# A New Conformation Exhibiting Near-Threefold Symmetry for Uncomplexed Valinomycin in Crystals from Dimethyl Sulfoxide

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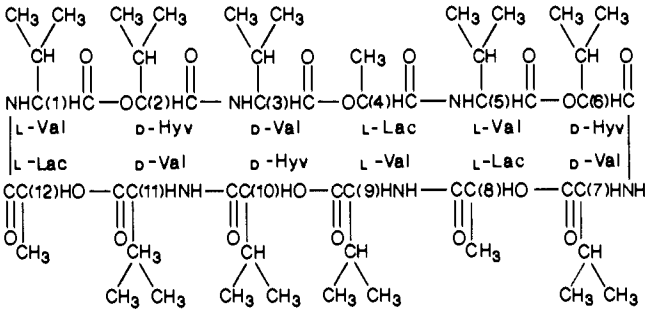
**Abstract:** Uncomplexed valinomycin, (L-Val-D-Hyv-D-Val-L-Lac)$_3$, grown from dimethyl sulfoxide solution, crystallizes in the orthorhombic space group $P2_12_12_1$. The peptide molecules assume a quasi-threefold symmetry with three type II $\beta$-bends (N···O = 3.05–3.24 Å) encompassing the three repeating L-Val-D-Hyv sequences. Three other possible $\beta$-bends encompassing D-Val, L-Lac residues, that occur in the $K^+$ complex of valinomycin, do not occur in this uncomplexed form since these N···O distances have been elongated to >6.0 Å. Three DMSO solvent molecules are hydrogen bonded to the three N atoms that do not participate in intrapeptide hydrogen bonding (N···O = 2.80–2.85 Å). The conformation found in this uncomplexed form has a polar cavity that could readily attract and encapsulate an ion such as $K^+$ by a simple folding motion. In three previous crystal forms, obtained from solvents less polar than DMSO, the uncomplexed valinomycin molecule has the shape of a bracelet that is flattened to eliminate any cavity. The cell dimensions are $a$ = 16.406 (6) Å, $b$ = 25.723 (6) Å, and $c$ = 18.712 (5) Å. For a molecular weight of 1345.7 for $C_{54}H_{90}N_6O_{18}\cdot 3(CH_3)_2SO$, $d_{calcd}$ = 1.132 g/cm$^3$. $R$ = 10.33% for 3281 reflections >3$\sigma(F)$. All three DMSO molecules are considerably disordered, except for the positions of the O atoms.

Valinomycin, a cyclic dodecadepsipeptide with the formula (and numbering sequence) shown in Chart I and an antibiotic produced by *Streptomyces fulvissimus*, has been the subject of extensive research since it was shown to have the ability to act as a mobile carrier to facilitate ion transport across cell membranes.[1,2] It forms complexes with $K^+$ or $Rb^+$ in preference over $Na^+$. Early NMR, IR, and ORD measurements of uncomplexed valinomycin and the $K^+$ complex in polar and nonpolar solvents[2-4] were interpreted in terms of three different conformations. The conformation for the $K^+$ complex, independent of polarity of solvent, was proposed to be a bracelet conformation with six NH···O hydrogen bonds and six $K^+$–O ligands. At the same time, a preliminary crystal structure analysis[5] of the complex made with $KAuCl_4$ indicated that the $K^+$ is octahedrally coordinated to carbonyl oxygen atoms and that six NH···O hydrogen bonds are formed, in agreement with the conformation proposed in solution. A later well-resolved crystal structure analysis[6] of the complex formed with $KI_3/KI_5$ confirmed these results and established the positions of all the atoms in detail, including the atoms in the side chains. The $K^+$–valinomycin complex has approximate $S_6$ symmetry (Figure 1).

The conformation of uncomplexed valinomycin in solution was shown to be solvent dependent. In nonpolar solvents, the predominant form has six intramolecular hydrogen bonds.[3,4] This observation had been interpreted as a bracelet conformation with approximate $S_6$ symmetry containing six $\beta$-bends and a pore in the middle. Crystal structures of several polymorphs, triclinic grown from *n*-octane,[7] acetone,[7] and ethanol–water[8] and monoclinic grown from *n*-octane,[8,9] all show the same conformation

Chart I




(Figure 2). This conformation obtained from nonpolar and medium polar solvents can be considered as a flattened bracelet with no central pore or cavity. It has only four 4 → 1 type hydrogen bonds ($\beta$-bends) and two 5 → 1 type. The conformation predicted from solution observations in nonpolar solvents has not yet been observed in the solid state.

