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Inclusion and Gelation Properties of Novel Tetra- and Hexasalicylide Derivatives

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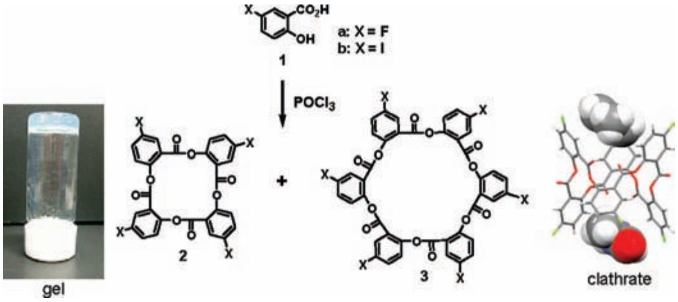
ABSTRACT



Some novel tetra- and hexasalicylide derivatives were synthesized. The tetrasalicylides having a 5-substituted halogen atom on the aromatic ring form organogels with several kinds of organic solvents, whereas the parent compound does not. In contrast, hexasalicylides form stable inclusion crystals with several organic guest molecules.

There has been increasing interest in host−guest inclusion compounds because of their potential applications such as separation of isomeric compounds, optical resolution of enantiomers, reaction medium of included molecules, and sensor materials.[1] Tri-*o*-thymotide **1** is one of the well-studied clathrate host compounds that form inclusion crystals with a wide variety of guest molecules.[1] The propeller-shaped tri-*o*-thymotide molecule **1** has the specific property of undergoing spontaneous resolution on crystallization, and many applications such as optical resolution of guest molecules, asymmetric reactions of included guests, separation of specific molecules from complex mixtures, determination of guest configuration, matrix isolation of labile molecules, and nonlinear optical properties have been studied.[2] However, inclusion properties of higher homologues of **1** have not been investigated so far. Herein, we report the synthesis, crystal structure, and inclusion properties of some novel tetra- and hexasalicylide derivatives (**2**, **3**). Upon exploring the inclu-

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(1) (a) *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Pergamon: Oxford, 1996; Vols. 1−11. (b) *Encyclopedia of Supramolecular Chemistry*; Atwood, J. L., Steed, J. W., Eds.; Marcel Dekker: New York, 2004; Vols. 1 and 2. (c) *Crystalline Molecular Complexes and Compounds*; Herbstein, F. H., Ed.; Oxford Science Publications: Oxford, 2005; Vols. 1 and 2.

(2) (a) Facey, G.; Ripmeester, J. A. *Chem. Commun.* **1990**, *1585*, 1587. (b) Bonner, W. A. *Origins Life Evol. Biosphere* **1990**, *29*, 317–328. (c) Xu, L.; Keehn, P. M.; Gnaim, J. M.; Green, B. S. *J. Org. Chem.* **1992**, *57*, 3208–3213. (d) Facey, G. A.; Ratcliffe, C. I.; Hynes, R.; Ripmeester, J. A. *J. Phys. Org. Chem.* **1992**, *5*, 670–682. (e) Aliev, A. E.; Harris, K. D. M.; Mahdyarfar, A. *J. Chem. Soc., Faraday Trans.* **1995**, *91*, 2017–2026. (f) Gnaim, J. M.; Schurig, V.; Grosenick, H.; Green, B. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1499–1502. (g) Pang, L.; Brisse, F. *J. Chem. Cryst.* **1996**, *26*, 461–465. (h) S.-Gonzalez, H.; Harris, K. D. M. *J. Solid State Chem.* **1999**, *148*, 63–74. (i) Gerdil, R.; Liu, H.; Bernardinelli, G. *Helv. Chem. Acta* **1999**, *82*, 418–434. (j) S.-Gonzalez, H.; Harris, K. M; D, *J. Mol. Struct.* **2000**, *519*, 41–54. (k) Gerdil, R.; Barchietto, G. *Helv. Chim. Acta* **2004**, *77*, 691–708. (l) Gupta, V. K.; Jain, A. K.; Kumar, P.; Agawal, S.; Maheshwari, G. *Sensors Actuators, B* **2006**, *113*, 182–186.

