Optical Resolution of 1,3-Dimethyl-5-phenyl-Δ^2-pyrazoline by Diastereoisomeric Complex Formation with an Optically Active Host Compound: X-Ray and Molecular Structure of the Complex

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The first example of optical resolution of a non-functionalized Δ^2-pyrazoline is reported using (*R,R*)-(−)-*trans*-4,5-bis(hydroxydi-*o*-tolylmethyl)-2,2-dimethyl-1,3-dioxacyclopentane as host; the X-ray analysis carried out at 200 K shows that the crystal contains the *S* enantiomer of 1,3-dimethyl-5-phenyl-Δ^2-pyrazoline.

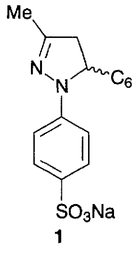
Mukai *et al.*[1] reported in 1979 the first, and until now the only, example of resolution of a Δ^2-pyrazoline. The compounds, *e.g.* **1**, have a sodium sulfonate in the *para* position of the 1-phenyl ring which was used for the resolution by forming a salt with an optically active amine. These pyrazolines were used for studying the mechanism of the C_5 epimerization of Δ^2-pyrazolines but owing to the sulfonate groups the experiments failed.[2] It was then decided to carry out the resolution of pyrazoline **2**[2] by chiral HPLC (over microcrystalline triacetylcellulose).[3] The experiment was successfully achieved, the (−)-enantiomer obtained was optically pure ($[\alpha]_D^{30}$ −342, Φ_D^{30} −596°) although its absolute configuration was not determined.[3] We describe here an alternative procedure which allows the simultaneous production of optically pure pyrazolines and determination of their absolute configuration. For consistency reasons, the same pyrazoline **2** was selected.

When a solution of (*R,R*)-(−)-*trans*-4,5-bis(hydroxydi-*o*-tolylmethyl)-2,2-dimethyl-1,3-dioxacylopentane **3**[4,5] (1.5 g, 2.87 mmol) and racemic **2** (1.0 g, 5.75 mmol) in toluene–hexane (1 : 4, 25 ml) was kept at room temp. for 12 h, a 1 : 1 inclusion complex was obtained as colourless prisms (0.90 g, mp 128–130 °C), which upon heating *in vacuo* (200 °C at 2 mm Hg) gave (*S*)-(−)-**2** in 96% e.e. {0.21 g, 42% yield, $[\alpha]_D^{25}$ −377 (*c* 0.14, MeOH)}. The optical purity was determined by HPLC on Chiralcel OD.[6]

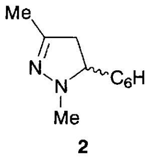
The crystal structure determination† shows that the 1 : 1 complex is formed by the (*R,R*) host molecules and the *S* enantiomer of the pyrazoline (Fig. 1). The absolute configuration was not determined since the configuration of the host was known from the synthesis.

A survey of the structures of Δ^2-pyrazolines reported in the CSD (October 1994 version)[7] shows that no other absolute configuration has been previously determined for this family of compounds. There is a compound (ref. code SOTBAE) of *S* configuration at position 4 but it was determined with regard to a chiral *N*-substituent (1*S*,4*R*).

As far as the host is concerned, it is the first time that a molecular structure with this host derivative presenting *ortho* substituents in the phenyl ring has been determined. Owing to steric effects, the C(sp^3)–C(ar) bonds appeared to be elongated [1.536(5)–1.542(6) Å] when compared with the tabulated length[8] of 1.513(14) Å and even longer than the averaged value of 1.529(6) Å reported for 20 similar host structures retrieved from the CSD. The substitution takes place in an asymmetric way, and the external angles at the *ortho* position are in the ranges 123.3(4)–126.3(4)° and 115.5(4)–118.5(4)°, respectively. The internal angle [116.5(5)–118.7(4)°] reflects the influence of substituent [tabulated $\Delta\alpha$ value of −1.9(2)°].[9] All distances in the O(1)–C(1)–C(2)–C(3)–C(4)–O(2) fragment are somewhat elongated (Fig. 1) compared to the average values reported for the 20 host structures: C–O = 1.435(8), C(1)–C(2) = 1.551(8) and C(2)–C(3) = 1.542(12) Å (24 hits, the standard deviation of the sample being given in parentheses). The conformation of this fragment seems to be rather rigid, probably as a consequence of the intramolecular hydrogen bond (Fig. 1).



