The Crystal Structure of a Conformational Isomer of Teucrin P_1 from *Teucrium Gnaphalodes*

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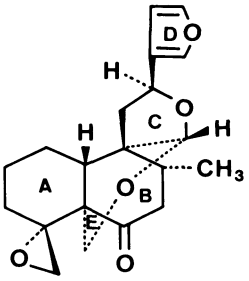
The crystal structure of an isomer of Teucrin P_1 isolated from *Teucrium gnaphalodes* has been determined by the X-ray method. Crystal data: orthorhombic, $P2_12_12_1$, a=13.849(4), b=15.545(3), c=7.896(2) Å, Z=4. The final R value is 0.048 for 1247 observed reflections with $F_o>2\sigma(F_o)$. The structure is disordered, and two kinds of components (molecules) with different conformations coexist in the crystal. The major component exists with a probability of 0.74, while the minor one with 0.26. A tetrahydropyran ring in the former takes a boat form, while the latter a chair form, indicating that in this complex fused-ring system a boat form of the tetrahydropyran ring is more stable than a chair one. The conformation of the major component is the same as that of naturally occurring Teucrin P_1, apart from the orientation of a furan ring.

Teucrin P_1 with the trans-clerodane skeleton shows significant antifeeding activity against insects. It has been isolated from two different species, *T. gnaphalodes*[1] and *T. polium*,[2,3] in the family of Labiatae. The absolute structure of Teucrin P_1 isolated from *T. gnaphalodes* (abbreviated as TPG below) has been obtained by X-ray analysis and spectroscopic methods.[1] The X-ray analysis confirmed that ring **A** has a chair conformation and ring **B** and ring **E** take boat conformations.[1]



Scheme

It is interesting that $[\alpha]_D$ of TPG, −13.0°, is different from that of Teucrin P_1 from *T. polium* (abbreviated as TPP), +6.6°. The difference may reflect the boat/chair conformational difference of such **A**, **B**, and **E** rings in the skeleton of Teucrin P_1.

An isomer of TPG (abbreviated as TPG isomer) has been obtained by a chemical treatment which is expected for generating the conformational changes on ring **B** and/or **E**.[4] The $[\alpha]_D$ of TPG isomer is +2.9° and is rather close to that of TPP.

Therefore the X-ray structure analysis of TPG isomer is undertaken to make clear what kind of conformational change induces the shift of $[\alpha]_D$ as well as to obtain a clue to elucidate the conformation of TPP.

Experimental

TPG isomer was prepared by treating TPG in solution of hexamethylphosphoric triamide and tetrahydrofuran under the catalysis of lithium diisopropylamide at 253 K for 55 min., and crystallized from ethyl acetate solution.[4] Colorless rod crystals were obtained, in which a crystal with approximate dimensions of 0.5×0.4×0.8 mm was selected for the X-ray measurement.

Crystal Data: $C_{20}H_{24}O_5$, M=344.39, orthorhombic, $P2_12_12_1$, T=297 K, a=13.849(4), b=15.545(3), c=7.896(2) Å, V=1699.9(8) Å^3, Z=4, D_c=1.34 g·cm^{-3}, μ(Cu $K\alpha$)=7.41 cm^{-1}, F(000)=736.

A Rigaku four-circle diffractometer with graphite-monochromated Cu $K\alpha_1$ radiation (1.5405 Å) was used. The unit cell parameters were determined from 10 reflections with $13°\leqq 2\theta \leqq 21°$. Intensity data with $2\theta \leqq 115°$ were collected with the θ—2θ scan technique. The θ scan rates and background counting time at both ends of a scan were: 6.0° min^{-1} and 6.7 s for $0°\leqq 2\theta \leqq 60°$; 3.0° min^{-1} and 13.4 s for $60°\leqq 2\theta \leqq 85°$; 1.5° min^{-1} and 26.8 s for $85°\leqq 2\theta \leqq 100°$; 1.0° min^{-1} and 40.2 s for $100°\leqq 2\theta \leqq 115°$. The scan width was $\Delta\theta=(1.5+0.15\times\tan\theta)°$. 1367 reflections were collected, among which 120 reflections less than $2\sigma(F_o)$ were considered as unobserved. No intensity decreases of 3 standard reflections (002, 400, and 120) were observed during the experiment. Lorentz and polarization effects were corrected but no absorption correction was made.

