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Remarkable Structures of Cyclotri(deoxycholate) and Cyclotetra(24-norcholate) Acetate Esters

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Abstract: X-ray crystallographic determinations and AM1 calculations have defined the solid-state and gas-phase structures of cyclotri(deoxycholate) and cyclotetra(24-norcholate). The latter cyclotetramer is one of the largest open macrocycles ever subjected to crystallography.

Cholic acid oligomers are excellent building blocks for construction of promising biocompatible nanostructures. Recent reviews show that these systems have remarkable diversity.[1−3] In general, such systems are earmarked by chirality and rigidity. Three major bioorganic chemical classes—carbohydrates, peptides, and steroids—all form macrocyclic compounds with potential host/guest applications. Cyclodextrins are hydrophilic on their outer surfaces and lipophilic within their cavities. The surfaces of cyclic peptides may vary in polarity with the identity of the amino acid side chains, but their interiors are usually lipophilic. In contrast, cyclocholates[4] can be lipophilic on their outer surfaces and hydrophilic within their cavities, depending on the oxygen-containing functionality of the particular cholanoic acid monomer. Our recent efforts have focused on preparation and structural characterization of cyclocholates that have large central cavities. In the present work we describe the crystallographic characterization of two cyclocholates, **1** and **2**, previously synthesized from selectively acetylated deoxycholic acid and 24-norcholic acid.[5]

Results and Discussion

Syntheses of Cyclocholates. The synthesis of the triacetate of cyclotri(deoxycholate) (**1**) was achieved (41%) by macrolactonization of 3α-hydroxy-12α-acetoxy-5β-cholan-24-oic acid with 2,6-dichlorobenzoyl chloride and DMAP in refluxing toluene for 24 h. This synthesis yielded 3.5% of the diacetate of cyclodi(deoxycholate). When the 12α-hydroxy was not protected by acetylation, this reaction gave 32% cyclic monomer with only 4.2% cyclic diol dimer. Cyclocholate **1** was isolated via chromatography and then recrystallized from chloroform/ether/hexanes to yield single crystals suitable for X-ray diffraction (Figure 1).

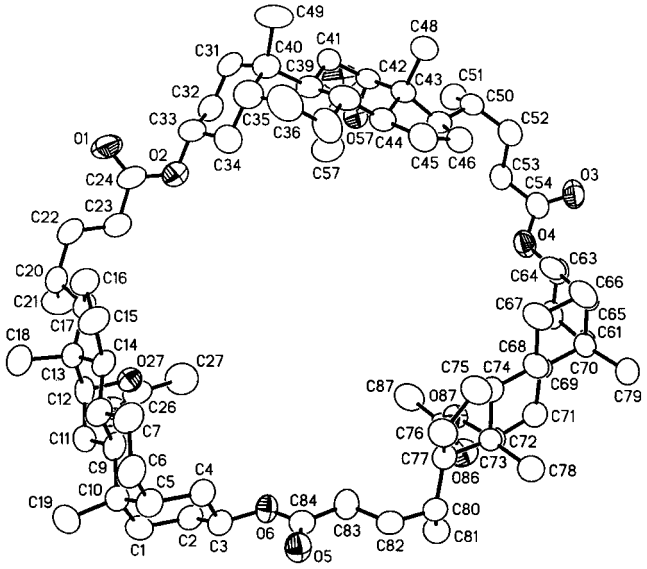

Figure 1. Molecular structure of compound **1** with the crystallographic numbering scheme. Thermal ellipsoids have been drawn at the 50% probability level, and hydrogens have been omitted for clarity.

The synthesis of the octaacetate of cyclotetra(24-norcholate) (**2**) was achieved (42%) by macrolactonization of 3α-hydroxy-7α,12α-diacetoxy-24-nor-5β-cholan-23-oic acid with 2,6-dichlorobenzoyl chloride and DMAP in refluxing toluene for 24 h. This synthesis yielded 15% of the hexaacetate of cyclotri(24-norcholate). Cyclocholate **2** was isolated via chromatography and then recrystallized from hexanes/ether/ethyl acetate to yield single crystals suitable for X-ray diffraction (Figure 2).

