

126. Structural Aspects of the Enantioselectivity of Tartrates with α -Amino-alcohol Salts

Part II

Crystal Structures of (1*R*,2*S*)-Norephedrine Hydrochloride and (1*R*,2*R*)-Norpseudoephedrine Hydrochloride

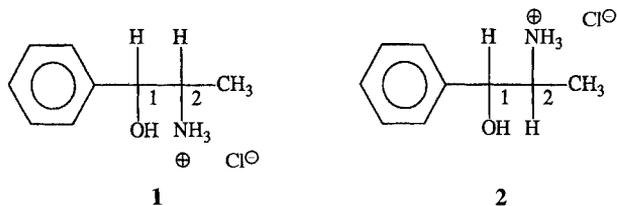
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Enantioselective host-guest complexes between α -amino-alcohol salts and chiral tartrates can not be crystallised up to now. To study structural aspects of their enantioselectivity, crystal structures of the components were determined. Norephedrine was used as a reference guest α -amino-alcohol. (1*R*,2*S*)-Norephedrine hydrochloride (monoclinic, space group $P2_1$, $Z = 4$, $a = 8.455$, $b = 10.331$, $c = 12.570$ Å, $\beta = 107.45^\circ$) and (1*R*,2*R*)-norpseudoephedrine hydrochloride (monoclinic, space group $P2_1$, $Z = 2$, $a = 5.493$, $b = 8.052$, $c = 11.986$ Å, $\beta = 104.62^\circ$) both adopt *M*-synclinal conformations with respect to the ammonium and hydroxy groups. Rather short intramolecular N...O distances indicate interaction between ammonium and hydroxy groups.

Introduction. – Chiral tartaric-acid diesters show remarkable enantioselectivity with salts of α -amino-alcohols [1][2] and are among the simplest known ionophores. Their enantioselectivity has been studied extensively by partition experiments in liquid phases [3]. Since the molecular complexes between tartaric-acid diesters and α -amino-alcohols could not be crystallised, crystal-structure analyses of the components have been accomplished in order to obtain information on structural aspects of enantioselectivity. The structures of the tartaric-acid diester hosts have been already discussed in [4]. Here, we describe the structures of α -amino-alcohol guests, and molecular-modeling studies of the host-guest complexes will be presented later [5]. Our investigations of stereoselective behaviour made use of *erythro*-norephedrine · HCl (**1**) and *threo*-norpseudoephedrine · HCl (**2**) as reference guest molecules. Their (1*R*)-enantiomers are preferred by (*S,S*)-tartaric-acid diesters.



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Force-Field Calculations. – The diastereoisomers of norephedrine, *erythro*-norephedrine, and *threo*-norpseudoephedrine can, in principle, adopt three different conformations about the central C(1)–C(2) bond (Fig. 1). The relative potential energies of these rotamers were calculated using the force-field program MMP2 [6].

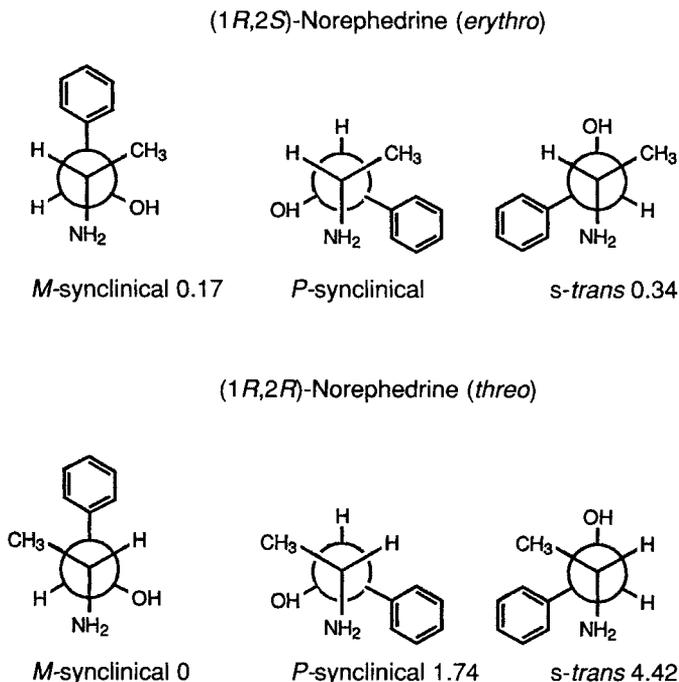


Fig. 1. Newman projections of possible rotamers for (1*R*,2*S*)-norephedrine and for (1*R*,2*R*)-norpseudoephedrine. Numbers at each rotamer indicate relative potential energies (kcal · mol⁻¹)

Unfortunately, this force field has no parameters for ammonium groups, therefore, the bases of the α -amino-alcohols were used instead. For the (1*R*,2*R*)-enantiomer of norpseudoephedrine, potential energies suggest a clear preference of the *M*-synclinal arrangement, with energies of 1.74 kcal · mol⁻¹ higher for the *P*-synclinal and of 4.42 kcal · mol⁻¹ higher for the *s-trans*- arrangement. For the (1*R*,2*S*)-enantiomer of norephedrine, however, the calculations showed no significant differences (Fig. 1). Both calculations are of course hampered by the use of the bases. Possible influences of dipolar interactions in the salts used for the experiments in solution might shift the minimum-energy conformation to a different arrangement.