The structure was determined by the direct method (*MULTAN* 78).[5] The absolute configuration of TPG isomer was conformed with that of TPG. The refinement was carried out by the block-diagonal least-squares method (*HBLS* VII).[6] The function minimized was $\Sigma w(|F_o|-|F_c|)^2$, and the weighting scheme was $w=[\sigma^2(F_o)+0.0042|F_o|^2]^{-1}$ at the final stage. In the course of the refinement, disorders were found at O(3) and O(4) atoms on ring **E** and **C** respectively. There are a major site (with higher probability of occurring, O(3A) and O(4A)) and a minor site (with lower one, O(3B) and O(4B)) for each of the two disordered O atoms. Their occupancies were estimated from the ratio of the integrated electron densities around each site, and the occupation ratio of O(3) is found to be

Table 1. The Final Fractional Coordinates($\times 10^4$) and Equivalent Isotropic Temperature Factors, with Their Estimated Standard Deviations in Parentheses

Atom	x	y	z	B_{eq}/Å^2
C (1)	−151 (3)	2373 (3)	9872 (6)	5.4 (2)
C (2)	102 (4)	2864 (3)	8239 (8)	6.7 (2)
C (3)	1179 (4)	2923 (3)	7983 (7)	7.0 (3)
C (4)	1657 (3)	2057 (2)	8051 (4)	4.5 (2)
C (5)	1401 (2)	1510 (2)	9596 (4)	3.8 (1)
C (6)	1797 (3)	607 (3)	9454 (6)	5.1 (2)
C (7)	1071 (4)	−99 (3)	9132 (7)	6.2 (2)
C (8)	228 (3)	−77 (2)	10440 (6)	5.1 (2)
C (9)	96 (3)	830 (2)	11222 (5)	4.4 (1)
C (10)	296 (2)	1481 (2)	9783 (4)	4.0 (1)
C (11)	−898 (3)	908 (3)	12069 (5)	4.9 (2)
C (12)	−713 (3)	1366 (2)	13738 (6)	5.4 (2)
C (13)	−1305 (3)	1073 (2)	15226 (5)	4.7 (2)
C (14)	−1267 (3)	263 (3)	16038 (6)	5.9 (2)
C (15)	−1887 (3)	277 (3)	17317 (6)	5.9 (2)
C (16)	−1942 (3)	1517 (3)	16085 (6)	6.5 (2)
C (17)	1968 (4)	1641 (3)	6468 (6)	6.4 (2)
C (18)	1839 (3)	1923 (3)	11197 (5)	5.5 (2)
C (19)	319 (4)	−806 (3)	11745 (9)	7.6 (3)
C (20)	794 (3)	1005 (3)	12745 (5)	4.7 (2)
O (1)	2657 (2)	2065 (2)	7542 (4)	5.7 (1)
O (2)	2646 (2)	454 (2)	9638 (5)	7.2 (2)
O (3A)	1223 (3)	1890 (2)	12588 (4)	4.6 (1)
O (3B)	1641 (6)	1122 (7)	12570 (12)	4.4 (4)
O (4A)	290 (2)	1046 (2)	14221 (4)	4.5 (1)
O (4B)	179 (6)	1530 (6)	13675 (12)	4.5 (4)
O (5)	−2328 (3)	1050 (2)	17387 (4)	7.3 (2)

identical with that of O(4). The occupancies of the major sites and the minor sites, 0.74 and 0.26 respectively, were fixed throughout the course of the refinement.

All the hydrogen atoms except for those attached to the carbon atoms directly bonded to the disordered O atoms with smaller occupancies are found in the difference Fourier map, and included in the refinements. The isotropic temperature factors of the H atoms are fixed to the equivalent temperature factors[7] of the corresponding carbon atoms to which they are bound. The final R and R_w are 0.048 and 0.064 respectively for 1247 reflections with $|F_o|>2\sigma(F_o)$. Atomic scattering factors were taken from International Tables for X-Ray Crystallography, VOL. IV.[8] The final atomic parameters with B_{eq}'s are given in Table 1.* All the computations were carried out on a FACOM M200 at Nagoya University Computation Center.

* The anisotropic thermal parameters of non-hydrogen atoms, the parameters of hydrogen atoms and the observed and calculated structure factors are preserved at the Chemical Society of Japan (Document No. 8634).