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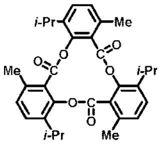
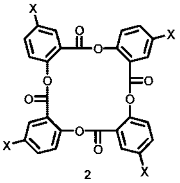
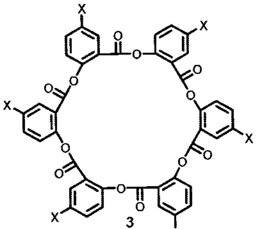
sion properties of these compounds, we found unexpected organogelation abilities of tetrasalicylides (**2b**−**e**) with a wide variety of organic solvents. In contrast, hexasalicylides (**3a**, **3b**) were found to form stable inclusion crystals with several organic solvents. The crystal structures of some tetra- and hexasalicylides were also studied.



1



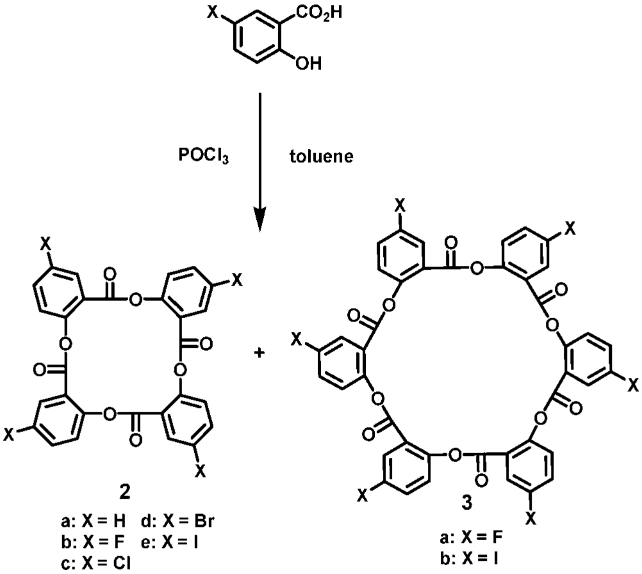
2
a: X = H d: X = Br
b: X = F e: X = I
c: X = Cl



3
a: X = F
b: X = I

A mixture of 2-hydroxybenzoic acid and $POCl_3$ was heated in toluene solution under reflux for 6 h. After the reaction mixture was cooled, the crystals deposited were separated by filtration and washed with toluene and MeOH. The crystalline solid was collected and extracted with hot chloroform using Soxhlet apparatus, and the extract was concentrated to give the tetrasalicylide. In the case of the reactions of 5-fluoro- and 5-iodosalicylic acids, a mixture of tetrasalicylide (**2**) and hexasalicylide (**3**) was formed, and the components were separated by recycling HPLC to give pure tetrasalicylide (**2**) and hexasalicylide (**3**), respectively (Scheme 1).

Scheme 1. Synthesis of Tetra- and Hexasalicylides



Upon crystallization from the solvents listed in Table 1, **2a** formed inclusion crystals with $CHCl_3$ and DMSO in 1:2 ratios. In contrast, tetrasalicylides (**2b**−**e**) having halogen atoms on the aromatic ring formed organogels (Figure 1, left). Among **2b**−**e**, **2c** showed excellent organogelation abilities for several organic solvents listed in Table 1.