Crystallographic Investigations. – The nonconclusive results of the force-field calculations led us to look at the crystal structures of both optically active diastereoisomers. A crystal-structure analysis of racemic *erythro*-norephedrine · HCl (1) was published some time ago [7]. The racemic substance crystallizes in the non-centrosymmetric space

group $P2_1$ with two enantiomeric molecules in the asymmetric unit. Both enantiomers have identical synclinal arrangements (torsion angles O–C(1)–C(2)–N -64.8° and -57.7°) but different conformations. One molecule has a torsion angle C(4)–C(1)–C(2)–N of 172.7° – an *s-trans*-arrangement of Ph ring and ammonium group – the other molecule has an *s-cis*-arrangement, with a torsion angle of 63.6° . A *s-cis* arrangement must be more stable than the *s-trans*-conformer because of dipole interactions.

Crystal Structure of (1R,2S)-Norephedrine · HCl (1). The optically active *erythro*-norephedrine · HCl (**1**) crystallizes in the same space group $P2_1$ as the racemic substance, also with two molecules per asymmetric unit. Both molecules have *M*-synclinal conformations with torsion angles O–C(1)–C(2)–N of -61.2° and -70.5° , respectively (see *Figs. 2 and 3*), and the same *s-trans*-arrangement of Ph ring and ammonium group as one of the molecules in the racemic crystal (torsion angles C(4)–C(1)–C(2)–N 175.2° and 165.2°).

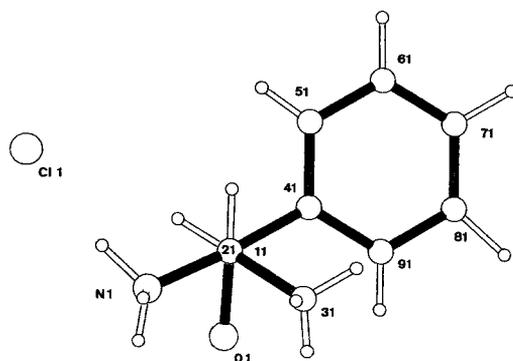


Fig. 2. Newman projection along the C(1)–C(2) bond of one of the two independent molecules in the crystal structure of (1R,2S)-norephedrine · HCl (**1**)

All H-atoms of the ammonium and the hydroxy groups are involved in H-bonds to Cl⁻ anions, every anion accepting four H-bonds (*Fig. 3*). The N...O distances are rather short, 2.741 Å and 2.881 Å, suggesting interaction between ammonium N- and hydroxy O-atoms. No intramolecular H-bond, however, exists between these groups (*cf. Table 2*).

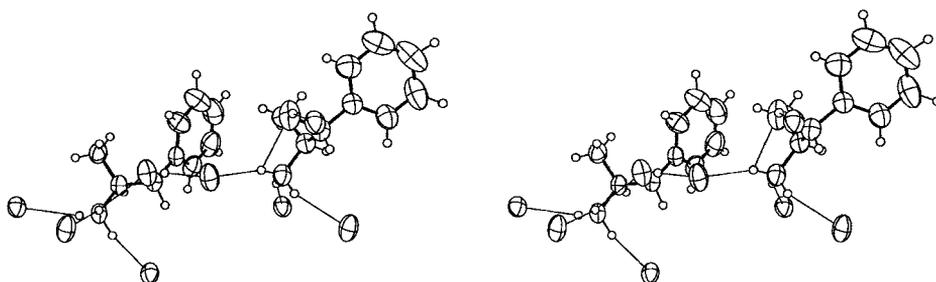


Fig. 3. ORTEP Stereoview of the (1R,2S)-norephedrine · HCl (**1**), showing the H-bonds to Cl-atoms

Crystal Structure of (1R,2R)-Norpseudoephedrine · HCl (2). The optically active *threo*-norpseudoephedrine · HCl (**2**) also crystallizes in the space group $P2_1$, but in this case with only one molecule per asymmetric unit. The preference of an *M*-synclinal arrangement (torsion angle O–C(1)–C(2)–N -54.7°) suggested by the force-field calculation is confirmed by the structure analysis. Fig. 4 shows the conformation in a *Newman* projection along the central C(1)–C(2) bond.

