Crystal Structures and Molecular Conformations of Isoprenaline Hydrochloride and (*S*)-Isoprenaline Hydrogen (2*R*,3*R*)-Tartrate

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The crystal structures of racemic form of isoprenaline hydrochloride (**I**) and (*S*)-isoprenaline hydrogen (2*R*,3*R*)-tartrate (**II**) were determined by X-ray diffraction method. Among the related compounds **I** has the least extended phenethylamine chain with a *gauche–gauche* conformation. The side chain of **II** has the usually observed perpendicular-*trans* conformation. The conformations observed for **I** and **II** are consistent with the intermolecular hydrogen bonding. The observed conformations are close to either a global or local minimum estimated by MMP2.

Isoprenaline hydrochloride, [(3,4-dihydroxyphenyl)-2-hydroxyethyl]isopropylammonium chloride (**I**) finds an important use as drug in relieving and preventing attacks of bronchial asthma; it is prescribed for emphysematous bronchitis pneumosclerosis.[1] Similar drug action of **I** to adrenaline and *dl* isoprenaline sulphate dihydrate[2] has caused us to investigate the structural and conformational properties of **I** and (*S*)-isoprenaline hydrogen (2*R*,3*R*)-tartrate (**II**). The structural and conformational characteristics of these compounds and their neurotransmitter receptor-binding conformational requirements have been a focus of research for the past twenty years. Although literature is not lacking on preferred conformations on phenethylamines,[3,4] the need to analyse more data becomes apparent when some noted discrepancies between observed and calculated energy minima do occur.[5] On molecular structure and biological activity, Griffin and Duax[6] ask whether adrenaline hydrogen tartrate can be described as one of conformational 'outliers', since the conformation of the aromatic ring to the side chain deviates from the usual perpendicular. Investigation of the tartrate salt is of interest in relation to the molecular conformation of the cationic moiety in hydrophilic environment.

In the present study, the observed and theoretical conformations that conform to energy minima of the title compounds are reported and discussed. The intermolecular hydrogen bonds in the crystalline state that are consistent with the observed conformation are commented. The observed conformations in **I** and **II** are compared to structurally similar catecholamines.

Experimental

X-Ray Structure Analysis. Experimental details and crystal data are listed in Table 1. Colorless crystals of **I** (TCI I 0260) and **II** (Adrich 18,881-6) were obtained by slow evaporation from 90% aqueous ethanol solution and an aqueous solution respectively. Intensity data for **I** and **II** were measured by the ω–2θ scan technique on a Rigaku AFC-5R four-circle diffractometer with graphite monochromated Mo $K\alpha$ radiation (λ=0.71073 Å) at 298 K. The data were corrected for Lorentz and polarization effects.

The structure of **I** was solved by Patterson method. The non-H atoms were refined anisotropically and the H-atoms isotropically by full matrix least-squares method: $\Sigma w(|F_o|-|F_c|)^2$ was minimized with $w=\sigma(F_o)^{-2}$. A correction for secondary extinction effect was applied with $I_{corr}=I_o(1+9.69\times10^{-7}I_c)$.

The structure of **II** was solved by direct method SIR,[7] and refined by block-diagonal least-squares