In polar solvents, particularly $(CH_3)_2SO$, the spectroscopic data indicated a conformation for valinomycin with only three hydrogen bonds, rather than six.[3,4] A dish-shaped structure[4] and a propeller conformation[3,10] with threefold symmetry were proposed. In the present crystal structure determination, orthorhombic crystals were grown from $(CH_3)_2SO$. The individual molecules have a dish-shaped conformation with approximate threefold symmetry, three intramolecular hydrogen bonds, and three $(CH_3)_2SO$ solvent molecules with their O atoms participating in hydrogen bonds with the NH moieties of the three L-Val residues (Figures 3 and 4). In this case, with an extremely polar solvent, the proposed solution structure and the crystal structure are similar.

## Experimental Section

Crystalline valinomycin purchased from Sigma Chemical Co. was dissolved in $(CH_3)_2SO$, and colorless, tabular crystals were grown by slow evaporation. A crystal of size 1.0 × 0.8 × 0.1 mm was sealed in a thin-walled glass capillary with some mother liquor and used for X-ray data collection on a four-circle automated diffractometer with Cu radiation and a Ni filter ($\lambda$ = 1.541 78 Å). The scan width was 2.0° + $2\theta(\alpha_2)° - 2\theta(\alpha_1)°$, the scan speed was 2°/min, and the background was measured for 10 s at either end of the scan. Three reflections (6, 0, 0), (0, 10, 0), and (0, 0, 10) monitored every 60 measurements, remained

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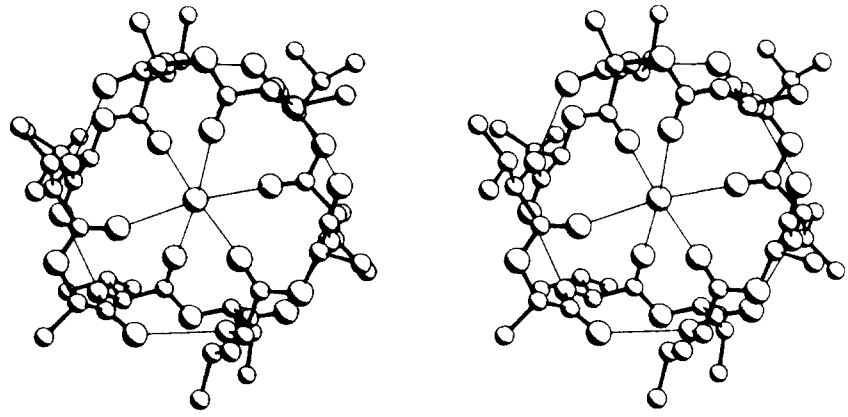

**Figure 1.** The $K^+$–valinomycin complex drawn by a computer with the experimentally determined coordinates.[6] The backbone has a bracelet conformation with six NH···O=C hydrogen bonds.

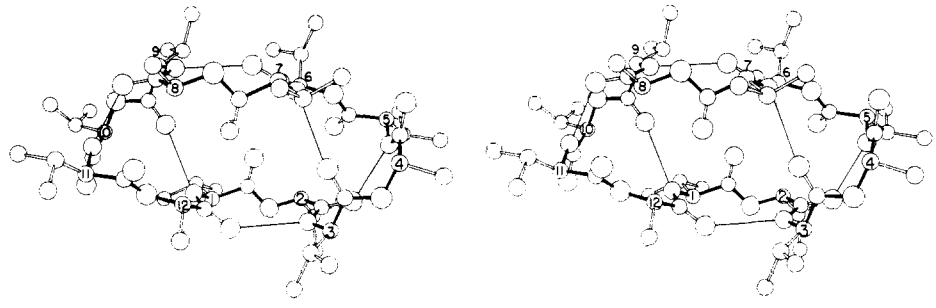

**Figure 2.** Conformation of uncomplexed valinomycin in crystals grown from nonpolar or medium-polar solvents[7-9] with four 4 → 1 hydrogen bonds and two 5 → 1 hydrogen bonds.

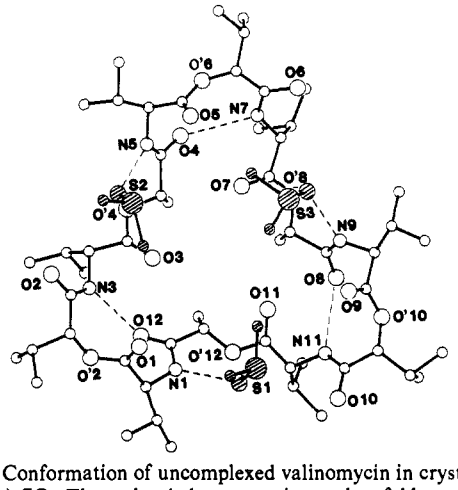


**Figure 3.** Conformation of uncomplexed valinomycin in crystals grown from $(CH_3)_2SO$. The molecule has approximate threefold symmetry and three 4 → 1 hydrogen bonds. The O atoms of three $(CH_3)_2SO$ solvent molecules (shaded) make NH···O=S hydrogen bonds with N(1), N(5), and N(9).