Discussion

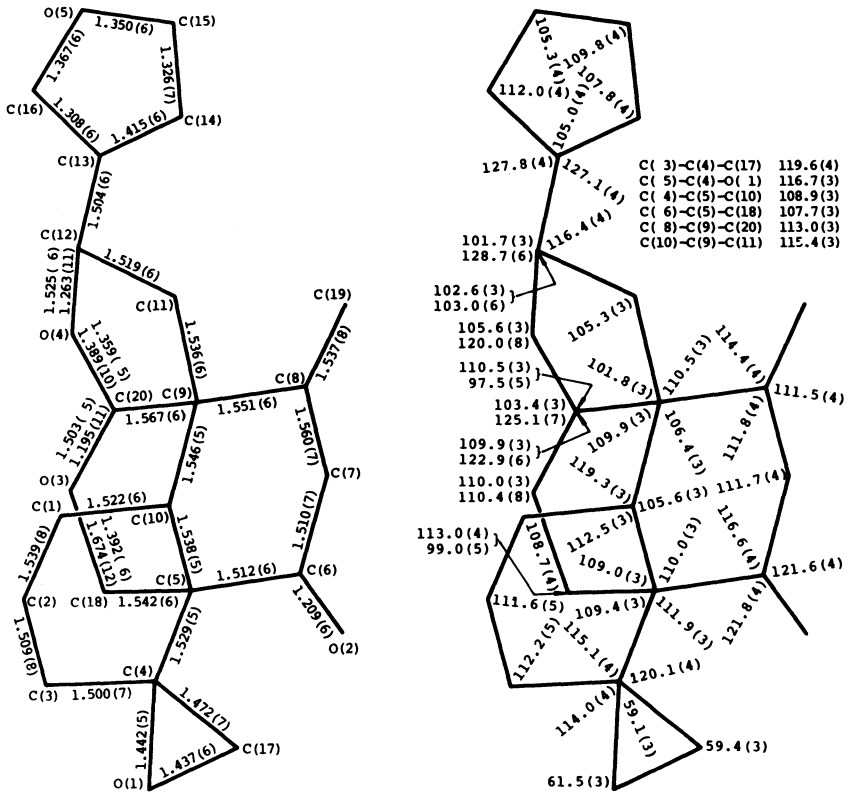
The bond distances and angles are shown in Fig. 1, together with the numbering of atoms.

Extraordinariness occurs in the bond distances and angles concerning the disordered atoms O(3) and O(4). The bond distance of O(3B)–C(18) 1.674(12) Å is longer by about 0.20 Å than that of the normal O–C bond; while O(3B)–C(20) and O(4B)–C(12) distances, 1.195(11) Å and 1.263(11) Å respectively, come to short by about 0.20 Å as compared with the normal value. The large deviations from the tetrahedral angle are found in the bond angles of O(4B)–C(12)–C(13), 128.7(6)° and O(3B)–C(20)–O(4B), 125.1(7)°. Such extraordinariness will partly be due to the errors brought about by the small occupancies for O(3B) and O(4B). On the contrary, there is not a significant anomaly for the distances and angles concerning O(3A) and O(4A).

The disorder occurring at O(3) generates two different conformations on ring **E**, a boat conformation when O(3) is at the major site (O(3A)), and a chair conformation when at the minor site (O(3B)). The disorder of O(4) also affects the conformation of the five-membered ring **C**, although it always keeps an envelope shape. In the case of the major shape corresponding to O(4A), C(12) is out of the O(4A)–C(20)–C(9)–C(11) plane by 0.55(2) Å, whereas in the minor shape containing O(4B), C(20) is displaced by 0.47(3) Å from the plane defined by O(4B)–C(12)–C(11)–C(9).

