sponsible for their production and points to the role of ion stability. It has been found in beam studies[18] that upon electron impact ionization, protonated water clusters with slightly more than 21 molecules preferentially fragment to $n = 21$, leading to its net production. In the present work there is little available thermal energy in the collisions at 120 K, which can lead to dissociation. The new findings show that magic numbers arise due to thermodynamic stability of the cluster ions rather than effects due to selective growth kinetics or selective fragmentation. Water clathrates are the most plausible structures proposed to account for the proton hydrate cluster magic numbers.[6,19-21] The proton resides within the network of small clusters, and the smooth trend of reactivity argues against a sudden conformational change[21] at $n = 21$. Hence, the results of this study are consistent with the model proposed by Castleman and co-workers[5,6] that (1) the anomalous cluster involving 21 water molecules with a proton has a very stable clathrate structure with a proton on its surface and (2) other distorted clathrate structures explain those weak features with $n = 24$, 26, and 28.

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(18) Echt, O.; Kreisle, D.; Knapp, M.; Recknagel, E. *Chem. Phys. Lett.* **1984**, *108*, 401.
(19) Siksna, Reinhards Water Clathrates as Aerosol Particles. Instituet for Hogspanningsforskning, Uppsala, Sweden, August 1973, UURIE:53:73.
(20) Kassner, J. L., Jr.; Hagen, D. E. *J. Chem. Phys.* **1976**, *64*, 1860.
(21) Nagashima, U.; Shinohara, H.; Nishi, N.; Tanaka, H. *J. Chem. Phys.* **1986**, *84*, 210.

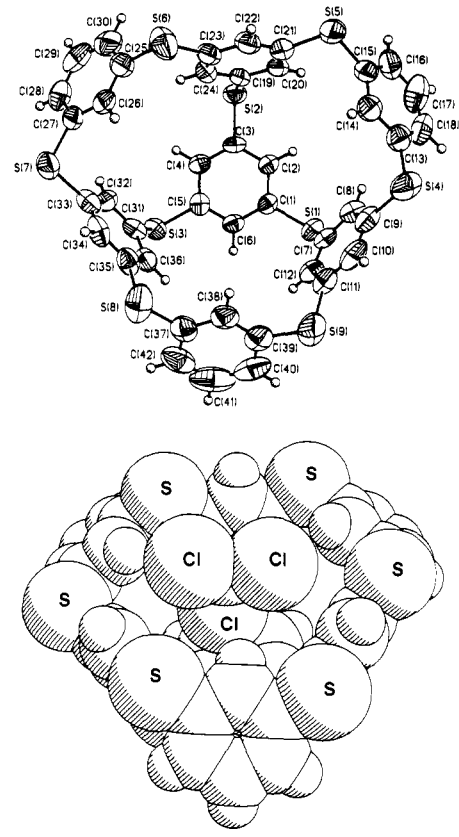

Figure 1. Two views of the molecular structure of compound **1**. In the upper illustration, the chloroform of crystallization is omitted in the interest of clarity.

Short Synthesis and Structure of a Large Molecular Bowl

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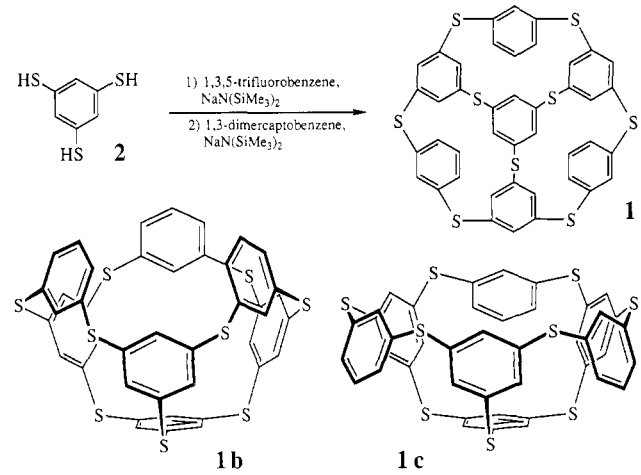
Molecular mechanics calculations[1] indicate that compound **1**, a network of aryl thioethers that looks unpromising in a planar projection, may adopt any of several low-energy bowl-shaped conformations, such as **1b** and **1c**, which differ only slightly in steric energy. These structures are potential hosts for small nonpolar molecules, and a simple synthesis of such compounds might permit their incorporation into more complex ligands with the ability to bind larger guests. We report here a two-step synthesis of **1** and the molecular structure of its chloroform clathrate.