constant within 3%. A total of 3815 reflections ($3281 > 3\sigma(F)$) were measured to $2\theta_{max} = 100°$. At scattering angles $2\theta > 100°$, very few diffracting planes had measurable intensity. The maximum values for $h$, $k$, and $l$ indices are 15, 25, and 16, respectively. Lorentz and polarization corrections were applied to the data. The cell parameters are $a$ = 16.406 (5) Å, $b$ = 25.723 (6) Å, and $c$ = 18.712 (5) Å for space group $P2_12_12_1$. The calculated density for $Z = 4$, $V = 7896.7$ Å$^3$, mol wt = 1111.4 + 234.3 for $C_{54}H_{90}N_6O_{18}\cdot 3(CH_3)_2SO$ is 1.132 g/cm$^3$.

The structure was solved by direct phase determination by using the random-tangent formula procedure in the SHELXTL computer program.[11] The correct solution was found near the end of 2000 trials. In the initial $E$ map, the positions of 74 atoms were found. The remainder of the non-hydrogen atoms were located in $E$ maps by partial structure development[12] and difference maps. Full-matrix least-squares refinement was used for the isotropic refinement of the non-hydrogen atoms. For all the anisotropic cycles, a block diagonal least-squares refinement was used with the first batch consisting of the three DMSO molecules and residues 1–5 (431 parameters) and the second batch consisting of residues 6–12 (435 parameters). All hydrogen atoms were put into idealized positions and were allowed to ride on covalently bonded atoms. The thermal factors for the molecule are ~20–30% higher for backbone atoms and ~40% higher for side-chain atoms than in similar hydrophobic peptides (e.g., the flattened bracelet form for valinomycin[7]). High thermal factors, which are really a measure of positional disorder in the crystal, are consistent with the rapid attenuation of scattering intensity at $2\theta > 100°$. The $CH_3$ groups of the DMSO solvent molecules have even higher values for the thermal factors, indicating a significant rotation about the SO bonds. Such positional disorders are difficult to approximate and contribute to a high agreement factor, as well as the large size of the crystal. For 3281 reflections measured $>3\sigma(F)$, $R = 10.3\%$ and $R_w = 9.3\%$ where $w = 1/[\sigma^2(|F|) + 0.000\,25\,(F)^2]$.

Fractional coordinates for the non-hydrogen atoms are listed in Table I. Torsional angles are shown in Table II. Bonds lengths (esd's ~0.02 Å for backbone atoms and ~0.03 Å for side-chain atoms) and bond angles (esd's ~1.0–1.5°) are very similar to those found for the other conformational form of uncomplexed valinomycin.[7]

## Results

**Conformation of Molecule.** The valinomycin crystallized in the orthorhombic space group $P2_12_12_1$, and, therefore, the molecule must lie in a general position. Nevertheless, the molecule assumes a near threefold rotation symmetry for the backbone ring, the side chains, and even the S=O groups of the three solvent molecules that make hydrogen bonds with the three NH groups of the L-Val residues, all of which is quite compatible with the threefold repetition in the sequence. The residues alternate between amino acid and hydroxy acid groupings. Each residue is in the trans conformation and is essentially planar as indicated by the $\omega_i$ values, which are near 180° (Table II). Three type II $\beta$-bends are formed encompassing L-Val, D-Hyv. Their hydrogen bonds lengths N(3)···O(12), N(7)···O(4), and N(11)···O(8) are 3.05, 3.22, and 3.24 Å, respectively. These values are significantly larger than those observed in uncomplexed valinomycin from nonpolar sol-

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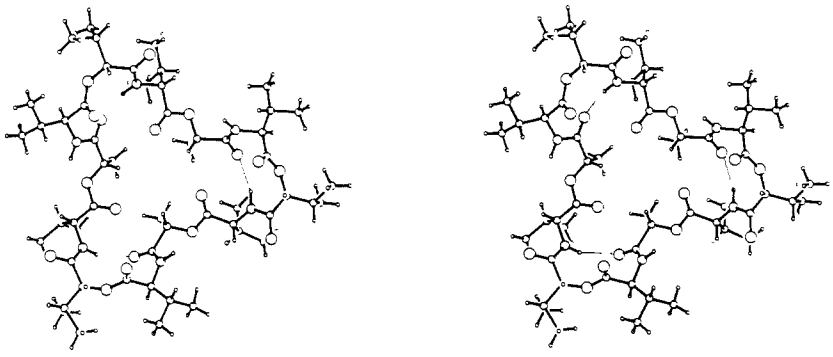

**Figure 4.** Stereodiagram of uncomplexed valinomycin in crystals grown from $(CH_3)_2SO$. Hydrogen atoms are included, but the solvent molecules are omitted. The view is rotated by 90° to that shown in Figure 3.