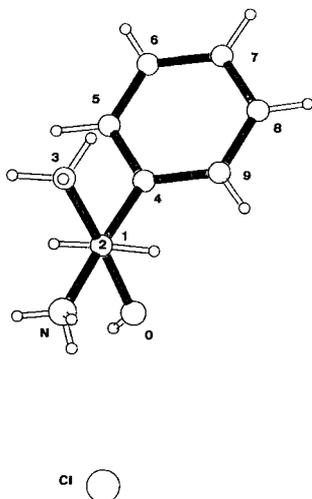


Fig. 4. *Newman* projection along the C(1)–C(2) bond in the crystal structure of (1R,2R)-norpseudoephedrine · HCl (**2**)

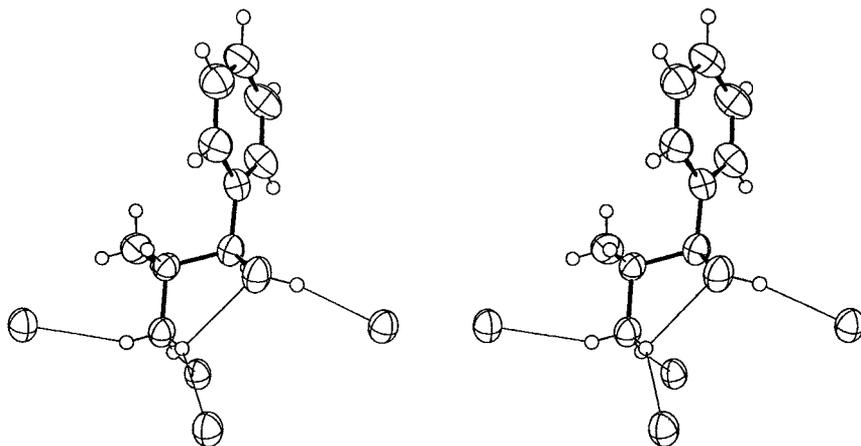


Fig. 5. *ORTEP* Stereoview of (1R,2R)-norpseudoephedrine · HCl (**2**), showing the H-bonds to Cl-atoms

The *s-trans*-arrangement of Ph and ammonium groups (torsion angle C(4)–C(1)–C(2)–N -176.8°) is the same as for *erythro*-norephedrine. Also the H-bonding scheme is very similar. Again, the four donor H-atoms of ammonium and hydroxy groups form H-bonds to Cl⁻ anions (Fig. 5). The interaction between ammonium N- and hydroxy O-atoms shortens the N...O distance to 2.709 Å, without formation of an intramolecular H-bond.

Discussion. – The results suggest, that a *s-cis*-arrangement of hydroxy and ammonium groups is the preferred conformation for both *erythro*- and *threo*-norephedrine. In the case of *erythro*-norephedrine, the energy difference between *M*- and *P*-synclinal arrangements seems to be small, so that crystal-packing influences might suffice to tilt the balance. A similar situation exists for the arrangement of the Ph with respect to the ammonium group. In the crystal structure of racemic *erythro*-norephedrine, *s-cis*- and *s-trans*-arrangements are observed. Again, crystal-packing forces could decide between the two arrangements.

Experimental. – Reflection intensities for both compounds were measured at r.t. with a four-circle diffractometer (Enraf-Nonius CAD4, graphite monochromatized MoK_α radiation). Crystal data for **1** and **2** are given in Table 1. Full lists of coordinates and isotropic displacement parameters as well as H-positions are deposited with the Cambridge Structural Data Centre and are available from the authors.

Table 1. Crystal Data for (1*R*,2*S*)-Norephedrine · HCl (**1**) and (1*R*,2*R*)-Norpseudoephedrine · HCl (**2**)

	1	2
Formula	C ₉ ONH ₁₃ · HCl	C ₉ ONH ₁₃ · HCl
Space group	<i>P</i> 2 ₁	<i>P</i> 2 ₁
Crystal system	monoclinic	monoclinic
<i>a</i> [Å]	8.455(2)	5.438(3)
<i>b</i> [Å]	10.331(4)	8.052(2)
<i>c</i> [Å]	12.570(3)	11.986(4)
β [°]	107.45(2)	104.61(4)
<i>V</i> [Å ³]	1047.4	507.8
<i>Z</i>	4	2
ρ_{calc} [g · cm ⁻³]	1.19	1.23
θ_{max} [°]	28	30
<i>h</i>	-11...11	-7...7
<i>k</i>	0...13	0...11
<i>l</i>	0...16	0...16
Reflections		
measured	2662	1578
used (<i>I</i> > 3 σ)	2041	1328
<i>R</i> factor	0.029	0.031

Both structures were solved by direct methods (SHELX-S86 [8]) and refined by full matrix least-squares analysis. For both structures, the positions of all H-atoms were taken from difference *Fourier* maps, and refined isotropically. The final *R* factors were 0.029 for **1** and 0.031 for **2**, using weights 1/ σ^2 in both cases. Some details of the molecular geometry are given in Tables 2–4.