Treatment of a mixture of 1,3,5-trimercaptobenzene[2] (**2**) and excess 1,3,5-trifluorobenzene in dimethylacetamide with 3 equiv of $NaN(SiMe_3)_2$ (added in portions over 6 h) at 70-100 °C for 48 h gives 1,3,5-tris((3,5-difluorophenyl)thio)benzene[3] (**3**) in 65% yield. Similar treatment of a mixture of **3** and 1,3-dimercaptobenzene at moderate dilution (5 and 15 mM, respectively) in dimethylacetamide with 6 equiv (relative to **3**) of $NaN(SiMe_3)_2$ gives **1** in 1.5% yield[4] after purification by preparative TLC (1:1 CH_2Cl_2-hexanes, $R_f = 0.8$). Compound **1** was easily identified by its first-order 500-MHz ^1H NMR spectrum and a mass spectrum dominated by the singly and doubly charged molecular ions.[5] Since the two sulfur-containing starting materials, 1,3,5-trimercaptobenzene and 1,3-dimercaptobenzene, are most conveniently prepared by heating the appropriate halobenzenes with excess sodium isopropylthiolate followed by reductive removal of the alkyl groups,[2,6] all 18 carbon-sulfur bonds in **1** were pre-

Scheme I



(1) MMPI [Allinger, N. L.; Sprague, J. T. *J. Am. Chem. Soc.* **1973**, *95*, 3893-3907] was used for the calculations by including ad hoc parameters for aryl thioethers.
(2) Testaferri, L.; Tiecco, M.; Tingoli, M.; Chianelli, D.; Montanucci, M. *Synthesis* **1983**, 751-755.
(3) For **3**: mp 102-105 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 6.72 (tt, $J_{HF} = 9$ Hz, $J_{HH} = 2$ Hz, 3 H), 6.80 (m, 6 H), 7.24 (s, 3 H); $^{13}C\{^1H\}$ NMR (75.4 MHz, $CDCl_3$) δ 103.3 (t, $J_{CF} = 25$ Hz), 113.4 (d, $J_{CF} = 27$ Hz), 132.7, 137.1, 138.0 (t, $J_{CF} = 10$ Hz), 163.1 (dd, $J_{CF} = 252$, 12 Hz); MS, m/z 510 (M^+, 50%), 398 ($M - C_6H_2F_2$, 26), 366 (26), 332 (13), 252 (28), 220 (100); exact mass 510.0008, calcd for $C_{24}H_{12}F_6S_3$ 510.0005.

(4) Neither prolonged reaction times nor addition of CsCl to the reaction mixture improved the yield of compound **1**.
(5) For **1**: ^1H NMR (500 MHz, CD_2Cl_2) δ 7.00 (d, $J = 2$ Hz, 6 H), 7.27 (t, $J = 2$ Hz, 3 H), 7.478 (t, $J = 8$ Hz, 3 H), 7.481 (t, $J = 2$ Hz, 3 H), 7.51 (s, 3 H), 7.60 (dd, $J = 8$, 2 Hz, 6 H); MS, m/z 816 (M^+, 100%), 408 (M^{2+}, 27%); exact mass 815.9371, calcd for $C_{42}H_{24}S_9$ 815.9364.
(6) Maiolo, F.; Testaferri, L.; Tiecco, M.; Tingoli, M. *J. Org. Chem.* **1981**, *46*, 3070-3073.

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pared by nucleophilic aromatic substitution reactions, which we believe to be unprecedented in the synthesis of a complex macrocycle.

Crystallization of **1** from $CHCl_3$–heptane gave crystals suitable for X-ray analysis.[7] This material proved to be a stable chloroform clathrate, and its structure is illustrated in Figure 1. Compound **1** adopts conformation **1c** in the crystal, in which the cavity is approximately 4.5 Å deep and 6 Å in diameter. Given the propensity of cavitands to form solvates,[8,9] it is not surprising that the chloroform of crystallization is nestled in the molecular bowl; however, we have no evidence of a specific association of **1** and chloroform in solution.

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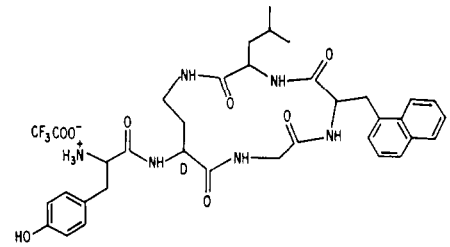
Supplementary Material Available: Crystallographic data and processing descriptions and tables of final atomic coordinates, bond lengths and angles, and anisotropic thermal parameters for **1**·$CHCl_3$ (10 pages). Ordering information is given on any current masthead page.