1



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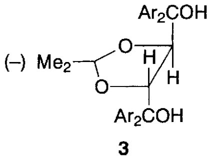

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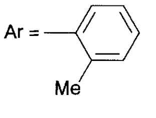

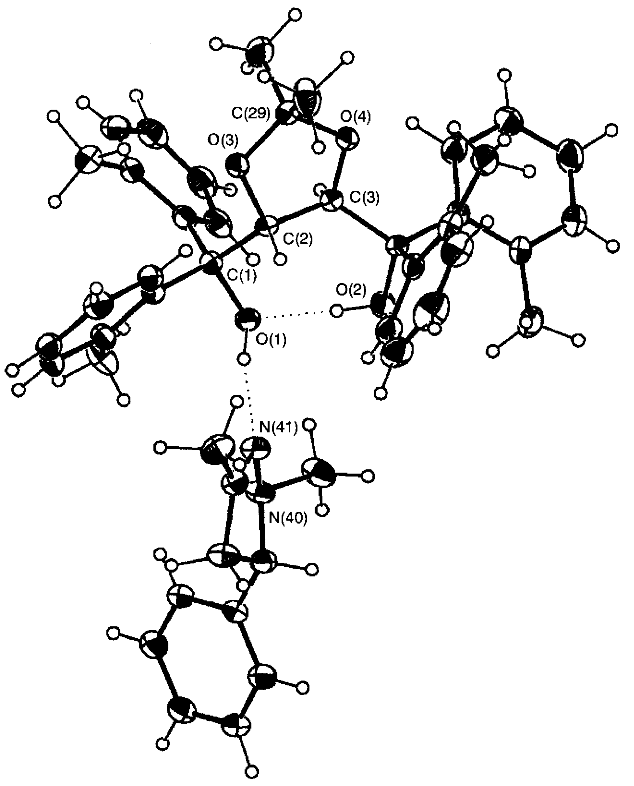

Fig. 1 Molecular structure of the host–guest association showing 30% probability ellipsoids for the non-hydrogen atoms. Dotted lines represent hydrogen bonds. Selected bond lengths (Å) and angles (°): O(1)–C(1) 1.444(5), C(1)–C(2) 1.562(5), O(2)–C(4) 1.434(5), C(2)–C(3) 1.551(5), C(3)–C(4) 1.563(5), O(1)–C(1)–C(2)–C(3) 57.7(4), C(1)–C(2)–C(3)–C(4) −97.0(4), C(2)–C(3)–C(4)–O(2) 70.1(4), O(3)–C(2)–C(3)–O(4) 25.0(4), C(2)–C(3)–O(4)–C(29) −22.5(4), C(3)–O(4)–C(29)–O(3) 11.2(4), O(4)–C(2)–O(3)–C(2) 6.5(4), C(29)–O(3)–C(2)–C(3) −19.8(4)°.

The absolute values of the corresponding torsion angles for the CSD data are: O(1)–C–C–C = 65(5), C–C–C–C = 90(12) and C–C–C–O(2) = 79(9)°. As mentioned above, one hydroxy group is always involved in an intramolecular hydrogen bond (Fig. 2) which is stronger and more linear than the corresponding mean values for the reported structures, 2.659(45) Å, 164(11)°. The other is used in holding the host and guest together through an O–H···N bond leaving the hydrophilic substituents in the inner part of the molecule. The other interactions joining the complexes are hydrophobic (C–H···phenyl interactions).