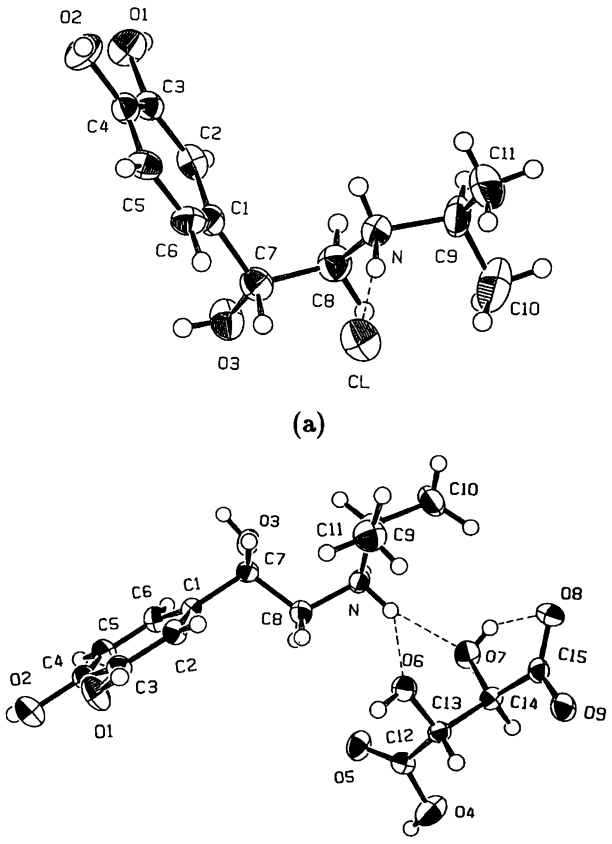

Fig. 1. The molecular structures with atomic numbering. Ellipsoids of 50% probability are drawn for the non-H atoms; the H atoms are represented as spheres equivalent to $B=1.0$ Å^2. Hydrogen bonds within the asymmetric unit are shown by broken lines. (a) Racemic form of isoprenaline hydrochloride (**I**). Only the (*R*)-form is shown. (b) (*S*)-isoprenaline hydrogen (2*R*,3*R*)-tartrate (**II**).

Table 1. Experimental Details and Crystal Data

	I	II
	$C_{11}H_{18}NO_3^+ \cdot Cl^-$	$C_{11}H_{18}NO_3^+ \cdot C_4H_5O_6^-$
M_r	247.72	361.35
Morpholgy	Plates	Plates
Size of specimen (l/mm)	0.25×0.23×0.08	0.48×0.38×0.08
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1/c$	$P2_12_12_1$
a/Å	10.444(6)	10.546(3)
b/Å	10.767(5)	19.227(9)
c/Å	12.148(7)	8.137(6)
β/°	114.57(4)	—
V/Å^3	1242(1)	1650(2)
D_x/Mg m^{-3}	1.324	1.454
Z	4	4
F(000)	528	768
μ/cm^{-1}	2.97	1.13
Radiation	Mo $K\alpha$	Mo $K\alpha$
$2\theta_{max}$/°	50	55
Range of h,k,l	$0 \leq h \leq 12$	$0 \leq h \leq 13$
	$0 \leq k \leq 12$	$0 \leq k \leq 24$
	$-14 \leq l \leq 14$	$-1 \leq l \leq 10$
Fluctuation of standard reflections/%	0.9	3.1
R_{int}	0.043	0.022
No. of unique reflections used	1336 $I_o > 2\sigma(I_o)$	1704 $\lvert F_o \rvert > 2\sigma \lvert F_o \rvert$
No. of parameters	218	319
R/wR	0.055/0.036	0.042/0.046
S	1.45	1.12
$(\Delta/\sigma)_{max}$	0.24	0.47
$\Delta\rho_{max}/\Delta\rho_{min}$/e Å^3	0.33/−0.28	0.16/−0.20

method: $\Sigma w(|F_o|-|F_c|)^2$ was minimized with $w=[\sigma(F_o)^2+0.0046|F_o|+0.0004|F_o|^2]^{-1}$. Anisotropic thermal parameters were adopted for non-H atoms, and H-atoms were refined isotropically. A correction for secondary extinction effect was applied with $I_{corr}=I_o(1+1.00\times10^{-6}I_c)$.

The atomic scattering factors were taken from the International Tables for X-Ray Crystallography.[8] Calculations were performed using the TEXSAN[9] at the X-Ray Laboratory of Okayama University, and by using HBLS-V and DAPH[10] and MOLCON[11] at the Okayama University Computer Center.

Conformational Analysis. The conformational energy minimization was carried out using MMP2 program.[12] The calculations were carried out on the isolated cations. The geometries obtained by the X-ray structure analyses were adopted for the minimization.

Results and Discussion

The final atomic parameters are listed in Table 2, and the bond lengths and angles in Table 3.[13] The molecular structures with atomic numbering are shown in Fig. 1. Selected torsion angles are given in Table 4. The molecular arrangements in the crystals are shown in Fig. 2. The geometry of the hydrogen bonds are listed in Table 5.

In **I** the isoprenalium cations related by a center of symmetry form a dimer through bifurcated hydrogen bonds between N and phenolic oxygens O(1) and O(2). The dimeric unit is shown in Fig. 3. The catechol rings are overlapped with an interplanar distance of 3.336 Å. The dimeric units related by a c glide plane and by a twofold screw axis form a sheet parallel to the (200) plane [Fig. 2(a)]. The ammonium N and O(1) serves as hydrogen bond donor, and Cl accepts three hydrogen bonds (Table 5).