Table 1. Gelation Properties of Tetrasalicylide Derivatives **2a**−**f**

solvent	2a	2b	2c	2d	2e
$CHCl_3$	C^{a}	PG (5)^{c}	G (5)^{b}		
THF		G (10)	G (10)		
dioxane		G (5)	G (10)		
cyclopentanone		G (5)	G (10)		
cyclohexanone		G (5)	G (10)		
DMSO	C		G (5)		
DMF			G (10)		
benzene		G (5)	G (5)	PG (5)	G (5)
toluene		G (5)	G (2)	PG (5)	
chlorobenzene		G (2)	G (2)	G (10)	G (5)
aniline		G (5)	G (10)		G (5)
pyridine		G (10)	G (5)		

^{a} C: 1:2 inclusion complex. ^{b} G: gel; values in parentheses refer to minimum concentration necessary for gelation (mg/mL). ^{c} PG: partial gel.

To obtain visual insight into the molecular aggregate, we prepared dry gels for scanning electron microscopy (SEM). Figure 1 (right) shows a typical result obtained from dried gels. The SEM photograph shows the three-dimensional network formed by entanglement of self-assembled nanofibers. It has been well recognized that anisotropic interactions through hydrogen bonding, CH/π, and π/π stacking are responsible for the linear aggregation of low molecular weight organic gelators, allowing the gel formation.[3]

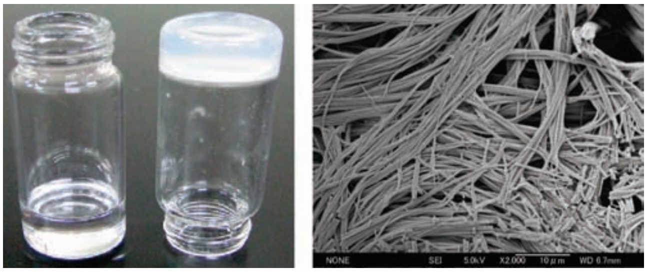


Figure 1. Photographs of typical toluene gels (left) and SEM image of dried gels (right).

Hexasalicylide derivatives (**3a** and **3b**) incorporate several kinds of organic guest molecules into stable inclusion complexes in the ratios indicated in Table 2. The host/guest stoichiometric ratios of 1:3 and 1:5 are exceptionally large, which indicates the high efficiency of guest accommodation

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(3) (a) Terech, P.; Weiss, R. G. *Chem. Rev.* **1997**, *97*, 3133. (b) Van Esch, J; De Feyter, S.; Kellog, R. M.; De Schryver, F.; Feringa, B. L. *Chem. Eur. J.* **1997**, *3*, 1238. (c) Van Esch, J; Schoonbeek, F.; De Loos, M.; Kooijman, H.; Spek, A. L.; Kellog, R. M.; Feringa, B. L. *Chem. Eur. J.* **1999**, *5*, 937. (d) Gronwald, O.; Shinkai, S. *Chem. Eur. J.* **2001**, *7*, 4328. (e) George, M.; Tan, G.; Jhon, V. T.; Weiss, R. G. *Chem. Eur. J.* **2005**, *11*, 3243. (f) Hoeben, F.J. M.; Jonkheijim, P.; Meijer, E. W.; Schenning, A. P. H. J. *Chem. Rev.* **2005**, *105*, 1491. (g) George, M.; Weiss, R. G. *Acc. Chem. Res.* **2006**, *39*, 489–497. (h) Ghosh, R.; Chakraborty, A.; Maiti, D. K.; Puranik, V. G. *Org. Lett.* **2006**, *8*, 1061–1064. (i) Langford, S. J.; Latter, M. J.; Lau, V. L.; Martin, L. L.; Mechler, A. *Org. Lett.* **2006**, *8*, 1371–1373. (j) Adarsh, N. N.; Kumar, D. K.; Dastidar, P. *Tetrahedron* **2007**, *63*, 7386–7396. (k) Baddeley, C.; Yan, Z.; King, G.; Woodward, P. M.; Badjic, J. D. *J. Org. Chem.* **2007**, *72*, 7270–7278.