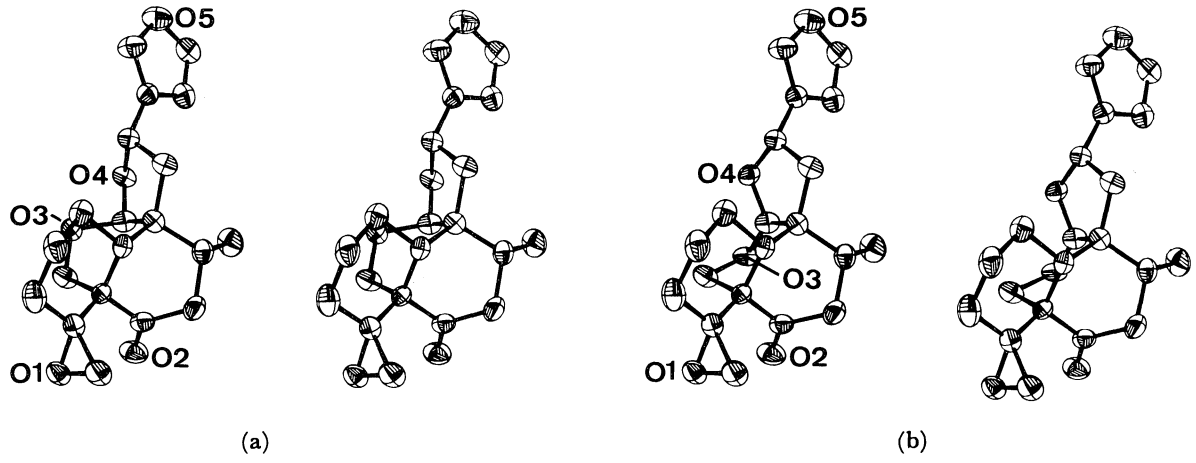
On the molecular structure, four combinations are possible if the disorders are taken into account. However, the molecules in the crystal will take either the structure with ring **E** in a boat conformation (major) and ring **C** in the major shape or that with ring **E** in a chair conformation (minor) and ring **C** in the minor shape, if the two unreasonable combinations, O(3A)–O(4B) and O(3B)–O(4A), are excluded for the reasons described below. First, the combination of O(3A) and O(4B) may readily be rejected because of the too small angle of O(3A)–C(20)–O(4B), 75.5°. Then, as for the combination of O(3B) and O(4A), it is difficult to judge which combination, O(3B)–O(4B) or O(3B)–O(4A), is more rational only from the information of the corresponding bond angles, O(3B)–C(20)–O(4B) 125.1(7)° and O(3B)–C(20)–O(4A) 126.6(6)° respectively. However, it can also be reasonably excluded taking account of the equality between the occupation ratios of O(3) and O(4), because the existence of this combination in the crystal will make the ratios unequal in the absence of the conformer with O(3A) and O(4B).

Therefore, the conformations of the rings of the major component are ring **A**, chair; ring **B**, boat; ring **E**, boat; and ring **C**, envelope with C(12) at the flap. Those of the minor one are ring **A**, chair; ring **B**,



(a) (b)

Fig. 1. (a) Bond distances (l/Å) and (b) bond angles (ϕ/°) for the major component (upper) and the minor component (lower). The estimated standard deviations are in parentheses.



(a) (b)

Fig. 2. Stereoscopic drawing: (a) the major component and (b) the minor component. Atoms are drawn with 50% probability thermal ellipsoids.

boat; ring **E**, chair; and ring **C**, envelope with C(20) at the flap. The *ORTEP* II[10] drawing of the major and minor components are shown in Fig. 2.

The gross structure of the major component is the same as that of TPG, so far as the conformation of each ring is concerned. They differ only in the orientation of ring **D** with respect to ring **C**, but they can be related by a rotation of about 180° around the bond of C(12)–C(13).

The conformational change of ring **E**, from boat to chair, is induced in the naturally occurring molecule by the chemical reaction described above, and the consequent change of the puckering of ring **C** occurs to generate TPG isomer (here referring to minor

component) that has $[\alpha]_D$ of +2.9°. During the crystallization, however, the conformation of TPG isomer transforms to that of TPG. This shows that the molecule with ring **E** in a boat conformation (major) is more stable than that with ring **E** in a chair one (minor), though the opposite result has been expected by the conformational analysis (*MM2*).[4,9] The most stable structure anticipated by the conformational analysis possesses chair conformations for both ring **E** and ring **B**.

As for TPP, its structure may be different from those of TPG and TPG isomer, because its $[\alpha]_D$ (+6.6°) is remarkably different from that of TPG (−13.0°) and also shows a significant difference from that of TPG isomer (+2.9°). Therefore we expect that TPP might possess a chair conformation for ring **B**.

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