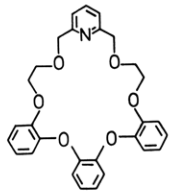
Chameleon Behavior of a Crown Host at Molecular Complexation

Summary: The 21-membered bi-concave macrocycle 1 is demonstrated to be a side-specific receptor for MeCN and $MeNO_2$ in the solid state.

Sir: Face differentiation and substrate recognition are central points of many biochemical processes.[1] Crown complexes are considered as very simple mimics of molecular recognition[2] both in solution[3] and in the crystalline state.[4] However, typical crown ligands, e.g., 18-crown-6,[5] are equal sided. For that reason, they cannot act as face-differing receptors but form complexes with identical substrate molecules bound to both ring faces.[4] On the other hand, more sophisticated ligands[4] which could have the opportunity to complex at different faces different molecules use only a single side for binding.[6]

We have recently reported on the selective inclusion complexation of $MeNO_2$ by a 21-membered tribenzopyridino crown 1 and communicated the crystal structure of the same complex.[7] Even then it was noticed that MeCN is also a suitable guest to form a crystalline complex with 1, but it is shown to be weaker (decomposes slowly on storage in air). Moreover the host/guest ratios differ (1:1 for the $MeNO_2$ complex but 1:2 for the complex with MeCN). Owing to these facts, a very different host-guest arrangement is suspected for 1·2MeCN. We have now been able to solve the crystal structure of the latter complex[8] (Figure 1) displaying highly unique behavior of 1 in respect to face differentiation.



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In the first instance, the net conformational geometry of 1 is the same in both complexes,[9] providing the host molecule with two concave faces (cf. A and B in Figure 1). One (A) has the rough appearance of an ice-cream cone and offers a relatively deep and narrow cavity, the other

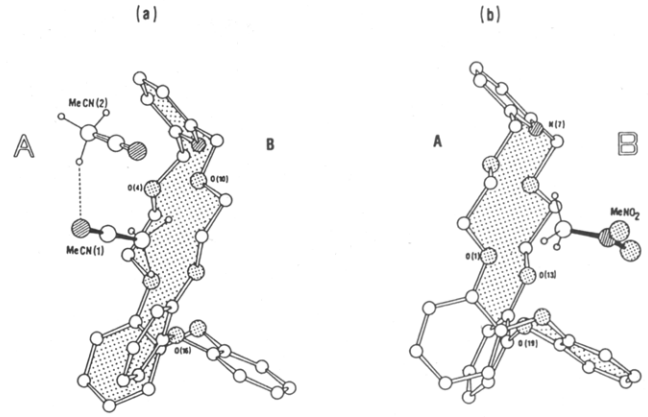

Figure 1. Molecular structures of (a) 1·MeCN (1:2) and (b) 1·$MeNO_2$ (1:1). A and B indicate the two faces of the host (cf. shaded surface). Heteroatoms involved in H bonds are specified by numbering for each complex.

(B) is similar to a bookrest with a relatively wide and low shielded hollow. For steric reasons A should be the face to bind spatially nondemanding guests, while B is prepared to accommodate a somewhat more voluminous species. Indeed, the MeCN and $MeNO_2$ guests which are rod-shaped and Y-shaped molecules, respectively, are correspondingly distributed among A and B in the present complexes (see Figure 1a,b).

Concerning the disposable binding sites, the two faces are also different. Face A provides three oxygens [O(4), O(10), and O(16)] being trigonally arranged and easily accessible for H bonds to the guest methyl (MeCN).[10] Naturally, face B is supplied with the remaining four donor sites of the host including the pyridino N, O(1), O(13), and O(19). All are involved in H bonding to the guest methyl ($MeNO_2$). Thus, face differentiation of 1 is also a result of acid–base relationship and electrostatic attraction. $MeNO_2$, which is more acidic than MeCN [$pK_a(MeNO_2) = 10$, $pK_a(MeCN) = 25$],[11] interacts more strongly with the highly basic pyridino nitrogen and therefore turns to face B, whereas the less acidic but more polar MeCN [d.c. (MeCN) = 37.5, d.c.($MeNO_2$) = 35.9][11] turns to face A, containing the oxygens with highest charge density [O(4) and O(10)]. In other words, MeCN finds a more complimental binding site at face A and $MeNO_2$ at face B, or 1 shows chameleon behavior toward MeCN and $MeNO_2$.