One may not differentiate between cyclic dimers, trimers, tetramers, etc. by NMR spectroscopy,[6] but relative R_f values

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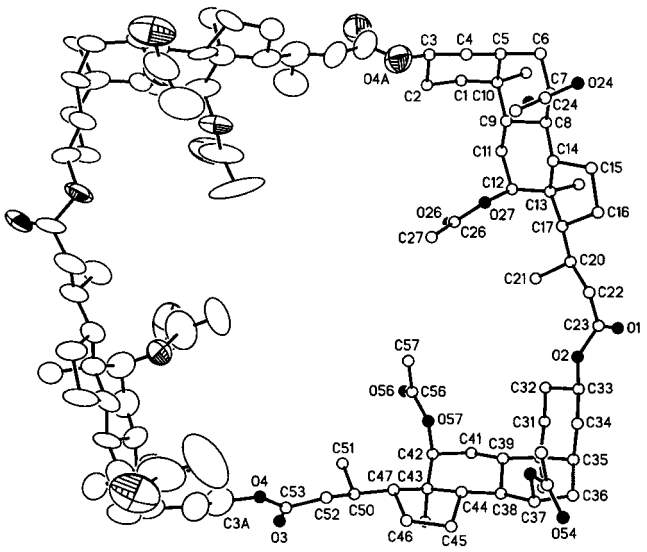
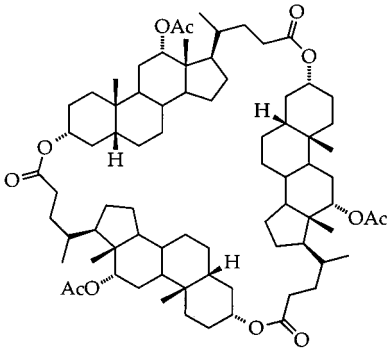
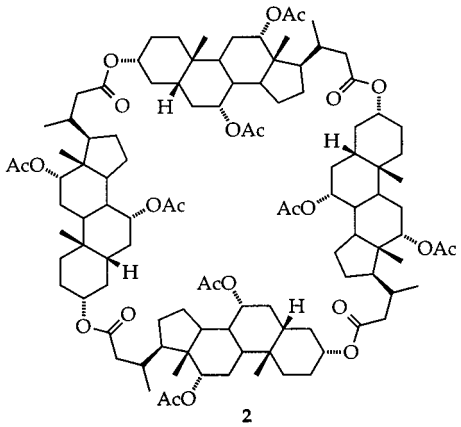


Figure 2. Molecular structure of compound **2**. One symmetry-independent half of the molecule is drawn with 50% probability thermal ellipsoids, and the other half is a ball-and-stick drawing of with the crystallographic numbering scheme.

and MS/FAB did. However, X-ray structures provide unequivocal characterization as well as more detailed structural information.



1



2

X-ray Structures of Cyclocholates 1 and 2. Cyclocholate **1** crystallized in the monoclinic space group $P2_12_12_1$ with $Z = 4$; thus, the molecule lies on a general position. The structure was solved by direct methods, and the resulting molecular structure of **1** is illustrated in Figure 1. Figure 3 shows the crystal packing and reveals a stacking of the macrocycles to form long, cylindrical channels along the crystallographic *a* axis. The molecular cavity, and thus the channels, are filled with disordered solvent molecules. These were initially modeled as discrete ether and chloroform molecules, but they were ultimately removed from the structure by the SQUEEZE/BYPASS procedure.[7] The final refinement converged satisfactorily to a conventional $R(F) = 0.0621$.