The catechol ring shows a distorted perpendicular conformation to the side chain as shown by τ_1 in Table 4. The corresponding values for the other related compounds show that their observed values range from 75 to 96° except adrenaline hydrogen tartrate.[14] A calculated local energy minimum for τ_1 occurs at 70°, which is close to the observed value in **I**. The conformation of the C(1)–C(7)–C(8)–N chain is *gauche*, τ_2=60.9(5)°, while for the other crystals show *trans* (Table 4). A calculated local minima for τ_2 of **I** occurs at 60 and 180°. However, the steric energy at 60° is estimated to be higher only by 0.4 kJ mol^{-1} than at 180°, the height of the energy barrier being 14.6 kJ mol^{-1}. Thus, the two forms are interconvertible in solution at room temperature. A distorted perpendicular-*gauche* conformation is characterized by the pair of τ_1 and τ_2 for **I**. The relevance of this orientation to bioactivity in terms of acceptor–receptor binding requirement may be inter-

Table 2. Final Atomic Parameters with Their esd's in Parentheses

$$B_{eq} = \left(8\pi^2/3\right) \sum_i \sum_j U_{ij} a_i^* a_j^* \boldsymbol{a}_i \cdot \boldsymbol{a}_j$$

Atom	x	y	z	B_{eq}/Å^2
I				
Cl	0.2451(1)	0.0216(1)	0.2380(1)	4.32(6)
O(1)	0.6774(3)	0.5426(3)	0.6784(3)	3.4(1)
O(2)	0.7843(3)	0.5063(3)	0.5217(3)	3.6(1)
O(3)	0.4591(3)	0.0953(3)	0.6805(3)	3.8(1)
N	0.2008(4)	0.2315(4)	0.3994(3)	2.9(2)
C(1)	0.5138(4)	0.2410(4)	0.5510(4)	2.5(2)
C(2)	0.5479(5)	0.3474(4)	0.6232(4)	2.8(2)
C(3)	0.6392(4)	0.4365(4)	0.6125(3)	2.4(2)
C(4)	0.6961(4)	0.4161(4)	0.5284(3)	2.6(2)
C(5)	0.6632(5)	0.3110(4)	0.4577(4)	2.7(2)
C(6)	0.5715(5)	0.2242(4)	0.4693(4)	2.7(2)
C(7)	0.4151(4)	0.1439(4)	0.5613(4)	3.0(2)
C(8)	0.2664(5)	0.1886(5)	0.5284(4)	3.3(2)
C(9)	0.0439(5)	0.2585(5)	0.3448(5)	4.1(2)
C(10)	−0.0377(7)	0.1501(8)	0.3580(7)	6.2(4)
C(11)	0.0029(7)	0.2947(7)	0.2151(6)	5.6(3)
II				
O(1)	0.4761(2)	0.3098(1)	−0.0479(3)	3.6(1)
O(2)	0.6329(2)	0.2326(1)	−0.2283(3)	3.6(1)
O(3)	0.5664(2)	0.0883(1)	0.4745(3)	3.7(1)
O(4)	−0.0990(2)	0.0218(1)	0.1626(3)	5.8(1)
O(5)	0.1087(2)	0.0387(1)	0.1911(3)	4.1(1)
O(6)	0.0566(2)	0.1494(1)	0.4050(3)	3.4(1)
O(7)	0.0393(2)	0.0286(1)	0.5794(3)	4.1(1)
O(8)	−0.0804(2)	0.1059(1)	0.7877(3)	3.1(1)
O(9)	−0.2241(2)	0.1442(1)	0.6069(3)	3.3(1)
N	0.3003(2)	0.0945(1)	0.5666(3)	3.0(1)
C(1)	0.5283(3)	0.1636(1)	0.2369(4)	2.4(1)
C(2)	0.4814(3)	0.2254(2)	0.1725(4)	2.8(1)
C(3)	0.5171(3)	0.2485(2)	0.0184(4)	2.8(1)
C(4)	0.6002(3)	0.2076(2)	−0.0758(4)	2.8(1)
C(5)	0.6457(3)	0.1460(2)	−0.0124(4)	3.3(1)
C(6)	0.6113(3)	0.1240(2)	0.1438(4)	3.3(2)
C(7)	0.4885(3)	0.1422(2)	0.4086(4)	2.7(1)
C(8)	0.3520(3)	0.1161(2)	0.4016(4)	2.9(2)
C(9)	0.3242(3)	0.1428(2)	0.7105(4)	3.0(2)
C(10)	0.2664(4)	0.1108(2)	0.8631(4)	4.2(2)
C(11)	0.2712(4)	0.2146(2)	0.6744(5)	5.1(2)
C(12)	0.0005(3)	0.0516(2)	0.2291(4)	2.9(1)
C(13)	−0.0397(3)	0.1021(2)	0.3633(4)	2.4(1)
C(14)	−0.0722(3)	0.0606(2)	0.5184(4)	2.9(1)
C(15)	−0.1299(3)	0.1083(2)	0.6502(4)	2.8(1)

