*O*-naphthoides **5** and **6**, respectively. Herein we report the synthesis, crystal structures, and some inclusion properties of the new tetra-, tri-, and hexa-*O*-naphthoides **4**−**6**.



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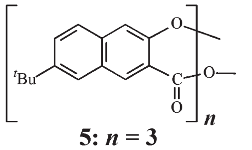
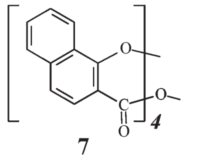


5: *n* = 3
6: *n* = 6



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3-Hydroxy-2-naphthoic acid (**2**), and its *tert*-butylated derivative, **3**, which was derived from the Friedel−Crafts *tert*-butylation of methyl 3-hydroxy-2-naphthoate, were heated with $POCl_3$, in toluene solution for 3 d under reflux conditions. After removal of the solvent, purification with preparative-layer TLC afforded only the tetra-2-*O*-naphthoide **4** (in 70% yield) from the reaction of **2**. From the analogous reaction of **3**, only the corresponding trimer **5**

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[1] (a) *Topics in Current Chemistry: Molecular Inclusion and Molecular Recognition. Clathrates I, 140*; Weber, E., Ed.; Springer-Verlag: New York, 1987. (b) *Supramolecular Chemistry*, 2nd ed.; Steed, J. W., Atwood, J. L., Eds.; John Wiley and Sons, Ltd.: Chichester, UK, 2009.

[2] Gerdil, R. *Top. Curr. Chem.* **1987**, *140*, 71.

[3] Baker, W.; Gilbert, B.; Ollis, W. D. *J. Chem. Soc.* **1952**, 1443.

[4] (a) Newman, A. C. D; Powell, H. M. *J. Chem. Soc.* **1952**, 3747. (b) Lawton, D.; Powell, H. M. *J. Chem. Soc.* **1958**, 2339.

[5] Arad-Yellin, R.; Green, B. S.; Knossow, M.; Tsoucaris, G. *J. Am. Chem. Soc.* **1983**, *103*, 4561 and references cited therein.

[6] Tanaka, K.; Hayashi, S.; Caira, M. R. *Org. Lett.* **2008**, *10*, 2119.

[7] Georghiou, P. E.; Li, Z.; Ashram, M.; Chowdhury, S.; Mizyed, S.; Tran, A. H.; AlSaraierh, H.; Miller, D. O. *Synlett* **2005**, 879.

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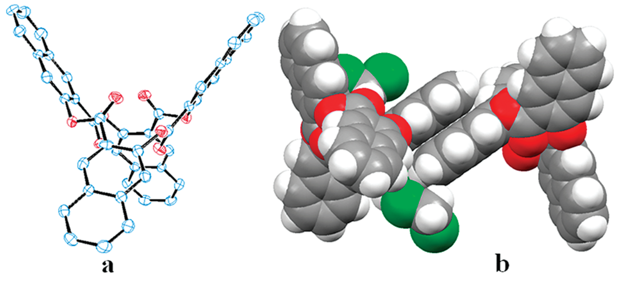
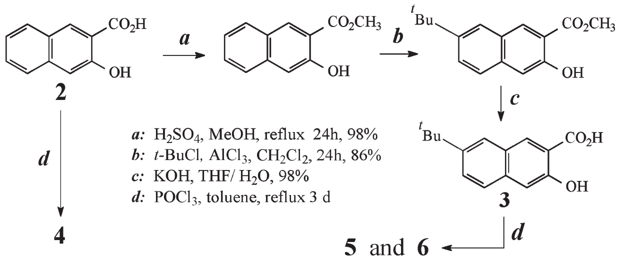


FIGURE 1. X-ray structure (a) of the tetra-2-*O*-naphthoide **4** (dichloromethane molecules omitted for clarity) and (b) showing the close $\pi-\pi$ stacking between a pair of molecules of the tetramer and the dichloromethane molecules.