Table 2. *H-Bond Geometry for 1 and 2*. D...A: Distance donor to acceptor atom, H...A: distance H to acceptor atom, D-H...A: angle donor-donor H-acceptor atom [°]. E.s.d. (in parentheses) refer to the last digit.

			D...A	H...A	D-H...A
1 (Molecule 1)					
N(1)–H(1)	Cl(1)	(1–x, 0.5+y, 2–z)	3.261(3)	2.49(3)	166(3)
N(1)–H(2)	Cl(2)	(2–x, 0.5+y, 2–z)	3.218(3)	2.42(3)	142(3)
N(1)–H(3)	Cl(1)		3.175(3)	2.16(3)	168(3)
N(1)–H(2)	O(1)		2.742(3)	2.33(3)	105(3)
O(1)–H(1)	Cl(2)		3.061(2)	2.29(4)	168(4)
1 (Molecule 2)					
N(2)–H(1)	Cl(1)	(1–x, y–0.5, 2–z)	3.173(3)	2.37(3)	160(3)
N(2)–H(2)	Cl(2)		3.136(3)	2.25(4)	161(3)
N(2)–H(3)	Cl(2)	(2–x, y–0.5, 2–z)	3.159(3)	2.36(3)	150(3)
N(2)–H(2)	O(2)		2.881(3)	2.64(3)	96(3)
O(2)–H(2)	Cl(1)	(2–x, y–0.5, 2–z)	3.151(3)	2.44(3)	164(4)
2					
N–H(3)	Cl	(x–1, y, z)	3.261(2)	2.47(3)	158(3)
N–H(2)	Cl		3.332(2)	2.60(4)	156(3)
N–H(1)	Cl	(1–x, y–0.5, 1–z)	3.166(2)	2.37(3)	155(3)
N–H(2)	O		2.710(2)	2.40(4)	105(3)
O–H	Cl	(1–x, 0.5+y, 1–z)	3.139(2)	2.23(3)	168(3)

Table 3. *Bond Lengths [Å] for 1 and 2* (e.s.d. in parentheses)

	1 (Molecule 1)	1 (Molecule 2)	2
C(1)–C(2)	1.523(3)	1.527(4)	1.520(3)
C(1)–C(4)	1.515(4)	1.496(4)	1.504(3)
C(1)–O	1.417(3)	1.412(3)	1.426(3)
C(2)–C(3)	1.510(4)	1.497(5)	1.518(3)
C(2)–N	1.506(3)	1.480(4)	1.492(3)
C(4)–C(5)	1.382(4)	1.396(5)	1.393(4)
C(4)–C(9)	1.378(4)	1.372(4)	1.385(3)
C(5)–C(6)	1.380(5)	1.372(5)	1.375(4)
C(6)–C(7)	1.369(6)	1.374(7)	1.377(4)
C(7)–C(8)	1.371(6)	1.349(7)	1.378(4)
C(8)–C(9)	1.391(5)	1.383(6)	1.380(3)

Table 4. Bond Angles [°] for 1 and 2 (e.s.d. in parentheses)

	1 (Molecule 1)	1 (Molecule 2)	2
C(2)–C(1)–C(4)	110.6(2)	111.7(2)	110.1(2)
C(2)–C(1)–O	105.2(2)	106.0(2)	105.7(2)
C(4)–C(1)–O	114.0(2)	113.7(2)	112.7(2)
C(1)–C(2)–C(3)	113.9(2)	114.7(2)	113.0(2)
C(1)–C(2)–N	107.2(2)	109.2(2)	108.8(2)
C(3)–C(2)–N	110.0(2)	109.8(3)	109.3(2)
C(1)–C(4)–C(5)	119.0(2)	119.2(3)	121.2(2)
C(1)–C(4)–C(9)	121.7(3)	122.8(3)	120.8(2)
C(5)–C(4)–C(9)	119.2(3)	118.0(3)	117.9(9)
C(4)–C(5)–C(6)	120.4(3)	120.6(3)	120.9(2)
C(5)–C(6)–C(7)	120.3(3)	119.8(4)	120.5(3)
C(6)–C(7)–C(8)	119.9(3)	120.8(4)	119.5(2)
C(7)–C(8)–C(9)	120.2(4)	119.7(4)	120.1(2)
C(4)–C(9)–C(8)	120.0(3)	121.2(4)	121.2(2)

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