**Table I.** Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$)

| | $x$ | $y$ | $z$ | $U$(eq)[a] | | $x$ | $y$ | $z$ | $U$(eq)[a] |
|---|---|---|---|---|---|---|---|---|---|
| S(1)[b] | 3436 (5) | 9510 (3) | 11078 (6) | 222 (4) | O′(6) | 5080 (5) | 9575 (3) | 5241 (4) | 80 (3) |
| O(1S1) | 4307 (7) | 9584 (5) | 11356 (7) | 159 (6) | $C^{\alpha}(6)$ | 4363 (9) | 9873 (6) | 5085 (9) | 86 (7) |
| C(1S1) | 3134 (11) | 8907 (8) | 11203 (14) | 262 (17) | C′(6) | 4294 (12) | 10324 (7) | 5520 (9) | 101 (8) |
| C(2S1) | 3399 (20) | 9563 (14) | 10239 (13) | 555 (43) | O(6) | 3727 (7) | 10671 (4) | 5498 (6) | 120 (5) |
| S(2) | 4752 (5) | 8060 (3) | 7638 (5) | 215 (4) | $C^{\beta}(6)$ | 4325 (13) | 10034 (6) | 4312 (8) | 119 (9) |
| O(1S2) | 5604 (14) | 8193 (7) | 7436 (8) | 272 (11) | $C^{\gamma 2}(6)$ | 4217 (12) | 9560 (7) | 3857 (10) | 160 (10) |
| C(1S2) | 4595 (17) | 8134 (16) | 8505 (14) | 462 (37) | $C^{\gamma 1}(6)$ | 4969 (15) | 10330 (7) | 4028 (12) | 202 (13) |
| C(2S2) | 4717 (32) | 7525 (11) | 7557 (18) | 873 (75) | N(7) | 4920 (8) | 10456 (4) | 5996 (6) | 86 (5) |
| S(3) | 3013 (7) | 10076 (4) | 7735 (6) | 292 (7) | $C^{\alpha}(7)$ | 4990 (9) | 10884 (5) | 6488 (7) | 74 (6) |
| O(1S3) | 3354 (8) | 10571 (5) | 7606 (7) | 178 (7) | C′(7) | 5112 (10) | 10689 (7) | 7251 (8) | 94 (7) |
| C(1S3) | 3448 (16) | 9633 (9) | 7168 (13) | 267 (17) | O(7) | 5316 (7) | 10283 (4) | 7416 (5) | 117 (5) |
| C(2S3) | 3226 (31) | 9792 (9) | 8310 (14) | 479 (43) | $C^{\beta}(7)$ | 5526 (11) | 11316 (6) | 6264 (9) | 103 (8) |
| N(1) | 5862 (7) | 9158 (4) | 11020 (5) | 100 (5) | $C^{\gamma 1}(7)$ | 6435 (11) | 11142 (6) | 6269 (9) | 127 (9) |
| $C^{\alpha}(1)$ | 5946 (10) | 8650 (6) | 11334 (8) | 104 (7) | $C^{\gamma 2}(7)$ | 5328 (12) | 11528 (6) | 5527 (7) | 122 (8) |
| C′(1) | 5767 (14) | 8220 (7) | 10787 (8) | 92 (8) | O′(8) | 5074 (6) | 11115 (3) | 7665 (5) | 88 (4) |
| O(1) | 5110 (8) | 8195 (5) | 10518 (7) | 141 (6) | $C^{\alpha}(8)$ | 5213 (11) | 11041 (7) | 8398 (9) | 96 (7) |
| $C^{\beta}(1)$ | 5486 (15) | 8600 (9) | 12015 (9) | 156 (11) | C′(8) | 4588 (13) | 11396 (8) | 8840 (11) | 108 (9) |
| $C^{\gamma 1}(1)$ | 5497 (17) | 8054 (8) | 12291 (10) | 208 (13) | O(8) | 4787 (8) | 11633 (5) | 9358 (6) | 143 (6) |
| $C^{\gamma 2}(2)$ | 5715 (21) | 8927 (10) | 12564 (13) | 277 (22) | $C^{\beta}(8)$ | 6065 (12) | 11239 (9) | 8543 (10) | 157 (11) |
| O′(2) | 6391 (7) | 7887 (4) | 10686 (5) | 98 (4) | N(9) | 3830 (10) | 11309 (4) | 8624 (6) | 99 (6) |
| $C^{\alpha}(2)$ | 6265 (10) | 7492 (6) | 10170 (7) | 93 (7) | $C^{\alpha}(9)$ | 3132 (9) | 11607 (5) | 8904 (9) | 87 (6) |
| C′(2) | 6570 (12) | 7678 (10) | 9396 (8) | 113 (9) | C′(9) | 2920 (9) | 11323 (7) | 9614 (8) | 92 (7) |