Cyclocholate **2** crystallized in the monoclinic space group $C2$ with $Z = 2$; thus, the molecule lies on a special position. The structure was solved by molecular replacement by using the program PATSEE[8] and a steroid fragment from the literature.[9] The molecular structure is shown in Figure 2. Cyclocholate **2** lies on a crystallographic 2-fold axis and thus possesses exact C_2 symmetry. This greatly facilitated the refinement of this very large structure. The crystal packing of cyclocholate **2** is shown in Figure 4 and is superficially similar to that of cyclocholate **1**. The molecules stack to form long channels along the crystallographic *b* axis, and these are filled with solvent molecules. Additional solvent molecules are present in the interstitial spaces, and overall about 45% of the volume of the unit cell is occupied by disordered solvent. These were initially modeled as two ethyl acetates and five ethers per molecule of **2**, but they were subsequently removed from the structure by the SQUEEZE/BYPASS procedure.[7] The final refinement converged to a satisfactory $R(F) = 0.0651$, but the disorder in the structure is still evident in the large ellipsoids for the pendant acetate groups.

The unacetylated monomers of deoxycholic acid and cholic acid used in this work frequently form channel inclusion compounds with carboxylic acids, alcohols, ketones, esters, ethers, alkanes, aromatic hydrocarbons, and azo dyes.[11] The cholic acid channels have large side pockets, while those of deoxycholic acid are very small. The crystal lattice of cholic acid is made up of pleated bilayers packed to form channels bounded by two steroid cis A-rings and two 17-side chains that contain guest molecules. Typically, there are no short-range host−guest interactions, and all the host hydroxy groups are involved in host−host hydrogen-bonding.

The crystal structures of the large, cyclic oligomers of **1** and **2** are rather different from the inclusion compounds of monomeric bile acids. The latter structures usually have definite order and stoichiometry, but the greater empty space present in the crystals of **1** and **2** and the small size of the crystallizing solvent led to solvent disorder and uncertain stoichiometry. Indeed, the structures of such "small molecules", containing more than 100 non-hydrogen atoms, tend to take on the characteristics of macromolecular crystal structures. Protein crystals are typically 50% water; by comparison, the structures of **1** and **2** contains 25% and 45%, respectively, solvent by volume. Such compounds make the best contacts that they can in the crystal, and the rest of the space is filled with disordered solvent. The solvent disorder often gives rise to weak X-ray data sets, and unusual measures may be required to solve and refine these structures.

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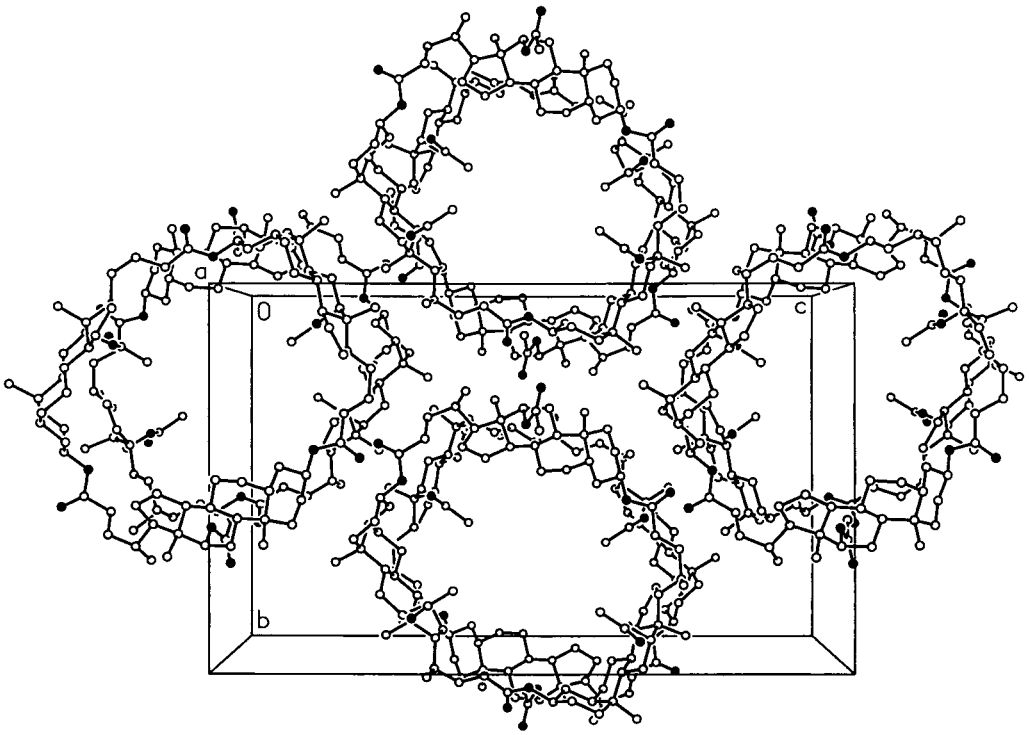