Table 2. Inclusion Properties of Hexasalicylide Derivatives **3a**,**b**[a]

guest	**3a**	**3b**
$CHCl_3$		1:1 (147)
cyclohexanone		1:3 (171)
DMSO	1:3 (159)	1:3 (115)
DMF	1:2 (125)	1:5 (142)
pyridine		1:5 (101)

[a] Host−guest ratios were determined by TG and ^{1}H NMR; values in parentheses refer to guest release temperature (°C).

of these host compounds (Figure 2). It is also remarkable that these hosts form stable inclusion crystals and the guest molecules are liberated at much higher temperatures than their guest boiling points. For example, the 1:1 inclusion crystal of **3b** with chloroform decomposed when the inclusion crystal was heated above 147 °C, although the boiling point of chloroform is only 61 °C.

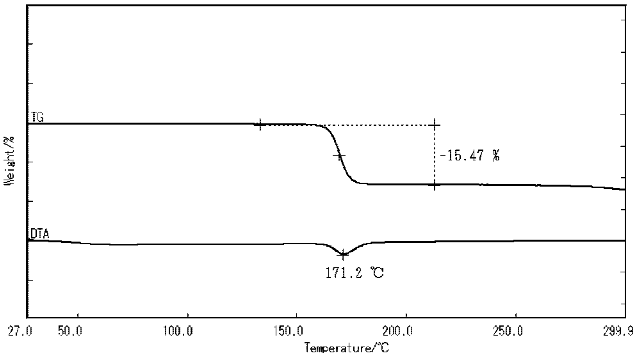

Figure 2. TG trace of 1:3 inclusion crystals of **3b** and cyclohexanone.

The observation that host **2c** displayed exceptional organogelation ability when interacting with solvents, whereas the parent host **2a** was found to form only inclusion compounds, prompted a comparative study of their crystal structures. The X-ray structure of the new host **2c** was therefore determined in this study[4] and compared with the published structure of **2a**.[5] Figure 3 shows the structure of **2c**.

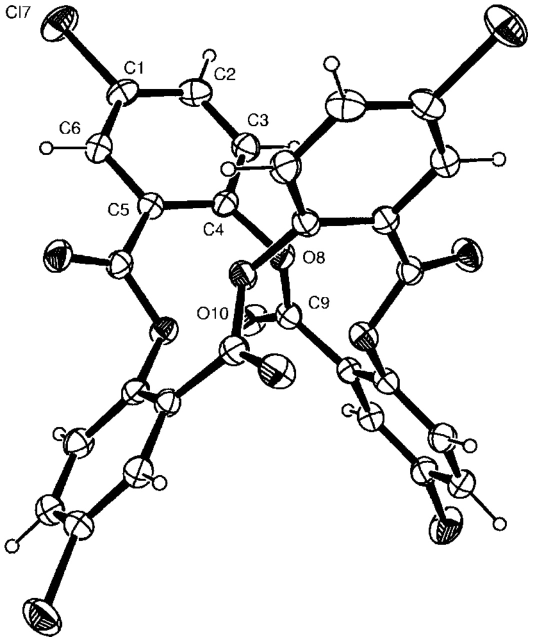

Figure 3. ORTEP diagram of the molecule of **2c** with thermal ellipsoids drawn at the 50% probability level.

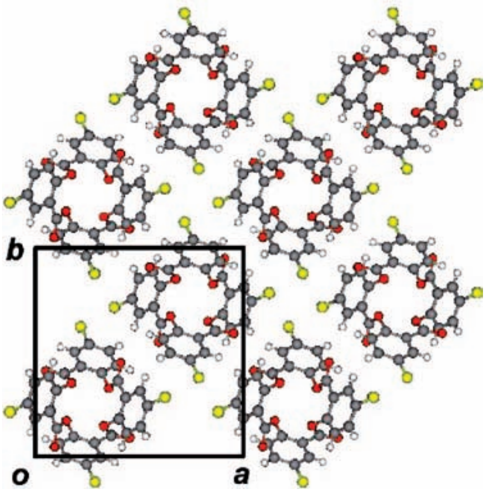

Figure 4. [001] projection of the crystal structure of **2c**.