Table 3. Bond Lengths and Angles with Their esd's in Parentheses

	I	**II**
	l/Å	l/Å
O(1)–C(3)	1.375(5)	1.366(4)
O(3)–C(7)	1.424(5)	1.428(4)
N–C(9)	1.519(5)	1.516(4)
C(1)–C(6)	1.371(5)	1.386(4)
C(2)–C(3)	1.397(5)	1.382(4)
C(4)–C(5)	1.376(5)	1.378(4)
C(7)–C(8)	1.512(6)	1.527(4)
O(2)–C(4)	1.364(5)	1.375(4)
N–C(8)	1.498(5)	1.507(4)
C(1)–C(2)	1.395(6)	1.390(4)
C(1)–C(7)	1.510(5)	1.516(4)
C(3)–C(4)	1.395(5)	1.405(4)
C(5)–C(6)	1.387(6)	1.388(4)
C(9)–C(10)	1.493(8)	1.514(5)
O(4)–C(12)		1.312(4)
O(8)–C(15)		1.235(4)
C(14)–C(15)		1.536(4)
O(6)–C(13)		1.405(4)
C(12)–C(13)		1.521(4)
C(14)–C(15)		1.536(4)
	ϕ/°	ϕ/°
C(1)–C(2)–C(3)	120.7(4)	121.3(3)
C(2)–C(1)–C(6)	119.4(4)	119.2(3)
C(2)–C(1)–C(7)	121.4(4)	118.8(3)
C(2)–C(3)–C(4)	118.4(4)	119.0(3)
O(1)–C(3)–C(4)	117.0(4)	117.7(3)
O(1)–O(3)–C(2)	124.6(5)	123.3(3)
O(2)–C(4)–C(3)	115.9(4)	117.0(3)
O(2)–C(4)–C(5)	123.2(5)	123.4(3)
C(3)–C(4)–C(5)	120.9(4)	119.6(3)
C(4)–C(5)–C(6)	119.7(5)	120.9(3)
C(6)–C(1)–C(7)	119.3(5)	122.0(3)
O(3)–C(7)–C(8)	104.3(4)	108.6(2)
C(8)–N–C(9)	117.2(4)	117.3(3)
N–C(9)–C(11)	107.0(5)	110.3(3)
C(1)–C(6)–C(5)	121.0(5)	119.9(3)
O(3)–C(7)–C(1)	113.3(4)	112.6(2)
C(1)–C(7)–C(8)	114.8(4)	108.4(2)
N–C(8)–C(7)	110.3(3)	113.3(3)
N–C(9)–C(10)	111.3(4)	108.5(3)
C(10)–C(9)–C(11)	112.9(6)	112.3(3)
O(4)–C(12)–O(5)		124.1(3)
O(6)–C(13)–C(12)		112.7(2)
C(12)–C(13)–C(14)		108.8(2)
O(7)–C(14)–C(13)		109.2(2)
C(13)–C(14)–C(15)		110.6(2)
O(8)–(15)–O(9)		127.4(3)
O(4)–C(12)–C(13)		110.6(3)
O(6)–C(13)–C(14)		107.4(2)
O(7)–C(14)–C(15)		110.1(2)
O(8)–C(15)–C(14)		116.2(3)
O(5)–C(12)–C(13)		125.3(3)
O(9)–C(15)–C(14)		116.4(3)

esting to elucidate.