Figure 3. Unit cell and packing of compound **1** viewed down the crystallographic *a* axis.

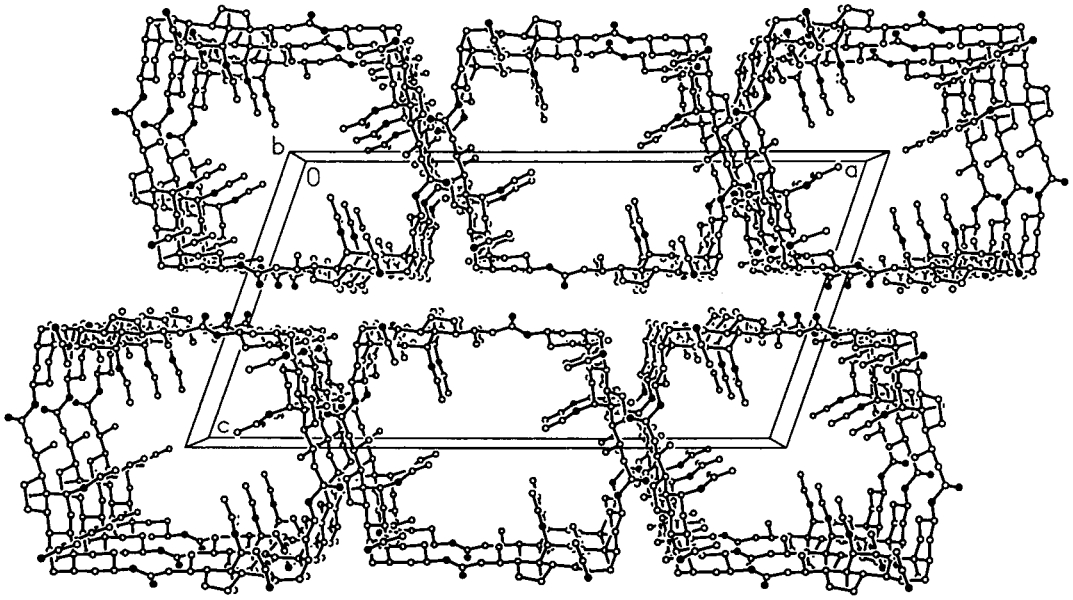

Figure 4. Unit cell and packing of compound **2** viewed down the crystallographic *b* axis.

Figures 3 and 4 show crystal packing views that reveal that the cyclocholates **1** and **2** have substantially more "empty" space (filled with disordered solvent) within their molecular channel than in the channels between adjacent molecules.

A broad search of the Cambridge Structural Database found only five X-ray structures of macrocycles containing two steroid nuclei,[12−17] but no macrocyclic structure formed from more than two steroids were found. Thus there are no structures comparable to those of compounds **1** and **2**, and the cavity in compound **2** is much larger than the cavities observed in any of the literature structures.

The X-ray crystal structure of **1** in Figure 1 clearly shows that one of the steroid moieties is twisted such that the associated 12α-OAc group is no longer thrust into the cyclocholate cavity.

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This is also evident in the crystal packing shown in Figure 3. The X-ray crystal structure of **2** in Figure 2 shows that only the 12α-OAc groups are thrust into the cyclocholate cavity, and in Figure 4 the remaining 7α-OAc groups appear to be making contact with the adjacent cyclocholate molecule.