| O(2) | 6486 (8) | 7309 (4) | 8966 (6) | 129 (5) | O(9) | 2640 (8) | 10887 (4) | 9639 (5) | 127 (5) |
| $C^{\beta}(2)$ | 6702 (16) | 6994 (6) | 10458 (9) | 137 (10) | $C^{\beta}(9)$ | 2491 (12) | 11651 (7) | 8389 (8) | 107 (8) |
| $C^{\gamma 1}(2)$ | 7593 (13) | 7099 (9) | 10602 (13) | 169 (11) | $C^{\gamma 2}(9)$ | 2723 (13) | 11934 (7) | 7714 (8) | 171 (11) |
| $C^{\gamma 2}(2)$ | 6179 (16) | 6810 (7) | 11118 (10) | 194 (13) | $C^{\gamma 1}(9)$ | 1806 (12) | 11924 (7) | 8715 (12) | 212 (14) |
| N(3) | 6827 (8) | 8130 (5) | 9294 (7) | 87 (6) | O′(10) | 3017 (5) | 11626 (3) | 10193 (5) | 82 (4) |
| $C^{\alpha}(3)$ | 7062 (9) | 8260 (6) | 8561 (7) | 80 (7) | $C^{\alpha}(10)$ | 2792 (10) | 11424 (5) | 10868 (8) | 87 (6) |
| C′(3) | 6677 (10) | 8785 (6) | 8399 (9) | 85 (7) | C′(10) | 3477 (12) | 11112 (5) | 11183 (8) | 80 (7) |
| O(3) | 6189 (7) | 8999 (4) | 8759 (6) | 108 (5) | O(10) | 3354 (8) | 10910 (4) | 11778 (5) | 145 (6) |
| $C^{\beta}(3)$ | 8014 (10) | 8284 (7) | 8552 (8) | 110 (8) | $C^{\beta}(10)$ | 2466 (16) | 11830 (7) | 11396 (17) | 211 (16) |
| $C^{\gamma 2}(3)$ | 8442 (10) | 7807 (6) | 8709 (10) | 120 (8) | $C^{\gamma 1}(10)$ | 2994 (14) | 12207 (8) | 11442 (9) | 183 (13) |
| $C^{\gamma 1}(3)$ | 8347 (9) | 8739 (5) | 8975 (8) | 123 (7) | $C^{\gamma 2}(10)$ | 1841 (13) | 12145 (9) | 10966 (11) | 189 (13) |
| O′(4) | 6918 (6) | 8916 (3) | 7758 (5) | 88 (4) | N(11) | 4233 (10) | 11116 (5) | 10862 (6) | 91 (5) |
| $C^{\alpha}(4)$ | 6655 (10) | 9429 (6) | 7524 (9) | 98 (7) | $C^{\alpha}(11)$ | 4892 (10) | 10773 (5) | 11113 (8) | 85 (6) |
| C′(4) | 6454 (12) | 9374 (7) | 6695 (9) | 107 (8) | C′(11) | 5182 (11) | 10485 (7) | 10540 (10) | 96 (8) |
| O(4) | 6526 (6) | 9778 (4) | 6336 (5) | 111 (4) | O(11) | 4967 (7) | 10463 (4) | 9910 (5) | 113 (5) |
| $C^{\beta}(4)$ | 7270 (12) | 9821 (7) | 7659 (9) | 134 (9) | $C^{\beta}(11)$ | 5547 (15) | 11101 (9) | 11484 (11) | 141 (11) |
| N(5) | 6089 (9) | 8974 (5) | 6473 (7) | 103 (6) | $C^{\gamma 1}(11)$ | 5239 (14) | 11433 (8) | 12109 (10) | 223 (13) |
| $C^{\alpha}(5)$ | 5816 (11) | 8918 (5) | 5724 (6) | 87 (7) | $C^{\gamma 2}(11)$ | 5948 (15) | 11459 (8) | 11036 (14) | 222 (19) |
| C′(5) | 5007 (14) | 9161 (6) | 5647 (9) | 107 (8) | O′(12) | 5801 (8) | 10165 (4) | 10728 (5) | 99 (5) |
| O(5) | 4422 (9) | 9037 (5) | 5939 (7) | 160 (7) | $C^{\alpha}(12)$ | 6199 (11) | 9850 (6) | 10230 (9) | 98 (7) |
| $C^{\beta}(5)$ | 5796 (13) | 8373 (6) | 5545 (8) | 116 (8) | O(12) | 6947 (7) | 9056 (4) | 10309 (5) | 107 (5) |
| $C^{\gamma 1}(5)$ | 5473 (14) | 8282 (7) | 4782 (8) | 166 (10) | C′(12) | 6351 (9) | 9314 (6) | 10496 (7) | 78 (6) |
| $C^{\gamma 2}(5)$ | 6586 (19) | 8115 (8) | 5589 (13) | 205 (15) | $C^{\beta}(12)$ | 6962 (11) | 10105 (6) | 9980 (8) | 115 (8) |