In **II** both the ammonium N and the catechol oxygens show hydrogen-bond donating characteristics as seen from Table 5. Their hydrogen atoms are accepted by the O atoms of the hydrogen tartrate ions. The ammonium N donates a hydrogen atom to the hydroxyl oxygens O-(6) and O(7) to form a bifurcated hydrogen bond, but it donates no hydrogen atom to the carboxylate group. No hydrogen bond between the carboxylate group and the ammonium N is also observed in adrenaline hydrogen tartrate.[14] In the crystal each isoprenalium cation is linked through hydrogen bonds to six hydrogen tartrate anions to form a three-dimensional network [Fig. 2(b), Table 5].

The carbon chain of the hydrogen tartrate anion takes

Table 4. Selected Torsion Angles of Isoprenaline Cations and Some Related Compounds Found in the Crystals

	I[a]	II[b]	III[c]	IV[d]	V[e]	VI[f]
	τ/°	τ/°	τ/°	τ/°	τ/°	τ/°
τ_1:C(2)–C(1)–C(7)–C(8)	63.5(5)	74.7(4)	−77.2(8)	−96.4(6)	179.2(3)	−90.4(4)
τ_2:C(1)–C(7)–C(8)–N	60.9(5)	−178.8(2)	174.6(6)	171.6(4)	−179.4(2)	167.5(2)
τ_3:C(7)–C(8)–N–C(9)	169.7(4)	45.6(4)	−156.3(6)	157.9(5)	—	—
τ_4:C(8)–N–C(9)–C(11)	−177.9(5)	−179.2(3)	176.8(6)	—	—	—

a) Isoprenaline hydrochloride (this work). b) (*S*)-Isoprenaline hydrogen (2*R*,3*R*)-tartrate (this work). c) Isoprenaline sulphate dihydrate.[2] There are two independent molecules with similar conformations in the crystal. The values refer to molecule A. d) Adrenaline.[15] e) Adrenaline hydrogen tartrate.[14] f) Noradrenaline.[16]