There is another interesting question associated with the whereabout of the second MeCN molecule of the 1:2 1·MeCN complex. According to Figure 1a it is involved in a second-sphere relationship with a close contact between the N-terminus of MeCN(1) and a methyl-H of MeCN(2) [N(13S)···C(21S) 3.412 Å, N(13S)···H(23S) 2.368 Å]. This mode of interaction possibly helps at H bonding of MeCN(1).[12] The crystal packing (supplementary material) shows the MeCN(2) molecules located in intermolecular channels of approximate dimension 7 × 8.5 Å.[13] By way of contrast, the directly bound MeCN(1) is taken up in the intramolecular cavity of 1.[14]

(1) (a) Stryer, L. *Biochemie*, 2nd ed.; Vieweg: Wiesbaden, 1983. (b) Chapeville, F.; Haenni, A.-L. *Chemical Recognition in Biology*; Springer Verlag: Berlin, 1980.

(2) (a) Cram, D. J. "Applications of Biochemical Systems in Organic Chemistry"; Jones, J. B., Sih, C. J., Perlman, D., Eds.; In *Techniques of Chemistry*; Weissberger, A., Ed.; Wiley: New York, 1976; Vol 10, Part II, pp 815–873. (b) Hayward, R. C. *Chem. Soc. Rev.* **1983**, *12*, 285–308.

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(4) (a) Weber, E. In *Synthesis of Macrocycles: The Design of Selective Complexing Agents*; Izatt, R. M., Christensen, J. J., Eds.; Wiley: New York, 1987; pp 337–419. (b) Vögtle, F.; Müller, W. M.; Watson, W. H. *Top. Curr. Chem.* **1984**, *125*, 131–164.

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(6) In other cases, hosts coordinating at a single side are intended. See: Meade, T. J.; Kwik, W.-L.; Herron, N.; Alcock, N. W.; Busch, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 1954–1962.

(7) Weber, E.; Franken, S.; Puff, H.; Ahrendt, J. *J. Chem. Soc., Chem. Commun.* **1986**, 467–469.

(8) 1·MeCN (1:2) crystallizes in the triclinic space group $P\bar{1}$ (No. 2). Cell dimensions: $a = 7.998$ (4) Å, $b = 9.749$ (3) Å, $c = 19.444$ (7) Å; $\alpha = 96.23$ (3)°, $\beta = 99.01$ (3)°, $\gamma = 96.47$ (3)°; $Z = 2$, $T = 193$ K, $D_{calcd} = 1.28$ g cm^{-3}, $R = 0.064$, 389 parameters refined with 4026 reflections with $\sigma(I) < 0.67(I)$.

(9) Some minor differences in respect to the torsion angles are around O(16) and O(19).

(10) Distances are: C(11S)···O(4) = 3.462 Å, C(11S)–H(12S)···O(4) = 143.4°; C(11S)···O(10) = 3.315 Å, C(11S)–H(11S)···O(10) = 143.4°; C(11S)···O(16) = 3.226 Å, C(11S)–H(13S)···O(16) = 152.9°.

(11) Weast, R. C. *Handbook of Chemistry and Physics*, 54th ed.; CRC: Cleveland, 1974.

(12) For a somewhat similar situation, see: Weber, G.; Jones, P. G. *Acta Crystallogr. Sect. C: Cryst. Struct. Commun.* **1983**, *C39*, 1577–1581.

(13) Slow evaporation of the channel-enclosed MeCN seems to be responsible for the low stability of the complex.