Computational Studies of Cyclocholates. The X-ray crystal structure of cyclocholate **1** is shown in Figure 1. Using the crystallographic numbering, the vertexes of an inscribed triangle can be defined by 027−057−087 with distances of 10.0 Å−11.2 Å−10.2 Å, respectively. It has been reported[10] that the MM2-optimized structure for cyclolithocholate trimer gave average distances linking oxygens of 10 Å. Classical mechanical treatments often give good results for systems upon which they are parametrized. Because of their simplicity and comparatively low computational cost, they are typically applied to macromolecules, giving way to more rigorous quantum mechanical treatments when the number of "heavy atoms" decreases. The quantum mechanical treatment of systems of this size (90 heavy atoms for **1**) lends itself to the AM1 semiempirical quantum mechanical method, because it strikes a balance between the computational expense associated with the more rigorous ab initio computation and the speed offered by classical mechanics. Such gas-phase treatments are useful to investigate these systems in the absence of intermolecular crystal packing effects associated with their crystal structures.

Figure 5 compares the crystal structures of the cyclocholates **1** and **2** with the geometries obtained by AM1 optimization of the X-ray structures. The AM1 structure of compound **1** possesses approximate C_3 symmetry, but the X-ray structure is less nearly symmetric, due to tilting of the steroid nuclei (presumably due to crystal packing forces). The vertexes of the inscribed triangle (027−057−087, described above) take on distances all equal to 9.6 Å in the AM1 structure. This results in an 11 Å diameter circle, which means that a molecule of triphenylene could be placed in this cavity. During optimization of **1**, the computed enthalpy of formation dropped by about 125 kcal/mol (from −594.8 kcal/mol for the enthalpy of formation of the crystal structure to −720.7 kcal/mol for the optimized structure). Such a reduction in enthalpy of formation is not unexpected for an AM1 geometry optimization of the X-ray structure of such a large molecule due to accumulation of small geometric errors in the X-ray structure and systematic errors in the C−H and C−C bond lengths found by quantum chemical methods. However, the actual difference in energy of the computed and X-ray conformations of **1** is estimated to be only 2.6 kcal/mol, based on an AM1 optimization in which the distances in the triangle 027−057−087 were constrained to their X-ray values. This small amount of energy could easily be provided by crystal packing forces. Similarly, the X-ray and AM1 structures of compound **2** differ by some tilting of the steroid nuclei and rotation of the pendant acetate groups, but these are also likely to be low-energy distortions. The rms deviation of the atomic positions in the experimental and calculated structures of **1** is 0.969 Å, and for **2** the value is 1.246 Å.

The following analysis suggests that cyclocholates **1** and **2** are the observed major cyclic oligomers, because their syntheses result in little or no additional strain over their monomeric forms. Using the AM1 enthalpies of formation for *i*-PrOH (−69.5 kcal/mol), HOAc (−103.0 kcal/mol), *i*-PrOAc (−106.2 kcal/mol), and H_2O (−59.2 kcal/mol), it is estimated that the formation of each ester group between a secondary alcohol and carboxylic acid requires 7.1 kcal/mol for the minimal strain case. The respective AM1 enthalpies of formation for 3α-hydroxy-12α-acetoxy-5β-cholan-24-oic acid and 3α-hydroxy-7α,12α-diacetoxy-24-nor-5β-cholan-23-oic acid are −305.6 and −377.9 kcal/mol. Thus, the respective enthalpies of reactions for the formation of **1** and **2** are 18.5 and 25.8 kcal/mol. Subtracting 3 × 7.1 kcal/mol from the former enthalpy value and 4 × 7.1 kcal/mol from the latter one gives −2.8 and −2.6 kcal/mol as estimated additional strain energies for **1** and **2**, respectively, above and beyond their corresponding monomeric units. We believe these small (exothermic) differences are not significant. These results lead us to conclude that these cyclocholates have little or no additional strain over that in the monomers, which may explain why they are the major cyclic oligomers in the respective syntheses, whereas other cyclic oligomeric sizes probably involve higher strain.