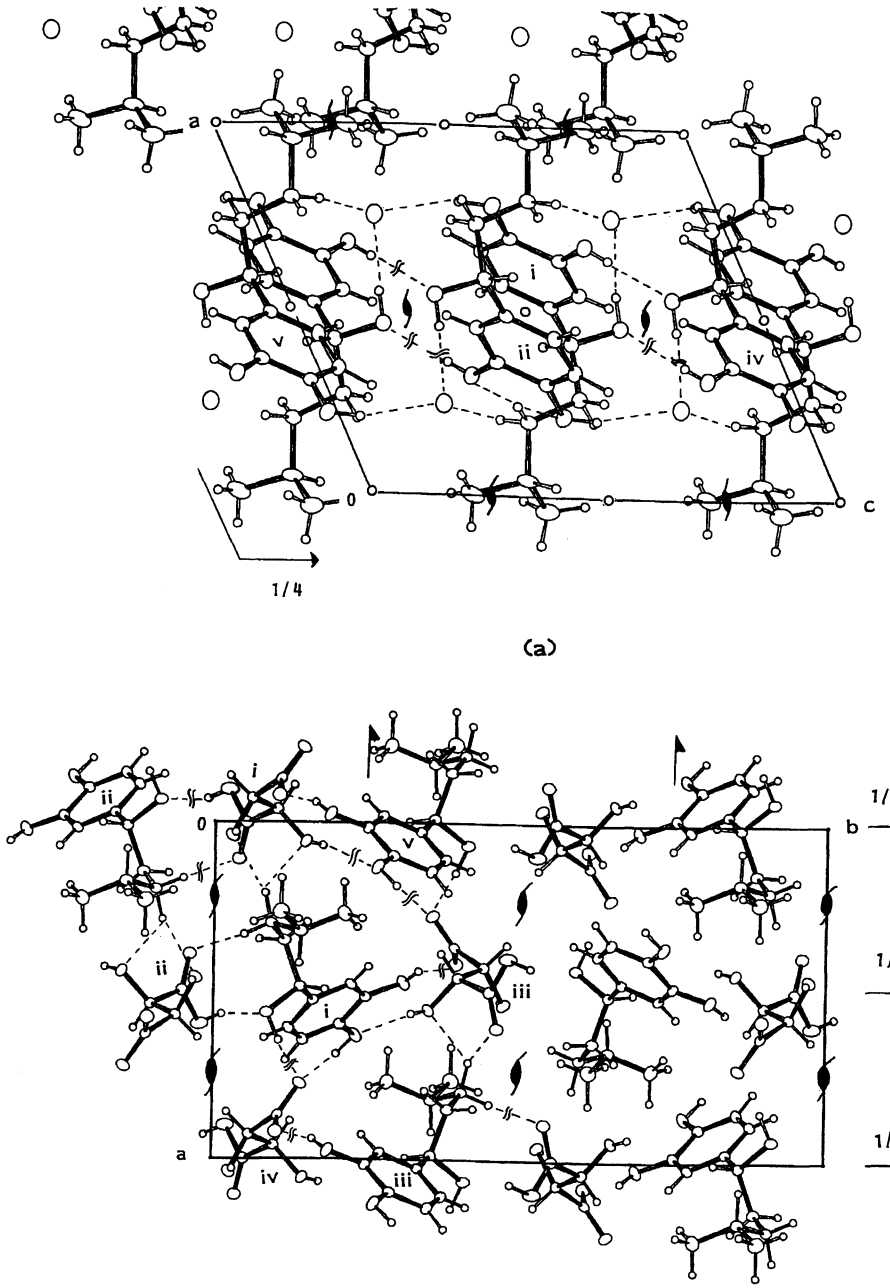

Fig. 2. The molecular arrangements in the crystals of **I** (a) and **II** (b). Intermolecular hydrogen bonds are shown by broken lines. The symmetry codes are given in Table 5.

Table 5. Geometry of Hydrogen Bonds

Donor(D)	Acceptor(A)	D···A l/Å	H···A l/Å	D–H···A ϕ/°
I				
N^{i}	Cl^{i}	3.150(4)	2.11(8)	173(7)
N^{i}	$O(1^{ii})$	3.070(6)	2.19(6)	165(5)
N^{i}	$O(2^{ii})$	2.965(6)	2.38(6)	122(5)
$O(1^{i})$	$O(3^{iv})$	2.706(6)	2.0(1)	176(11)
$O(2^{v})$	Cl^{i}	3.044(4)	2.22(9)	164(8)
$O(3^{iii})$	Cl^{i}	3.093(4)	2.3(1)	165(5)
II				
N^{i}	$O(6^{i})$	3.073(4)	2.38(3)	128(2)
N^{i}	$O(7^{i})$	3.032(4)	2.11(3)	158(3)
N^{i}	$O(5^{ii})$	2.917(4)	1.97(4)	172(4)
$O(1^{v})$	$O(8^{i})$	2.733(3)	1.83(4)	163(4)
$O(2^{i})$	$O(9^{iv})$	2.638(3)	1.73(4)	170(4)
$O(3^{i})$	$O(9^{vi})$	2.682(3)	1.73(4)	165(4)
$O(4^{ii})$	$O(3^{i})$	2.635(4)	1.70(4)	162(4)
$O(6^{iii})$	$O(2^{i})$	2.804(3)	2.05(3)	155(3)
$O(7^{i})$	$O(8^{i})$	2.583(3)	2.00(4)	125(3)

Symmetry codes: for **I**, (i) x,y,z; (ii) $1-x$, $1-y$, $1-z$; (iii) $1-x$, $-y$, $1-z$; (iv) $1-x$, $1/2+y$, $3/2-z$; (v) $1-x$, $-1/2+y$, $1/2-z$; for **II**, (i) x,y,z; (ii) $1/2-x$, $-y$, $1/2+z$; (iii) $1/2+x$, $1/2-y$, $-z$; (iv) $1+x$, y, $-1+z$; (v) $-1/2+x$, $1/2-y$, $1-z$; (vi) $1+x$, y, z.