SCHEME 1. Synthesis of the 2-Naphthoide Macrocycles



and hexamer **6** were obtained, in 15% and 10% yields, respectively (Scheme 1).

The X-ray structures of **4**−**6** are shown below. Figure 1 is of the tetramer, **4**, which crystallized with two dichloromethane (DCM) molecules in a channel-type clathrate, in which one of the DCM molecules has a close contact distance of 2.259 A with a carbonyl oxygen.[10] The structure is in a *1,3-alternate*-type conformation, similar to what is commonly seen with many different calix[4]arenes. A similar conformation was observed with the analogous tetra-1-naphthoide **7**, derived from 1-hydroxy-2-naphthoic acid under similar conditions by Gerdil and Bernardinelli[9] and by Tanaka et al.[6] with the tetrasalicylide obtained from the reaction of 5-chlorosalicylic acid under similar conditions. The packing in **4** reveals close (3.396 Å) $\pi-\pi$ stacking of the naphthyl rings between pairs of molecules in the crystal lattice which could account for the fact that once crystallized, redissolution in the same or other common solvents tested could not easily be achieved. As a consequence possibly, in contrast to **7**, which forms clathrates with several different solvents,[10] we have been unable to produce other clathrates with tetramer **4**. Other short contacts of note from the X-ray structure of **4**, involving the DCM molecules, include 2.816, 2.944, and 3.369 Å distances for the Cl(1)···H(24), Cl(2)···H(15), and the Cl(3)···C(13), respectively.

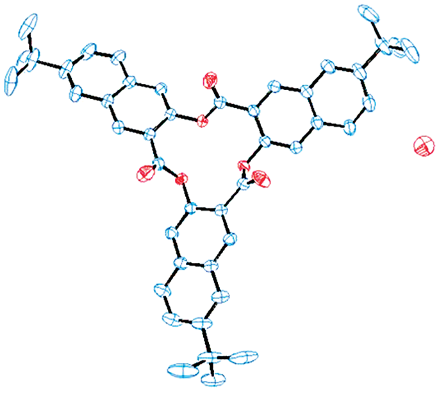


FIGURE 2. X-ray structure (ORTEP 30% thermal ellipsoids) of tri-2-*O* -naphthoide **5** containing a water molecule (hydrogen atoms omitted for clarity).

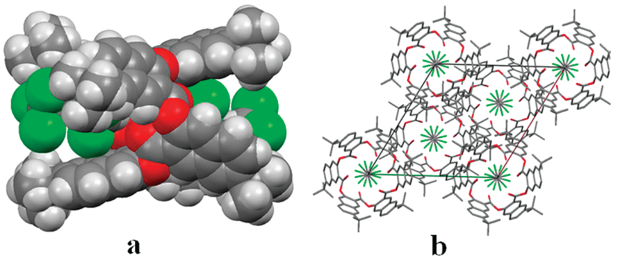


FIGURE 3. X-ray structure (a) space-filling and (b) packing diagram viewed along the *c* axis of hexa-2-*O*-naphthoide **6** showing the inclusion of four molecules of chloroform.

Figure 2 shows the X-ray structure of the trimer **5**, which crystallized from wet methanolic dichloromethane solution as a water molecule-containing channel-type racemate containing equal amounts of the *P* and *M* forms.[11] The molecule is propeller-shaped and has C_3-symmetry and reveals short contacts of 2.619 and 2.619 Å for the carbonyl oxygen atom to a hydrogen atom of a *tert*-butyl group, O(2)···H(13b), and to a hydrogen atom on a naphthyl ring, O(2)···H(4), respectively. By analogy to TOT, **5** could be expected to be potentially capable of effecting chiral discrimination with either racemic or chiral guests. Our efforts to date, with three different chiral reagents, however, have not succeeded in being able to demonstrate similar properties for **5**. This finding is not unlike similar efforts which have been reported by others to date with other TOT analogues that failed to afford any chiral recognition properties.[12]