(14) From that point of view inclusion of MeCN(2) may be regarded as a channel clathrate with the directly bound host–guest unit forming the host matrix.

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Hence, the structures presented here are unique, at least in two points. They are the first examples on the organic ligand sector where face differentiation of a host toward an uncharged molecular guest is definitively shown, and also first- and second-sphere coordination,[15] or cavitate[16] plus clathrate binding[17] of the same guest species within the same crystal, to our knowledge, has not been documented before. Moreover, it should be mentioned that MeCN, just as $MeNO_2$, causes problems with respect to the complexation of 18-crown-6.[4]

For other face differentiations it would be desirable to have more extensive cavities either at face A or B, or at both sides of 1-type hosts. In this respect, we are going to substitute the phenylenes of **1** gradually for naphthylenes, which are more shielding groups.

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Supplementary Material Available: Tables of positional and thermal parameters (Tables I and II), bond distances and bond angles involving non-hydrogen atoms (Tables III and IV), endocyclic torsion angles for the host macrocycle (Table V), and figures with different stereoscopic representations of the host–guest unit (Figures 2 and 3) and of the crystal packing (Figure 4) (10 pages). Ordering information is given on any current masthead page. A list of observed and calculated structure factors is available directly from the author.

(15) Cf.: Colquhoun, H. M.; Stoddart, F. J.; Williams, D. J. *Angew. Chem.* **1986**, *98*, 483–503; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 487–507.
(16) Cram, D. J. *Science (Washington, D.C.)* **1983**, *219*, 1177–1183.
(17) Weber, E. "Molecular Inclusion and Molecular Recognition—Clathrates I" *Topics in Current Chemistry*; Springer Verlag: Berlin, 1987; Vol. 140.
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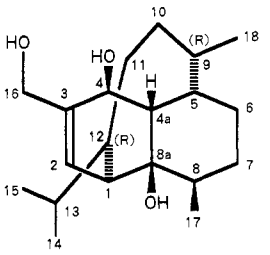
The Structure of Vinigrol, a Novel Diterpenoid with Antihypertensive and Platelet Aggregation-Inhibitory Activities

Summary: The structure of vinigrol (**1**), a novel diterpenoid isolated from a fungus as an antihypertensive and platelet aggregation-inhibiting substance, has been determined by using chemical derivatizations, spectroscopic measurements, and an X-ray crystal analysis.

Sir: Vinigrol (**1**) is a novel diterpenoid recently isolated from *Virgaria nigra* as an antihypertensive and platelet aggregation-inhibiting substance.[1a] Herein we report the structure elucidation of this natural product on the basis of chemical and physical evidence and X-ray crystal analysis.

(1) (a) Ando, T.; Tsurumi, Y.; Ohata, N.; Uchida, I.; Yoshida, K.; Okuhara, M. *J. Antibiot.*, in press. (b) Ando, T.; Yoshida, K.; Okuhara, M. *J. Antibiot.*, in press.

Vinigrol (**1**) was isolated as colorless prisms: $C_{20}H_{34}O_3$ (FDMS, m/z 323 ($M^+ + H$). Anal. Calcd for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.20; H, 10.23; mp 108 °C; $[\alpha]_D$ −96.2° (c 1.05, $CHCl_3$). The ^{13}C NMR spectrum ($CDCl_3$) of **1**[2] revealed all the carbon signals which are assignable to a trisubstituted olefin (δ 128.5 (d),[3] 136.5 (s)) and three alcohols (primary, secondary, and tertiary) (δ 67.6 (t),[3] 72.7 (d),[3] 75.5 (s)), the remainder being 15 signals attributable to seven methines (δ 33.1 (d), 34.6 (d), 35.9 (d), 40.3 (d), 44.3 (d), 45.1 (d), 51.3 (d)), four methylenes (δ 27.3 (t), 28.6 (t), 28.9 (t), 29.7 (t)), and four methyls (δ 15.5 (q), 20.6 (q), 21.5 (q), 24.8 (q)).