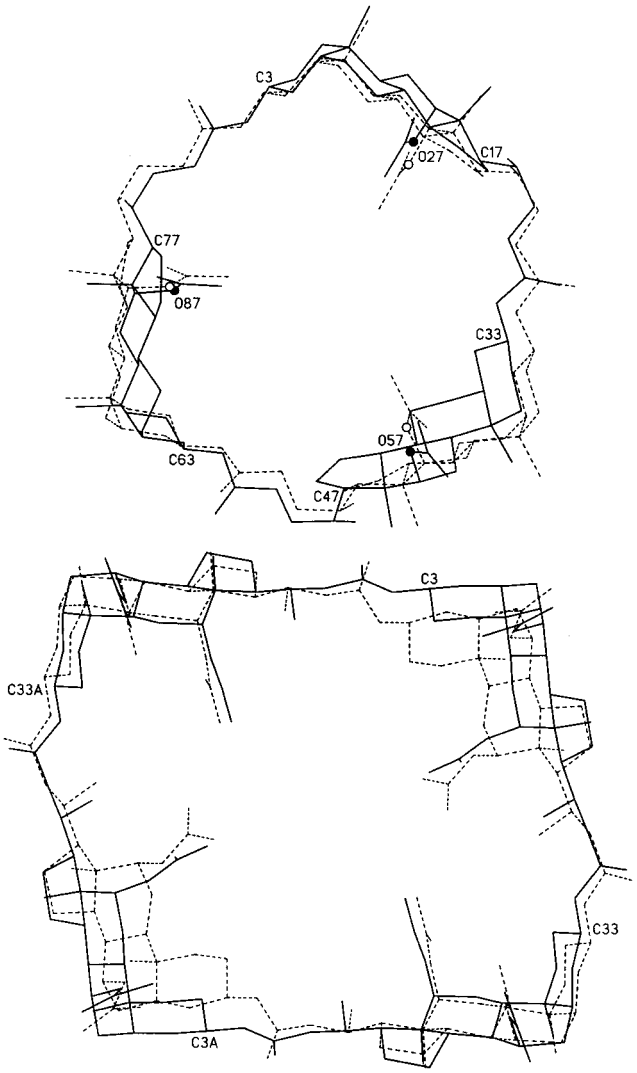

Figure 5. Superposition of the X-ray and AM1 structures of compounds **1** (above) and **2** (below). The oxygen atoms O27, O57, and O87 have been highlighted in **1** (see text). The overlays were made by using the OFIT function in SHELXTL, and all nonhydrogen atoms were used for the fitting. The rms deviation of the atomic positions in the experimental and calculated structures of **1** is 0.969 Å, and for **2** the value is 1.246 Å.

Conclusion

This work is the first X-ray crystallographic study of two cyclocholates with highly significant structural differences for maximum contrast; one is a cyclic trimer with one acetyl group per steroid unit and the other is a cyclic tetramer with two acetyl groups per steroid unit and one less carbon in the 17-side chain. According to our literature search, this crystallographic study records the first determination of macrocycles possessing three and four cholic acid moieties, with the latter having the largest known cavity. In the crystal the cyclocholate cavities are aligned to form channels possessing substantial amounts of "empty" space. In the crystal of **2**, the 12α-OAc groups project into these channels, while the 7α-OAc groups are oriented peripherally. These results and gas-phase AM1 (and MM2) studies show that very different interactions exist between the 7α-OAc and 12α-OAc groups in these systems.

These large cyclocholates may provide a framework for the construction of new enantioselective host molecules, chiral ligands, or chiral auxiliaries. They are prepared from readily available starting material derived from natural products, and they contain useful interior and peripheral functionality. In addition, their conformations can be predicted relatively well by modern computational methods. However, the key to their further development will be a capability, not yet achieved, to modify selectively the various functional groups in an efficient manner, so that a wide variety of guests may be accommodated.

Experimental Section

Column chromatography was performed using Grade 62 (60−200 mesh) silica gel and *n*-hexane/ethyl acetate eluant. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were determined at 250 and 63 MHz (Bruker), respectively, using $CDCl_3$ containing 1% TMS. FAB/MS spectra were determined by the Midwest Center for Mass Spectrometry, Lincoln, NE.