[a] $U(\text{eq}) = 1/3\sum_i\sum_j U_{ij}a_i^*a_j^*a_ia_j$. [b] The first 12 entries are the atoms in the three cocrystallized $(CH_3)_2SO$ molecules.

**Table II.** Conformational Angles in Valinomycin–3DMSO

| i | L-Val 1 | D-Hyv 2 | D-Val 3 | L-Lac 4 | L-Val 5 | D-Hyv 6 | D-Val 7 | L-Lac 8 | L-Val 9 | D-Hyv 10 | D-Val 11 | L-Lac 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $\phi_i(N_i\text{–}C^{\alpha}_i)$ | −64 | 91 | 133 | −142 | −86 | 100 | 122 | −140 | −83 | 85 | 126 | −137 |
| $\psi_i(C^{\alpha}_i\text{–}C'_i)$ | 121 | −4 | 177 | 41 | 112 | 5 | −173 | 53 | 117 | 9 | 179 | 23 |
| $\omega_i(C'_i\text{–}N_{i+1})$ | −178 | −178 | −176 | 174 | 179 | 180 | −177 | −176 | 176 | −173 | −178 | −179 |
| $\chi^1_i(C^{\alpha}_i\text{–}C^{\beta}_i)$[a] | 173 | −56 | −68 | | 177 | −58 | −69 | | 177 | −53 | −64 | |
| | −61 | 70 | 63 | | −62 | 67 | 53 | | −62 | 48 | 57 | |

[a] The two entries per Val and Hyv residues give the torsion angles about $N_iC^{\alpha}_iC^{\beta}_iC^{\gamma 1}$ and $N_iC^{\alpha}_iC^{\beta}_iC^{\gamma 2}$.

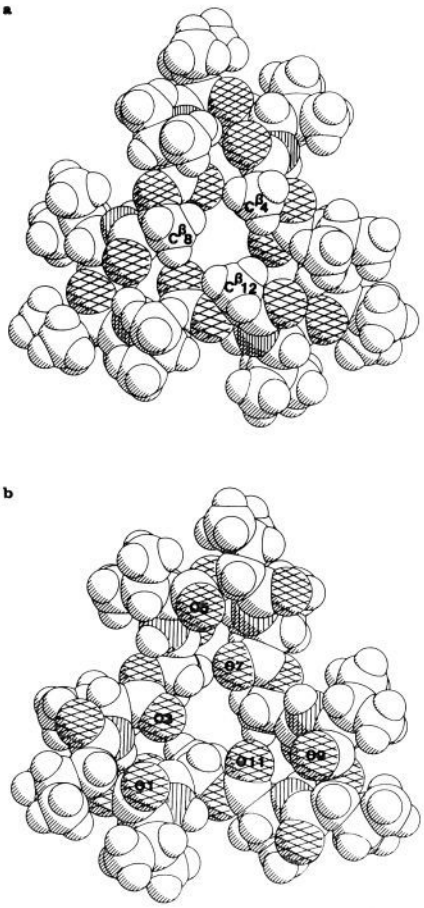


**Figure 5.** Space-filling drawings of valinomycin in crystals from $(CH_3)_2SO$. (a) Botton view. (b) Top view. In both views, the N atoms are hatched and the O atoms are cross-hatched.

vents,[7] 2.90–3.07 Å, and in the $K^+$ complex,[6] ~2.93 Å. The other three N atoms, N(1), N(5), and N(9), are separated from O(10), O(2), and O(6), the atoms that participate in hydrogen bonding in the bracelet conformation, by 6.26, 6.37, and 6.08 Å. Instead these NH moieties form strong hydrogen bonds with the three DMSO molecules with N···O distances of 2.85, 2.81, and 2.80 Å, respectively.