The conformation of the dioxolane ring is a distorted half-chair where the C(2) and C(3) lie above and below the plane defined by the other three atoms, respectively. Both conformations, half-chair and envelope, have been observed for the studied host although in all of them C(2) and C(3) are involved in the greatest puckering of the molecule. The pyrazoline displays an envelope conformation. The Cremer and Pople parameters[10] for both rings are: q_2 = 0.243(4), 0.287(5) Å and ϕ_2 = −22.9(8), −35.1(8)°, respectively (the ϕ_2 values for the undistorted conformations are −18 and −36°).

There are no voids in the structure, the total and local packing coefficients being 0.66 and 0.52, respectively. The host defines a three-dimensional framework in which channels parallel to the *c* axis are filled by the *S*-pyrazoline molecules. The form of these channels can be described as hour-glass type as tested by means of the quotients of the specific inertial moments of volume over those of surface.[11]

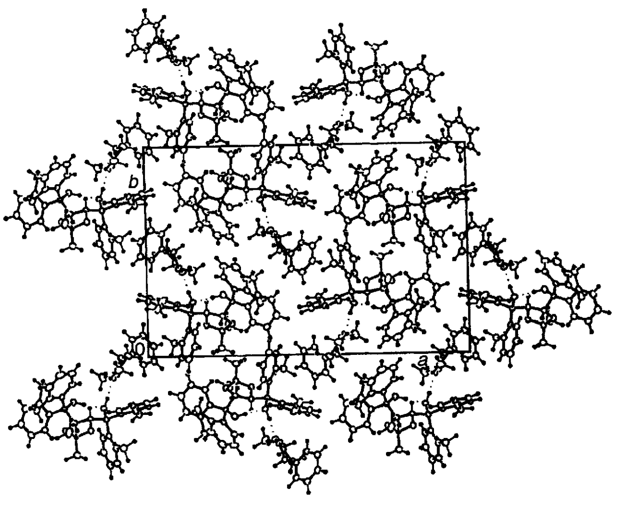

Fig. 2 Crystal packing diagram as projected along the *c* axis (Å,°): O(2)–H···O(1) 0.91(6), 2.645(4), 1.74(6), 173(5); O(1)–H···N(41) 0.95(5), 2.718(4), 1.83(5), 154(4); C(50)–H(50)···C(101) (1 − *x*, *y* − 1/2, 3/2 − *z*): 1.07(7), 3.714(5), 2.70(6), 157(5); C(32)–H(321)···C(102) 1.07(7), 3.497(5), 2.82(6), 121(4); C(32)–H(321)···C(103) (1 − *x*, 1/2 + *y*, 1/2 − *z*): 1.07(7), 3.492(6), 3.02(7), 108(4); C(46)–H(461)···C(103) (*x*, *y*, *z* −1) 1.12(8), 3.541(6), 3.10(9), 104(5) [C(101), C(102) and C(103) stand for the centroid of the C(5)–C(10), C(11)–C(16) and C(47)–C(52) rings]

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Footnote

† *Crystal data*: $C_{35}H_{38}O_4.C_{11}H_{14}N_2$, orthorhombic, $P2_12_12_1$, a = 26.8808(41), b = 17.8222(20), c = 8.1556(4) Å, V = 3907.1(8) Å^3, D_c = 1.185 g cm^{-3}, Z = 4, μ = 5.54 cm^{-1}, T = 200 K, crystal dimensions 0.47 × 0.23 × 0.17 mm, 3780 independent reflections, $R(R_w)$ = 0.045 (0.053) for 3045 [$I > 2\sigma(I)$] observed reflections. Max. final ΔF peak 0.24 e Å^{-3}. Philips PW1100, four circle diffractometer, Cu-Kα radiation, graphite monochromator, ω/2θ scan, θ_{max} = 65°. Refinement on F_o with full matrix. Anisotropic thermal model for the non-hydrogen atoms while H atoms, obtained unambiguously from difference Fourier synthesis were refined isotropically. Most of the calculations were performed using the XTAL System[12] on a VAX6410 computer. The atomic scattering factors were taken from the International Tables for X-Ray Crystallography, vol. IV.[13] The weighting schemes were established as to give no trends in $<\omega\Delta^2F>$ *vs.* $<F_o>$ and $<\sin\theta/\lambda>$. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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