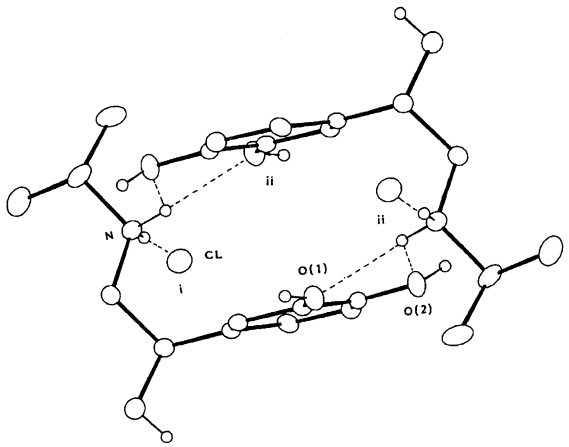

Fig. 3. The dimeric unit of **I**. The broken lines denote intermolecular hydrogen bonds.

a *trans* zig-zag conformation; C(12)–C(13)–C(14)–C(15) −172.4(3)°. The conformation of the carbonyl O(5) with respect to O(6) deviates from a *cis*: O(5)–C(12)–C(13)–O(6) 20.0(5)°. On the other hand, the carboxylate O(8) takes a *cis* conformation to O(7): O(7)–C(14)–C(15)–O(8) −6.2(5)°, which is favored by intramolecular hydrogen bond between the oxygen atoms.

The orientation of the phenyl ring to its side chain shows the usually observed perpendicular-*trans* conformation, which is characterized by τ_1 and τ_2. However, τ_3 of **II**, C(7)–C(8)–N–C(9), has a peculiar value of 45.6(4)° in comparison to the others. The observed conformation is consistent with the hydrogen bonds involving O(3) and N. The observed value is close to 60° for a calculated local minimum. The global minimum for τ_3 occurs at 175° which is close to the observed values for the other compounds. The difference in steric energies at τ_3=60 and 175° is estimated to be only 3.3 kJ mol^{-1}. The height of the energy barrier between the conformations is 17.6 kJ mol^{-1}.

τ_1 of adrenaline hydrogen tartrate shows a peculiarity. While its phenyl ring to side chain conformation is *trans*, adrenaline and the other compounds show perpendicular conformation.[15] The presence of the hydrogen tartrate anion in both situations seems to be the underlying factor for the observed 'outlier' conformations. This strengthens the notion that intermolecular hydrogen bonds play an important role in shaping the conformation in these catecholamines, however, the observed conformations are close to either a local or global minimum in steric energy.

References

1) G. Meletyeva and L. Antova, "Pharmaceutical Chemistry," Mir Publishers, Moscow (1988), pp. 434—452.
2) M. Mathew and G. J. Palenik, *J. Am. Chem. Soc.*, **93**, 497 (1971).
3) R. B. Barlow, O. Johnson, J. A. K. Howard, D. C. Walton, and G. Koelliner, *Acta Crystallogr., Sect. B*, **45**, 397 (1989).
4) J. J. Urban, C. J. Cramer, and G. R. Famini, *J. Am. Chem. Soc.*, **114**, 8226 (1992).
5) D. Carlstrom, R. Bergin, and G. Falkenburg, *Q. Rev. Biophys.*, **3**, 257 (1973).
6) J. F. Griffin and W. L. Duax, "Molecular Structure and Biological Activity," Elsevier Science Publishing, New York (1982), pp. 117—133.
7) "SIR," M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, G. Polidovi, R. Spagna, and D. Viterbo, *J. Appl. Crystallogr.*, **22**, 389 (1989).
8) "International Tables for X-Ray Crystallography," Kynoch Press, Birmingham (Present Distributor Kluwer Academic Publishers, Dordrecht) (1974), Vol. IV, pp. 72—98.
9) "TEXSAN. Single Crystal Structure Analysis Software. Version 5.0," Molecular Structure Corporation, The Woodlands, Texas (1989).
10) T. Ashida, "HBLS-V and DAPH. The Universal Crystallographic Computing System-Osaka," The Computation Center, Osaka Univ. (1973).
11) S. Fujii, "MOLCON. The Universal Crystallographic Computing System- Osaka," The Computation Center, Osaka Univ. (1979).
12) N. L. Allinger. "MM2-Molecular Mechanics Version 2," Department of Chemistry, Univ. of Georgia, (1980).
13) Tables of anisotropic thermal parameters for non-hydrogen atoms, bond lengths and angles involving the hydrogen atoms, and structure factors have been deposited as Document No. 66043 at the Office of the Editor of Bull. Chem. Soc. Jpn.
14) D. Carlstrom, *Acta Crystallogr., Sect. B*, **29**, 163 (1972).

15) A. M. Anderson, *Acta Chem. Scand. B*, **29**, 243 (1975).
16) A. M. Anderson, *Acta Chem. Scand. B*, **29**, 871 (1975).