The conformation of the molecule is in the form of a shallow dish with all the nonpolar side chains lying on the exterior of the dish (Figure 5a). The outer diameter is ~15.6 Å and the height is ~5.0 Å. The dish could fit on a sphere with a radius of ~8.6 Å. The bottom of the dish rests on the three $C^{\beta}H_3$ side chains from L-Lac[4], L-Lac[8], and L-Lac[12], with $C^{\beta}(4)\cdots C^{\beta}(8)$ = 4.47 Å, $C^{\beta}(8)\cdots C^{\beta}(12)$ = 4.23 Å, and $C^{\beta}(12)\cdots C^{\beta}(4)$ = 4.44 Å. These three $CH_3$ groups effectively close the hydrophobic exterior surface at the bottom of the dish (Figure 5a). The inner surface of the dish is covered with protruding carbonyl oxygens (Figure 5b). Three carbonyl oxygens from the D-Val residues, O(3), O(7), and O(11), form a triangle near the interior bottom of the dish with O(3)···O(7) = 4.39 Å, O(7)···O(11) = 4.73 Å, and O(11)···O(3) = 4.78 Å. The three carbonyl oxygens from the L-Val residues, O(1), O(5), and O(9), are near the rim with O(1)···O(5) = 8.91 Å, O(5)···O(9) = 8.90 Å, and O(9)···O(1) = 8.19 Å.

**Complexation.** The conformation of the valinomycin found in the crystal from DMSO suggests a simple complexation mechanism with $K^+$. The polar inner surface of the peptide molecule presumably attracts a $K^+$ ion. The three carbonyl oxygens near the interior bottom of the dish, O(3), O(7), and O(11), are very nearly in position to form three of the six octahedral ligands to the ion. In the $K^+$ complex,[6] the O···O distances in the ligands are near 3.9 Å, whereas in the uncomplexed peptide they are near 4.6 Å, thus necessitating some minor migration of the carbonyls toward the center of the dish. The remaining three ligands to the

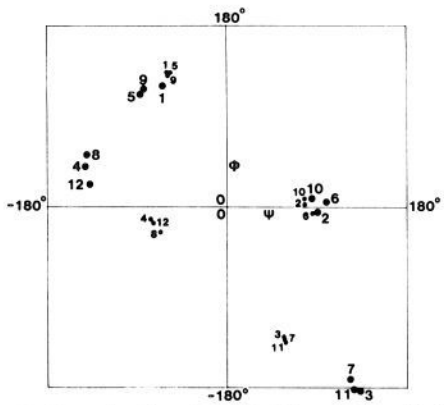


**Figure 6.** Conformational angles $\phi$(N–C$^{\alpha}$) and $\psi$(C$^{\alpha}$–C′) for uncomplexed valinomycin from DMSO (shown as large dots) and for the $K^+$ complex (shown as small dots).

$K^+$ would be formed by folding the three lobes of the backbone over the $K^+$ ion. This simple motion not only would provide the $K^+$ with three additional ligands to O(1), O(5), and O(9), but would bring O(10), O(2), and O(6) near N(1), N(5), and N(9) to facilitate the formation of the three remaining NH···O hydrogen bonds that are present in the bracelet conformation. Of course, during the complexation, the $K^+$ ion would have to be stripped of its hydration sphere.

The conformational angles for the $K^+$ complex and the present conformation of the uncomplexed valinomycin are plotted in Figure 6. Residues 1,5,9 and 2,6,10, which are part of the $\beta$-bends in the uncomplexed valinomycin, lie very near to the $\phi$, $\psi$ values for the same residues in complexed valinomycin. Residues 3,7,11 and 4,8,12 must each undergo rotations of ~60° in $\phi$ and ~45° in $\psi$ in the complexation process.

The open, trigonal conformation of the uncomplexed molecule has a polar cavity that appears to be ready to accept and encapsulate an ion such as $K^+$, whereas the flattened bracelet conformation without a pore or cavity, found in crystals grown from nonpolar or medium-polar solvents[7-9] does not seen to be conducive for attracting ions.

**Other Conformations.** Valinomycin complexed with very large or very small metal ions and uncomplexed analogues of valinomycin have exhibited other conformational forms. For example, uncomplexed isoleucinomycin, (L-Ile-D-Hyv-D-Ile-L-Lac)$_3$, grown from heptane, has an asymmetric structure with five 4 → 1 type hydrogen bonds and one 5 → 1 type.[13] Half of the molecular backbone resembles a bracelet, and the remainder resembles the flattened form of uncomplexed valinomycin grown from octane or ethanol.[7-9] Uncomplexed *meso*-valinomycin (L-Val-D-Hyv-D-Val-L-Hyv)$_3$, grown from dimethylformamide–petroleum ether, does have a bracelet conformation with a pore.[14] The $\phi$, $\psi$ angles differ by 10–30° from the bracelet in $K^+$–valinomycin.