Figure 3 is of the X-ray structure of the hexamer **6** that was crystallized from chloroform/methanol and is in a *1,3,5-alternate* conformation.[13] Four chloroform molecules are clearly contained within the cavities of the two alternate groups of naphthyl rings, as a cage-type clathrate. The only significant short contacts revealed in the structure are 3.387

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(8) Crystal data for **4**: $C_{46}H_{28}Cl_4O_8$, M = 850.48, colorless prism (dichloromethane:methanol), space group $C2/c$ (no. 15), a = 40.421(12) Å, b = 11.179(3) Å, c = 16.906(5) Å, β = 95.979(6)°, V = 7598(4) Å^3, Z = 8, D_c = 1.487 g/cm^3, F_{000} = 3488.00, μ(Mo Kα) = 3.699 cm^{-1}, T = 123(1) K, $2\theta_{max}$ = 61.8°, 62787 reflections collected, 7442 unique (R_{int} = 0.0573). Final GoF = 1.173, R1 ($I > 2.00\sigma(I)$) = 0.1071, R(all reflections) = 0.1093, wR2(all reflections) = 0.3185.

(9) (a) Gerdil, R.; Bernardinelli, G. *Acta Crystallogr.* **1985**, *C41*, 1523. Unsolvated compound **7** crystallized in the $P4_2/n$ space group. (b) An incorrect structure for this compound is shown as "Figure 7.34" In *Supramolecular Chemistry*, 2nd ed.; Steed, J. W., Atwood, J. L., Eds.; John Wiley & Sons, Ltd.: Chichester, UK, 2009.

(10) Suwinska, K.; Gerdil, R. *Acta Crystallogr.* **1987**, *C43*, 898. The clathrates all crystallized in the centrosymmetric *P*1 space group.

(11) Crystal data for **5**: $C_{45}H_{42}O_6$ (H_2O), M = 696.84, colorless prism, space group $R\bar{3}$ (no. 148), a = 15.849(5) Å, c = 26.950(9) Å, V = 5863(3) Å^3, Z = 6, D_c = 1.184 g/cm^3, F_{000} = 2220, μ(Mo Kα) = 0.79 cm^{-1}, T = 153(2) K, $2\theta_{max}$ = 61.8°, 25563 reflections collected, 2699 unique (R_{int} = 0.0307). Final GoF = 1.128, R1 ($I > 2.00\sigma(I)$) = 0.0835, R(all reflections) = 0.0839, wR2(all reflections) = 0.2405.

(12) (a) Harris, T. D.; Oruganti, S. R.; Davis, L. M.; Keehn, P. M.; Green, B. S. *Tetrahedron* **1987**, *43*, 1519−1540 and references cited therein. (b) Ollis, W. D.; Stoddart, J. F. *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Academic Press: London, UK, 1984; Vol. 2, p 170.

and 3.172 Å between a chlorine atom, i.e., Cl(1) of the innermost chloroform molecule to C(2) and C(3) of each of the naphthalene rings, respectively.

In conclusion, we have synthesized and characterized three new naphthalene ring-containing macrocyclic oligomeric lactones. The clathrate properties of these compounds were investigated by their X-ray structures. Hexamer **6** was shown to be a good molecular receptor for chloroform. The propeller-shaped trimer **5** did not show any chiral recognition properties.

Experimental Section

Tetra-2-*O*-naphthoide (4). To a stirred solution of 3-hydroxy-2-naphthoic acid (0.94 g, 5.0 mmol) in toluene was added $POCl_3$ (0.7 mL, 7.5 mmol) dropwise. The reaction mixture was heated at reflux until all of the starting material, by TLC, was consumed. The reaction mixture was cooled to room temperature and the off-white precipitate was filtered by suction filtration. The crude product was purified by preparative TLC, using a 50:40:10 *n*-hexane, dichloromethane, ethyl acetate solvent system, to afford **4** in 70% yield, mp > 300 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.54 (m, 4H), 7.57−7.60 (m, 4H), 7.67 (s, 4H), 7.79 (d, J = 8.0 Hz, 4H), 8.07 (d, J = 8.0 Hz, 4H), 8.98 (s, 4H); ^{13}C NMR (CD_2Cl_2) δ 121.7, 122.1, 127.4, 127.8, 129.8, 129.9, 131.4, 135.3, 136.6, 147.7, 163.9. HRMS (TOFEI) calcd for $C_{44}H_{24}O_8$ 680.1471, found 680.1476.