The molecule is located on a special site of $\bar{4}$ symmetry with the orientations of the four arylcarboxylate units alternating up and down. These four units are held together by trans ester linkages (representative dihedral angle C4−O8−C9−C5^i = 180° (i = y, $3/2-x$, $1/2-z$)). Evidence of internal steric strain is the short intramolecular distance between a central oxygen atom (O8) and its $\bar{4}$-related neighbor, where O···O is 2.663(2) Å. These central oxygen atoms are more evident in Figure 4, the crystal packing diagram. The projected square arrays of Cl atoms (arranged around a 4_2-axis) are also a notable feature. Close contacts of 3.520(2) Å occur between the diagonally related Cl atoms, linking molecules in chains along the crystallographic a- and b-directions. There are two unique intermolecular hydrogen bonds of type C−H···O:

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(4) Crystal data for **2c**: $C_{28}H_{12}Cl_4O_8$, M = 618.18, tetragonal, space group $P4_2/n$ (No. 86), $a = b = 13.2927(3)$ Å, $c = 7.3547(2)$ Å, V = 1299.55(5) Å^3, $Z = 2$, $D_c = 1.580$ g/cm^3, $F_{000} = 624$, Mo Kα radiation, λ = 0.71073 Å, T = 113(2) K, $2\theta_{max}$ = 50.6°, 17580 reflections collected, 1184 unique (R_{int} = 0.0646). Final GooF = 1.098, R1 = 0.0332, wR2 = 0.0831, R indices based on 943 reflections with $I > 2\sigma(I)$ (refinement on F^2), 92 parameters, 0 restraints. Lp and absorption corrections applied, μ = 0.508 mm^{-1}.

(5) Du, D.-M.; Chen, X.; Hua, W.-T.; Jin, X.-L. *Jiegou Huaxue.* **2003**, *22*, 512–516.

C2−H2···O10^{ii} (ii = 1−*x*, 1−*y*, 1−*z*) and C6−H6···O10^{iii} (iii = 1/2+*y*, 1−*x*, 1/2+*z*), with C···O 3.372(2) and 3.398(2) Å, respectively. When the full symmetry of molecule **2c** is applied, a complex network involving a total of 16 C−H···O hydrogen bonds per molecule arises. It is noteworthy that these H-bonds involve the two H atoms ortho to the Cl atom and the carbonyl oxygen atom O10 as acceptor exclusively. Close stacking of molecules in the *z*-direction is achieved by interlocking of the V-shaped grooves formed by diad-related arylcarboxylate planes.

The parent compound **2a** (monoclinic, $P2_1/n$) crystallizes with two independent molecules in the asymmetric unit.[5] These have pseudo-$\bar{4}$ symmetries and conformations very similar to one another and to that of the chlorinated analogue **2c**. However, in its own crystal, **2a** displays minimal C−H···O hydrogen bonding,[5] and the enhanced ability of host **2c** to form hydrogen bonds may be related to its tendency to form gels. The crystal packing of **2a** also differs from that of **2c**. In **2a**, close packing is achieved by insertion of a phenyl ring of one molecule within the V-groove of a neighboring molecule. The result is extensive molecular overlap when the crystal structure is viewed down the common direction of the host pseudo-$\bar{4}$ axes (Figure 5).

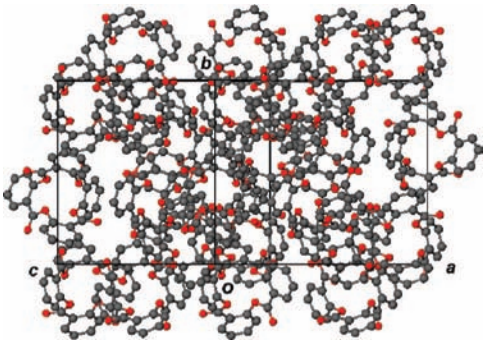

Figure 5. Crystal packing in **2a** viewed approximately parallel to the [101] direction.

