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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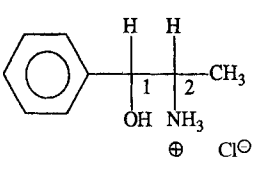
Enantioselective host-guest complexes between α-amino-alcohol salts and chiral tartrates can not be crystallised up to now. To study structural aspects of their enantioselectivity, crystal structures of the components were determined. Norephedrine was used as a reference guest α-amino-alcohol. (1*R*,2*S*)-Norephedrine hydrochloride (monoclinic, space group $P2_1$, $Z = 4$, $a = 8.455$, $b = 10.331$, $c = 12.570$ Å, $\beta = 107.45°$) and (1*R*,2*R*)-norpseudoephedrine hydrochloride (monoclinic, space group $P2_1$, $Z = 2$, $a = 5.493$, $b = 8.052$, $c = 11.986$ Å, $\beta = 104.62°$) 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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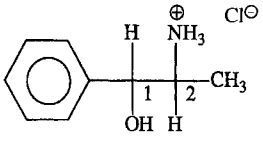

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Force-Field Calculations. – The diastereoisomers of norephedrine, *erythro*-norephedrine, and *threo*-norpseudoephedrine can, in principle, adopt three different conformations about the central C(1)–C(2) bond (*Fig. 1*). The relative potential energies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

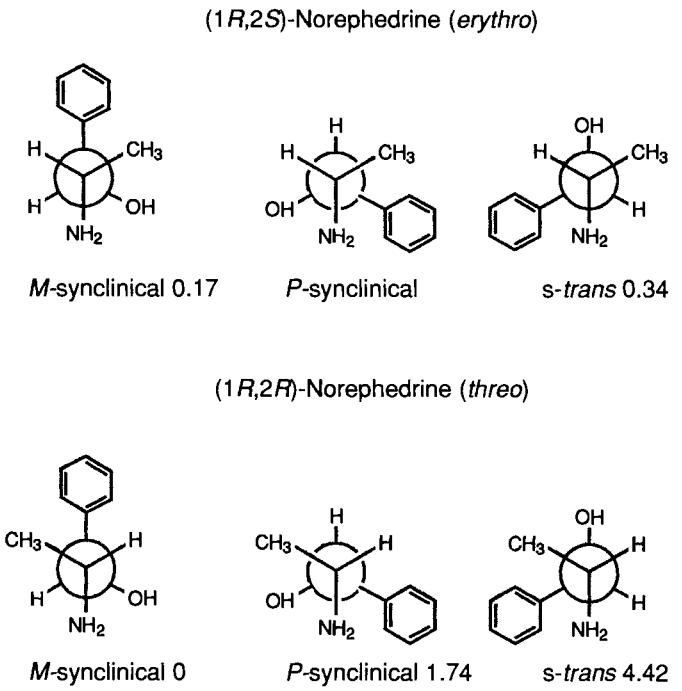

Fig. 1. Newman *projections of possible rotamers for (1*R,2S*)-norephedrine and for (1*R,2R*)-norpseudoephedrine*. Numbers at each rotamer indicate relative potential energies (kcal · mol^{-1})

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*-arrangment 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 (1*R,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°).

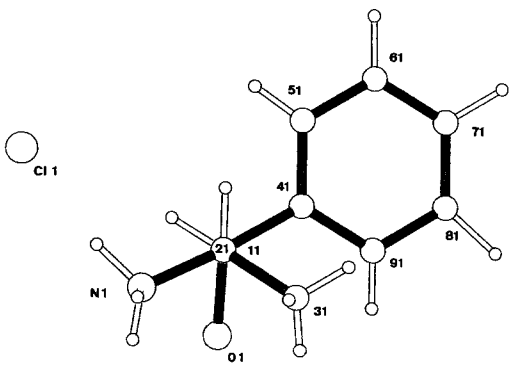

Fig. 2. Newman *projection along the C(1)–C(2) bond of one of the two independent molecules in the crystal structure of (1*R,2S*)-norephedrine · HCl* (**1**)

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*).

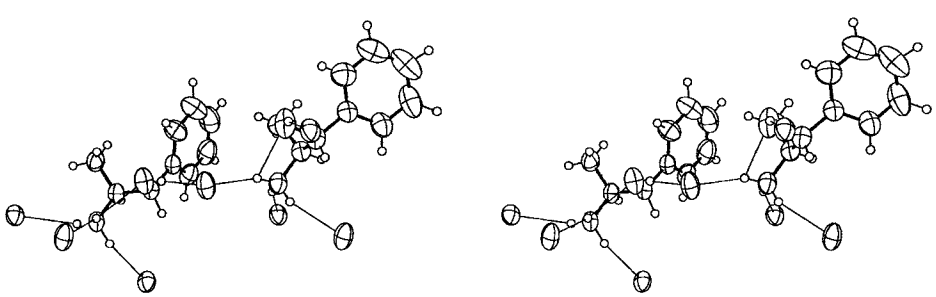

Fig. 3. *ORTEP Stereoview of the (1*R,2S*)-norephedrine · HCl* (**1**), *showing the H-bonds to Cl-atoms*

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.