The $Rb^+$ complex of prolinomycin, (L-Val-D-Pro-D-Val-L-Pro)$_3$, was found to have a conformation similar to that of $K^+$–valinomycin.[15] In the $Na^+$ complex of valinomycin, the $Na^+$ ion, considerably smaller than a $K^+$ ion, was found external to the bracelet formed by the backbone,[16] and a water molecule occupied the position inside the bracelet normally occupied by a $K^+$ ion. For complexation with a much larger ion such as $Ba^{2+}$, the backbone of valinomycin extends into a large ellipse with two $Ba^{2+}$ ions located at the foci.[17] There are no intramolecular hydrogen bonds in this complex. The $Ba^{2+}$ ions each form three ligands

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with peptide carbonyls and the remaining ligands to cations and cocrystallized water molecules.

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**Supplementary Material Available:** Anisotropic thermal parameters for non-hydrogen atoms, atomic coordinates of hydrogen atoms, bond lengths, and bond angles (5 pages); observed and calculated structure factors (12 pages). Ordering information is given on any current masthead page.

# Diels–Alder Reaction of Dienes Having Stereogenic Allylic Substituents: Control of Diastereoface Selectivity by the Dienophile

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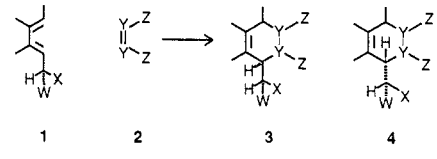
**Abstract:** The face selectivity of the Diels–Alder reaction of dienes having a stereogenic allylic carbon, as illustrated by structure **5**, has been examined. Whereas *N*-phenylmaleimide and maleic anhydride afforded adducts resulting from like topicity, tetracyanoethylene and 4-phenyl-1,2,4-triazoline-3,5-dione yielded products from unlike approach. The stereochemistries of the products have been established by NOE studies and in one case by an X-ray structure determination. Our results and those of other groups demonstrate that the dienophiles have a significant effect on the face selectivities observed. Recent computational methodologies applied to the face-selectivity problem by Houk and Hehre fail to account for our observations.

The diastereofacial selectivity of the Diels–Alder reaction has been the subject of two recent reviews.[1] The most common approach for obtaining facial selectivity in intermolecular cases is to link the diene or dienophile to a chiral auxiliary. Ideally, the auxiliary blocks one face of the diene or dienophile, a face-selective cycloaddition takes place, the auxiliary is removed, and one obtains an adduct enriched in one enantiomer. Rationalizations of relative topicity are usually based on a conformational analysis of the interaction of the auxiliary with the ground state of the substrate. The alternate approach to face selectivity is to incorporate a stereogenic center within the diene or dienophile, usually at an allylic position. The products of cycloaddition are diastereomers and remain so because the stereogenic center is built into the product. Attempts to rationalize the relative topicity of the Diels–Alder reaction in the presence of allylic centers have involved theoretical arguments. Houk has put forward models that involve calculation of the preferred conformer in cycloaddition transition states,[2] while Hehre has computed the favored electrostatic interactions of the ground states.[3] On the basis of a limited number of results, we had postulated an empirical rule that suggested that relative topicities for Diels–Alder reactions of chirally functionalized dienes and dienophiles should be of opposite sign.[4] In the present paper, we present more complete data covering the cycloaddition of a range of dienophiles with a group of related chirally substituted dienes. Our results and those of other recent reports are consistent with each other and will require a revision of the simple rules for predicting the effects of substituents on the face selectivity of the Diels–Alder reaction.

## Results

Table I (Chart I) records the stereochemical outcomes of 20 Diels–Alder reactions carried out in our laboratory or reported in the literature where an acyclic diene of type **1** reacts with a dienophile of type **2** to produce diastereomeric adducts **3** (resulting from a like process) and **4** (resulting from an unlike process)[5] (Scheme I).

Scheme I




The first entry records our repetition of the original example (to the best of our knowledge) of a face-selective Diels–Alder reaction controlled by a chiral allylic substituent, namely the reaction of maleic anhydride (**6**) with (*E*)-2-hydroxy-3,5-hexadiene (**5a**).[6] The British group reported a single adduct obtained as

[†] Author to whom correspondence concerning the X-ray analysis of structure should be addressed.

[‡] Northeastern University.

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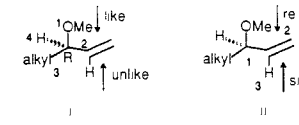
(5) We use the Seebach–Prelog convention (Seebach, D.; Prelog, V., *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 654–660) describing the relative topicities of the approach or addition to the face of an enantiomer, e.g. addition to the *si* face of the double bond with an adjacent *R* allylic center is unlike. Hehre uses "anti" for unlike and Houk applies "erythro" for unlike. To be consistent, we define the configuration of the allylic center by always assigning the $sp^2$ carbon of the double bond a higher priority than the $sp^3$ carbon attached to the allylic center (shown in i). Also, in defining the facial configuration of the double bond, we always assign the priority of the allylic carbon as 1 and the vinylic carbon as 2 (shown in ii).

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