The novel hexasalicylide host **3a** is located on a center of inversion.[6] Aryl carboxylate units are linked by trans ester linkages (C−C−O−C range −176.1(2) to +176.7(2)°) and alternate in orientation. Space-filling models show that in this conformation the central region of the host is blocked by oxygen atoms of the ester groups with O···O distances of 2.806(2) and 3.157(2) Å. The molecule therefore presents two bowl-shaped cavities to potential guest molecules, above and below the belt of constricting oxygen atoms.

Figure 6 illustrates the inclusion of two DMF molecules within a cavity created by two host molecules in the compound **3a**·(DMF)$_2$. Each DMF molecule inserts into the bowl-like cavity generated by three alternate arylcarboxylate units, the whole assembly shown having a center of inversion. Inspection of the crystal packing shows that guest molecules are fully surrounded by host molecules. Only one weak host−guest hydrogen bond was detected: C13−H13···O31^{ii} with C···O 3.353(2) Å (ii = 2−*x*, 1−*y*, 1−*z*, atom O31 being that of the DMF molecule).

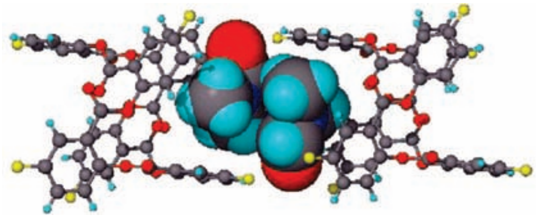

Figure 6. Inclusion of DMF molecules by host **3a**.

H-bonding between host molecules is minimal; only one bond with C···O < 3.4 Å was found, namely C4−H4···O19^{ii} (ii = *x*, 1+*y*, *z*) with C···O = 3.143(2) Å. In contrast to **2c**, where Cl-induced acidity in flanking C−H groups appears to promote C−H···O hydrogen bonding, the F atoms surprisingly do not appear to manifest analogous effects in the crystal of inclusion compound **3a**·(DMF)$_2$.

While the factors favoring organogelation are not fully understood, self-assembly via noncovalent interactions, including H-bonding, have been indicated as playing a role.[7] For the novel host compounds reported here, the small sample of crystal structures gives some indications of H-bonding potential in the solid state. Possible structural differences in crystals of the gelator **2c** and the nongelator **2a** that may account for their different behaviors include the presence of numerous intermolecular C−H···O hydrogen bonds and close Cl···Cl contacts for the former compound versus only relatively few C−H···O hydrogen bonds for the latter. Further X-ray studies and investigation of the nature of molecular association in the gels are necessary to develop a possible mechanism for organogelation and to understand the different behaviors of the two series of host compounds.

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Supporting Information Available: Synthetic procedure, spectroscopic characterization, and CIF files for compounds **2c** and **3a**·(DMF)$_2$. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Crystal data for **3a**·(DMF)$_2$: empirical formula $C_{24}H_{16}F_3NO_7$, M = 487.38, triclinic, space group P-1 (No. 2), a = 9.5721(7) Å, b = 10.0848(7) Å, c = 12.5819(6) Å, α = 69.849(4)°, β = 73.108(4)°, γ = 75.513(4)°, V = 1075.7(1) Å^3, Z = 2, D_c = 1.505 g/cm^3, F_{000} = 500, Mo Kα radiation, λ = 0.71073 Å, T = 213(2)K, $2\theta_{max}$ = 52.8°, 7836 reflections collected, 4386 unique (R_{int} = 0.0490). Final GooF = 1.031, R1 = 0.0371, wR2 = 0.0885, R indices based on 3333 reflections with $I > 2\sigma(I)$ (refinement on F^2), 319 parameters, 0 restraints. Lp corrections applied, μ = 0.128 mm^{-1}.

(7) Pal, A.; Ghosh, Y. K.; Bhattacharya, S. *Tetrahedron* **2007**, *63*, 7334–7348.