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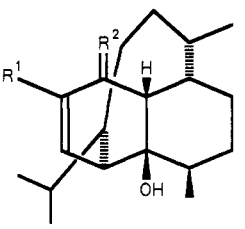

2 $R^1 = CH_2OCOCH_3$; $R^2 = \alpha\text{-}OCOCH_3$; β-H
3 $R^1 = CH_2OH$; $R^2 = O$
4 $R^1 = CHO$; $R^2 = \alpha\text{-}OH$; β-H
5 $R^1 = CHO$; $R^2 = O$
6 $R^1 = CH_2OSi(CH_3)_2C(CH_3)_3$; $R^2 = \alpha\text{-}OH$; β-H
7 $R^1 = CH_2OSi(CH_3)_2C(CH_3)_3$; $R^2 = \alpha\text{-}OCOC_6H_5$; β-H

Acetylation of **1** (Ac_2O/pyridine) gave diacetate **2** (EIMS, m/z 406 (M^+); δ_H 2.10 (s, 3 H), 2.04 (s, 3 H), 4.61 (AB q, J = 12 Hz, 2 H), 5.48 (s, 1 H)).[4] Jones' oxidation of **1** (CrO_3–H_2SO_4/H_2O–acetone) gave ketone **3** as a major product (EIMS, m/z 320 (M^+); δ_H 6.89 (d, J = 6.2 Hz, 1 H), 4.31 (s, 2 H); 54%), together with minor products **4** (EIMS, m/z 320 (M^+); δ_H 9.50 (s, 1 H), 7.01 (d, J = 5.9 Hz, 1 H), 4.63 (s, 1 H); 5%) and **5** (EIMS, m/z 318 (M^+); δ_H 10.16 (s, 1 H), 7.81 (d, J = 6.5 Hz, 1 H); 5%). Since these chemical and spectroscopic methods were found to be impractical for structural determination of this unusual diterpenoid, we decided to submit crystals of **1** or its derivatives to X-ray crystal analysis.

The crystals of **5** were found to be optimum, which formed in the orthorhombic space group $P2_12_12_1$ with a = 18.105 (1) Å, b = 10.355 (1) Å, and c = 9.296 (1) Å; V = 1739.5 (2) Å^3; Z = 4; D_x = 1.22 g cm^{-3}. The structure was determined by the direct method (MULTAN 74) and successive block-diagonal least-squares and Fourier syntheses. Parameters were refined by using anisotropic temperature factors to R = 0.050 for 1644 independent

(2) ^1H NMR ($CDCl_3$) of **1**: δ 5.81 (d, J = 5.6 Hz, 1 H), 4.25 (AB q, J = 12 Hz, 2 H), 4.20 (s, 1 H), 2.32 (d, J = 5.6 Hz, 1 H), 2.23 (d, J = 3.6 Hz, 1 H), 2.12 (m, 1 H), 1.96 (m, 1 H), 1.8–1.5 (m, 5 H), 1.4–1.0 (m, 6 H), 1.0–0.8 (m, 12 H).
(3) The signals at δ 128.5, 67.6, and 72.7 correspond to the proton signals at δ 5.81, 4.25, and 4.20 in the ^1H NMR spectrum of **1** (see ref 2).
(4) ^1H NMR ($CDCl_3$) of **2**: δ 6.14 (d, J = 6 Hz, 1 H), 5.48 (s, 1 H), 4.65 (d, J = 12 Hz, 1 H), 4.57 (d, J = 12 Hz, 1 H), 2.44 (d, J = 6 Hz, 1 H), 2.17 (m, 1 H), 2.10 (s, 3 H), 2.05 (d, J = 3.6 Hz, 1 H), 2.04 (s, 3 H), 2.0–1.85 (m, 3 H), 1.80 (m, 1 H), 1.65 (m, 1 H), 1.53–1.48 (m, 2 H), 1.40 (m, 1 H), 1.35 (m, 1 H), 1.3–1.0 (m, 4 H), 0.99 (d, J = 6.8 Hz, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H).

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