General Procedure for Preparation of Cyclocholates. A mixture of monomer (0.6 mmol), 2,6-dichlorobenzoyl chloride (0.6 mmol), DMAP (2.46 mmol), and dry toluene (20 mL) was heated at reflux for 24 h. The solvent was removed in vacuo and the residue was flash chromatographed on a silica gel column to afford cyclooligomers.

Triacetate of Cyclotri(deoxycholate). Mp: 288−290 °C. Yield: 41%. ^{1}H NMR: δ 0.73 (s, 9H, C18), 0.85 (d, 9H, C21), 0.91 (s, 9H, C19), 2.11 (s, 9H, 12-OAc), 4.75 (m, 3H, 3β-H), 5.05 (m, 3H, 12β-H). FAB/MS (3-NBA+NaI): 1422 [MNa + NaI], 1272 [MNa]. Anal. Calcd for $C_{78}H_{120}O_{12}$: C, 74.96; H, 9.62. Found: C, 75.22; H, 9.65.

Octaacetate of Cyclotetra(24-norcholate). Mp: 287−289 °C.[18] R_f (1:1 hexanes:ethyl acetate): 0.44. Yield: 42%. ^{1}H NMR: δ 0.77 (s, 12H, C18), 0.84 (d, 12H, C21), 0.90 (s, 12H, C19), 2.07 (s, 12H, 7-OAc), 2.11 (s, 12H, 12-OAc), 2.4 (d, 8H, C22), 4.67 (m, 4H, 3β-H), 4.92 (m, 4H, 7β-H), 5.09 (m, 4H, 12β-H). FAB/MS (3-NBA + NaI): 1865.3 [MNa]. Anal. Calcd for $C_{108}H_{160}O_{24}$: C, 70.41; H, 8.75. Found: C, 70.74; H, 8.91.

X-ray Crystallographic Analysis of Compounds 1 and 2. X-ray diffraction data were collected by using graphite-monochromated Mo Ka radiation (0.71073 Å) on a Siemens SMART CCD diffractometer at B100 °C, and the data were processed by using Siemens SAINT. Specific crystal, reflection, and refinement parameters are contained in Table 1.

The structure of **1** was solved in the orthorhombic space group $P2_12_12_1$ (No. 19) by direct methods using Siemens SHELXTL,[19] and it was refined by full-matrix least-squares on F^2 using SHELXTL. The molecule lies on a general position, as do two solvent molecules that were best modeled as diethyl ether and chloroform. The solvents gave indications of moderate to severe disorder and, in the case of chloroform, partial occupancy. In an initial refinement, all non-H atoms of **1** were refined anisotropically, and hydrogens were included with a riding model. The solvents were refined isotropically as ideal rigid bodies, and a two-site disorder model was used for the chloroform. Refinement of this discrete-atom model converged to $R(F) = 0.0943$, but the generally poor description of the included solvent (and its uncertain identity) suggested that an alternative approach should be investigated. For this reason, the SQUEEZE/BYPASS procedure[7] implemented in PLATON-96[20] was employed to account for the solvent electron density. With only compound **1** included in the instruction file for PLATON-96, the SQUEEZE option found a total electron count of 426 e in a volume of 2163 Å^3 for the solvent regions in the unit cell (25% of the unit cell volume). This electron count corresponds well to that for four ethers plus four chloroforms (400 e) and suggests, perhaps, that the chloroform site is not partially occupied. The SQUEEZE-processed data were used for all subsequent cycles of refinement. All non-hydrogen atoms were refined anisotropically, with hydrogens riding [CBH = 0.98, 0.99, or 1.00 Å, U(H) = 1.2U(C) or 1.5U(C_{methyl})]. The final refinement parameters are given in Table 1.