Tri- and Hexa-2-*O*-naphthoide (5 and 6). To a stirred solution of 7-*tert*-butyl-3-hydroxy-2-naphthoic acid (1.22 g, 5.0 mmol) in toluene was added $POCl_3$ (0.7 mL, 7.5 mmol) dropwise. The reaction mixture was heated at reflux until all of the starting material, by TLC, was consumed.The reaction solvent was removed under reduced pressure to give a crude product that was purified by preparative TLC, using a 50:50 *n*-hexane, dichloromethane solvent system, to afford **5** and **6** in 10% and 15% yields, respectively:

5: mp > 300 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 27H), 7.58 (s, 3H), 7.65 (dd, J = 9.0, 1.5 Hz, 3H), 7.71 (d, J = 8.9 Hz, 3H), 7.86 (d, J = 1.5 Hz, 3H), 8.93 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 31.1, 34.9, 120.8, 121.2, 124.3, 126.9, 128.2, 130.9, 134.3, 135.4, 146.5, 149.5, 164.1. HRMS (TOFEI) calcd for $C_{45}H_{42}O_6$ 678.2981, found 678.2991.

6: mp > 300 °C. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 1.26 (s, 54H), 7.34 (s, 6H), 7.47 (d, J = 8.7 Hz, 6H), 7.50 (dd, J = 8.7, 1.4 Hz, 6H), 7.76 (s, 6H), 8.78 (s, 6H);^{13}C NMR (CD_2Cl_2) δ 31.2, 35.1, 121.0, 121.6, 124.4, 127.0, 128.5, 131.0, 134., 135.4, 146.7, 149.9, 164.0. MS (MALDI-ToF) (*m*/*z*) 1395.54 $[M + K]^+$, 1379.56 $[M + Na]^+$.

Chiral Resolution Studies. The following chiral guests were examined with trimer **5** under ambient conditions with the solvent system(s) indicated: (+)-1-(1-bromoethyl)-4-nitrobenzene (a) in a DCM/methanol/hexane solvent mixture, (b) in a $CHCl_3$/methanol solvent mixture, and (c) in the neat chiral solvent; (+)-2-bromooctane (a) in CS_2, (b) in a DCM/methanol/*n*-hexane solvent mixture, and (c) in the neat chiral solvent; and (−)-1-(3-methylphenyl)ethanol (a) in CS_2, (b) in a DCM/methanol/*n*-hexane solvent mixture, and (c) in a DCM/*n*-hexane solvent mixture.

Acknowledgment. This work was supported by The Department of Chemistry MUN, and the Natural Sciences and Engineering Research Council of Canada.

Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra and X-ray crystallographic data (CIF) of the new compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Crystal data for **6**: $C_{90}H_{84}O_{12}$ $(CHCl_3)_4$, M = 1835.04, colorless prism, space group $R\bar{3}$ (no.148), a = 16.6442(16) Å, c = 27.928(3) Å, V = 6700.3(12) Å^3, Z = 3, D_c = 1.364 g/cm^3, F_{000} = 2856, μ(Mo Kα) = 4.32 cm^{-1}, T = 153(1) K, $2\theta_{max}$ = 59.4°, 20958 reflections collected, 2622 unique (R_{int} = 0.0291). Final GoF = 1.908, R1 ($I > 2.00\sigma(I)$) = 0.1111, R(all reflections) = 0.1113, wR2 (all reflections) = 0.3914. The crystallographic data for compounds **3−6** have been deposited with the Cambridge Crystallographic Data Centre; deposition nos. 795679, 795680, and 795681. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via www.ccdc.cam.ac.uk/conts/retrieving.html.