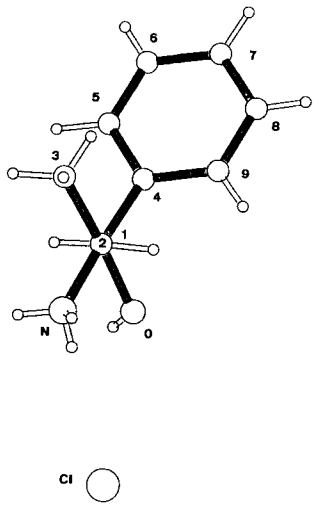

Fig. 4. Newman *projection along the C(1)–C(2) bond in the crystal structure of (1R,2R)-norpseudoephedrine · HCl* (**2**)

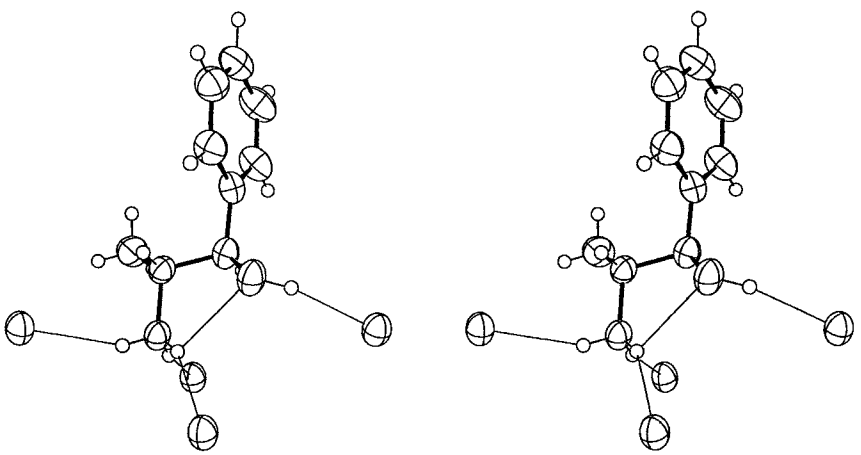

Fig. 5. *ORTEP Stereoview of (1R,2R)-norpseudoephedrine · HCl* (**2**), *showing the H-bonds to Cl-atoms*

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,2S*)-Norephedrine · HCl* (**1**) *and (1*R,2R*)-Norpseudoephedrine · HCl* (**2**)

	1	**2**
Formula	$C_9ONH_{13} \cdot HCl$	$C_9ONH_{13} \cdot HCl$
Space group	$P2_1$	$P2_1$
Crystal system	monoclinic	monoclinic
a [Å]	8.455(2)	5.438(3)
b [Å]	10.331(4)	8.052(2)
c [Å]	12.570(3)	11.986(4)
β [°]	107.45(2)	104.61(4)
V [Å^3]	1047.4	507.8
Z	4	2
ρ_{calc} [g · cm^{-3}]	1.19	1.23
θ_{max} [°]	28	30
h	–11...11	–7...7
k	0...13	0...11
l	0...16	0...16
Reflections		
measured	2662	1578
used ($I > 3\sigma$)	2041	1328
R 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 $1/\sigma^2$ 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)

REFERENCES

[1] V. Prelog, S. Mutak, K. Kovacevic, *Helv. Chim. Acta* **1983** *66*, 2279.
[2] V. Prelog, M. Dumic, *Helv. Chim. Acta* **1986** *69*, 5.
[3] a) M. Egli, ETH-Dissertation No. 8729, 1988; b) V. Prelog, M. Egli, M. Kovacevic, submitted to *Angew. Chem.*
[4] M. Egli, M. Dobler, *Helv. Chim. Acta* **1989** *72*, 1136.
[5] M. Egli, M. Dobler, in preparation.
[6] N.L. Allinger, H. L. Flanagen, *J. Comput. Chem.* **1983**, *4*, 399.
[7] H. Hebert, *Acta Crystallogr., Sect. B* **1979**, *35*, 2054.
[8] G.M. Sheldrick, SHELXS-86, 'Crystallographic Computing 3', Eds. G.M. Sheldrick, C. Krüger, and R. Goddard, Oxford University Press, Oxford, 1985, p. 175.