Table 1. Crystallographic Data for Compounds 1 and 2

	1	**2**
chemical formula	$C_{78}H_{120}O_{12}\cdot C_4H_{10}O\cdot 0.5CHCl_3$	$C_{108}H_{160}O_{24}\cdot 5C_4H_{10}O\cdot 2C_4H_8O_2$
formula weight	1383.54	2389.17
crystal size (mm)	0.40 × 0.20 × 0.20	0.40 × 0.35 × 0.20
space group	$P2_12_12_1$ (No. 19)	$C2$ (No. 5)
a, Å	15.282(3)	39.787(3)
b, Å	18.6210(7)	10.0705(7)
c, Å	30.408(1)	20.968(1)
α, deg	90	90
β, deg	90	109.105(1)
γ, deg	90	90
V, Å^3	8653(2)	7938.6(9)
Z	4	2
ρ_{calcd}, g/cm^3	1.062	0.999
μ, mm^{-1}	0.11	0.07
T, K	173	173
θ_{max}, deg	27.22	27.15
total no. of reflns	48 148	21 028
no. of unique reflns	18 411	14 402
no. of obsd reflns [$I > 2\sigma(I)$]	8538	4066
$R(F)$ (obsd data)[a]	0.0621	0.0651
$wR(F^2)$ (obsd data)[a]	0.1151	0.1281
S (obsd data)[a]	1.131	1.121
$R(F)$ (all data)[a]	0.1368	0.1735
$wR(F^2)$ (all data)[a]	0.1359	0.1521
S (all data)[a]	0.891	0.675

[a] $R(F) = \sum||F_o| - |F_c||/\sum|F_o|$; $wR(F^2) = [\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$; S = goodness-of-fit on $F^2 = [\sum w(F_o^2 - F_c^2)^2/(n - p)]^{1/2}$, where n is the number of reflections and p is the number of parameters refined.

The structure of **2** was solved in the monoclinic space group $C2$ (No. 5) by molecular replacement using the program PATSEE[8] and the atomic coordinates for the steroid nucleus of a literature structure of norcholic acid (CSD refcode HIPFOB[9]). Compound **2** lies on a special position with crystallographic $C2$ symmetry (thus $Z = 2$). Three solvent molecules, best described as two ethers and one ethyl acetate, were located on general positions, and a third ether was disordered across a C_2 axis. A stoichiometry of $C_{108}H_{160}O_{24}\cdot 5C_4H_{10}O\cdot 2C_4H_8O_2$ is thus obtained, but it is somewhat speculative. The structure was refined by full-matrix least-squares on F^2 using SHELXTL. Non-H atoms in

(18) A melting point of 263−265 °C was also obtained upon recrystallization from ethyl acetate−chloroform.

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compound **2** were refined anisotropically with hydrogens riding. All of the solvent molecules gave indications of moderate to severe disorder and, in some cases, partial occupancy. Ultimately, they were described as as ideal rigid bodies and refined isotropically. Refinement of this discrete-atom model converged to $R(F) = 0.1502$, but the solvent was poorly described and there remained "empty" areas of the structure that probably contain even more highly disordered solvent. Once again, the SQUEEZE/BYPASS procedure was employed to account for the solvent electron density. With only compound **2** included in the instruction file for PLATON-96, the SQUEEZE option found a total electron count of 1100 e in a volume of 3556 Å^3 for the solvent regions in the unit cell (45% of the unit cell volume). This electron count corresponds to 1.8 times that expected for the solvent included the discrete-atom model (10 ethers and four ethyl acetates possess 612 e), and it is another indication of the extent and severity of the solvent disorder in this crystal. The SQUEEZE-processed data were used for all subsequent cycles of refinement. All nonhydrogen atoms were refined anisotropically, with hydrogens riding [CBH = 0.98, 0.99, or 1.00 Å, $U(H) = 1.2U(C)$ or $1.5U(C_{methyl})$]. The final refinement parameters are given in Table 1.

AM1 Calculations. The AM1[21] method was used for these calculations as implemented in the program *AMPAC with Graphical User Interface*.[22] Ground-state species (reactants and products) were optimized with respect to a minimum energy geometry and were then characterized by frequency calculations with the requirement that there be no negative eigenvectors present.[23,24]

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