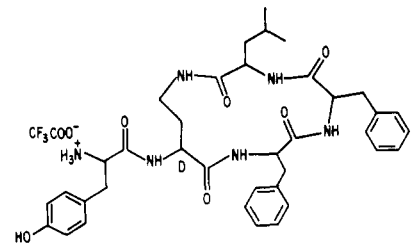
(7) A crystal of compound **1** measuring 0.08 × 0.24 × 0.26 mm was used for the X-ray measurements. Crystal data: $C_{42}H_{24}S_9 \cdot CHCl_3$, formula weight 936.6; monoclinic, space group $P2_1/c$; a = 19.603 (4) Å, b = 11.188 (3) Å, c = 19.689 (4) Å, β = 100.30 (2)°, V = 4249 (2) Å^3, Z = 4, d_{calcd} = 1.46 g/cm^3. Intensity measurements were made with $3° < 2\theta < 114°$ by using graphite-monochromated Cu Kα radiation at room temperature on a Nicolet $R3m$ diffractometer. A total of 5741 unique reflections were measured, and after background, Lorentz, and polarization corrections were applied, 3728 were considered to be observed [$|F_o| > 3\sigma(F_o)$]. Empirical absorption corrections were also applied, and the structure was solved by direct methods using the SHELXTL software. The occupancy of the chloroform was initially allowed to vary, and it was later fixed at the indicated full occupancy. The large temperature factors of the chloroform atoms as well as residual peaks in the difference Fourier maps suggested that the chloroform is disordered, but attempts to describe the disorder were not successful. In the final stages of refinement, all non-hydrogen atoms were refined with anisotropic temperature factors, and a riding model with idealized geometry was used for the hydrogens. Refinement with 496 parameters converged at R = 0.092 and R_w = 0.095 with goodness of fit = 1.66. Full details are provided in the Supplementary Material.

(8) Moran, J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826–5828.

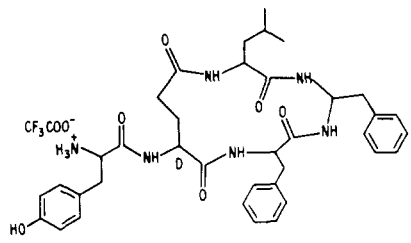
(9) Cram, D. J.; Karbach, S.; Kim, H.-E.; Knobler, C. B.; Maverick, E. F.; Ericson, J. L.; Helgeson, R. C. *J. Am. Chem. Soc.* **1988**, *110*, 2229–2237.



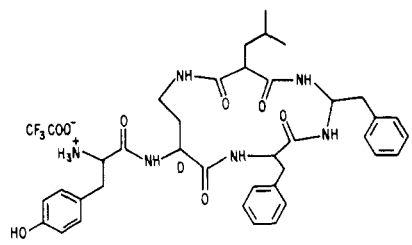
Tyr-c[D-A$_2$bu-Gly-(L and D)-Nal(1)-Leu]



Tyr-c[D-A$_2$bu-Phe-Phe-(L and D)-Leu]



Tyr-c[D-Glu-Phe-gPhe-(L and D)-retroLeu]



Tyr-c[D-A$_2$bu-Phe-gPhe-(S and R)-mLeu]

Figure 1. Structures of a series of cyclic molecules related to enkephalin and dermorphin. Within this series Tyr-c[D-A$_2$bu-Gly-D-Nal(1)-Leu], Tyr-c[D-A$_2$bu-Phe-gPhe-*R*-mLeu], and Tyr-c[D-Glu-Phe-gPhe-D-retro-Leu] are composed of a fraction of isomers containing cis amide structures.

Cis/Trans Isomers in Cyclic Peptides without N-Substituted Amides

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With the use of proton NMR, we observed configurational isomers containing cis amide bonds within a series of 14-membered cyclic peptides. These molecules are constrained but do not contain proline or any other N-substituted amino acid residues. To our knowledge this is the first report for such a cyclic peptide of this size that has an observable population of cis configurational isomers. Indeed the isomers of one of the compounds (Tyr-c[D-Glu-Phe-gPhe-D-retroLeu]) is composed of only 28% of the all trans structure, with two cis amide containing isomers accounting for 51% and 21%, respectively.

The cyclic molecules, shown in Figure 1, were synthesized as part of our program to study structure-activity relationship in the field of peptide opiates and are related to the cyclic analogue of enkephalin designed by Schiller and coworkers, Tyr-c[D-A$_2$bu-Gly-Phe-Leu].[1] The first analogue replaces the phenylalanine at position four with a β-(1-naphthyl)alanine, a modification of the steric character of this biologically important aromatic side chain. The other analogues shown in Figure 1 contain phenylalanine at position three in place of glycine and incorporate the retro-inverso modification.[2] This family of analogues will allow us to examine the relationship between the enkephalins and the opiate active dermorphin and morphiceptin which contain phenylalanine at the third position.[3,4]

During the NMR analysis of three of the analogues (Tyr-c[D-A$_2$bu-Gly-D-Nal(1)-Leu], Tyr-c[D-A$_2$bu-Phe-gPhe-*R*-mLeu], and Tyr-c[D-Glu-Phe-gPhe-D-retroLeu])[5,6] the proton spectra

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(1) Schiller, P.; DiMaio, J. *Nature (London)* **1982**, *297*, 74–76.
(2) Goodman, M.; Chorev, M. *Acc. Chem. Res.* **1979**, *12*, 1–7.
(3) Erspamer, V.; Melchiorri, P. In *Growth Hormone and Other Biologically Active Peptides*; Pecile, A., Müller, E. E., Eds.; Excerpta Medica: Amsterdam, 1980, pp 185–200.
(4) Chang, K.-J.; Killian, A.; Hazum, E.; Cautrecasas, P.; Chang, J.-K. *Science* **1981**, *212*, 75–77.

0002-7863/89/1511-6847$01.50/0