Stereochemistry and Conformation in Solution of Diltiazem Hydrochloride, a 1,5-Benzothiazepine Coronary Vasodilator

Robert Glaser*
Department of Chemistry, Ben Gurion University of the Negev, Beersheva 84105, Israel
Benjamin Sklarz
Abic Ltd., Chemical and Pharmaceutical Industries, Netanya, Israel

Major and minor species have been observed in a *ca.* 12:1 ratio in the ambient-temperature ^1H n.m.r. spectrum of crystalline (+)-(*M*,2*S*,3*S*)-diltiazem hydrochloride (**1**) dissolved in $(CD_3)_2SO$, $CDCl_3$, or CD_2Cl_2. The two solution species were characterized by ^1H and ^{13}C n.m.r. spectroscopy, including various 2D-n.m.r. techniques. The ^1H n.m.r. spectroscopic parameters of the major solution species are fully consistent with the (*M*,2*S*,3*S*)-twist-boat 1,5-benzothiazepine ring conformation noted in the solid state in which the methoxyphenyl and acetoxy moieties are, respectively, axially, and equatorially oriented. Dissolution of crystalline diltiazem hydrochloride (+)-(**1**) results in a diastereoisomerization to form a minor species the stereochemistry of which appears to be the 1,5-benzothiazepine ring-inverted (*P*,2*S*,3*S*)-boat (twist-boat) analogue. The heptagonal-ring-inversion process [(*M*,*S*,*S*) $\rightleftharpoons$ (*P*,*S*,*S*)] converts axial and equatorial substituent orientations. In molecular-mechanics calculated models for both (*P*,*S*,*S*)-twist-boat and boat conformations, the $(C{=}O)CH_3$ methyl protons are located almost directly above the benzo ring centre as a result of the axial-like acetoxy orientation. This is consistent with the finding that $(C{=}O)CH_3$ protons suffer a $\Delta\delta$ 0.49 ppm upfield shift in the minor solution (*P*,*S*,*S*)-species. Variable-temperature ^1H n.m.r. [300 MHz; $(CD_3)_2SO$] experiments showed dynamic behaviour. The $\Delta G^{\ddagger}$ for the diastereoisomerization process was measured to be 17.2(1) kcal mol^{-1} by line-shape analysis on variable-temperature spectra.

(+)-Diltiazem hydrochloride [(+)-(2*S*,3*S*)-*cis*-3-(acetoxy)-5-(2-dimethylaminoethyl)-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one hydrochloride[1] (+)-(**1**)] is a vasodilator cardiac drug with calcium-blocking activity.[2] The (2*S*,3*S*)-absolute configuration of the (+)-enantiomer was first determined by Inoue *et al.*[1] by *X*-ray crystallography, and a pictorial representation of the molecular structure was given.† Further details of the structure of (+)-(**1**) have been provided by Kojić-Prodić *et al.* (see Figure 1).[3] These authors found a twist-boat ‡ conformation for the heptagonal-ring in crystalline (+)-(**1**) (see Table 1.[3] They also assigned an *M*-descriptor[4] for the skew chirality of the 1,5-benzothiazepine system, on the basis of the synclinal (*gauche*) S(1)–C(2)–C(3)–C(4) torsion angle (ω_2) having a negative value in the solid state (see Figure 1). An *M*-conformation was also assigned for the (+)-(**1**) seven-membered ring in solution, using c.d. measurements.[3] However, ^1H n.m.r. spectroscopic evidence showed dynamic behaviour for (+)-(**1**) in $(CD_3)_2SO$.[3] Using higher field n.m.r. instruments, we observed two species [(*P*,*S*,*S*) and (*M*,*S*,*S*)] at the slow-exchange limit for isomer interconversion when crystalline (*M*,*S*,*S*)-(+)-(**1**) was dissolved in solvents such as CD_2Cl_2, $CDCl_3$, or $(CD_3)_2SO$. This paper describes the structure determination and assignment of n.m.r. spectral parameters for both diastereoisomers.

Results and Discussion

Major and minor species were observed in a *ca.* 12:1 ratio in the ambient-temperature ^1H n.m.r. spectrum of crystalline (+)-(*M*,*S*,*S*)-(**1**) dissolved in either $(CD_3)_2SO$, $CDCl_3$, or CD_2Cl_2. The ^1H and ^{13}C n.m.r. spectral parameters are listed in Tables 2 and 3. The major and minor species have been assigned as (*M*,*S*,*S*)-(**1**) and (*P*,*S*,*S*)-(**1**), respectively, based upon the relative large chemical shift differences noted for the 'externally diastereotopic' $CH_3C{=}O$ methyl protons (see below).

Proton N.M.R. Spectral Parameters.—The major-species benzylic H(2) resonance in $(CD_3)_2SO$ was assigned after decoupling, at *ca.* 7.37 ppm [H(13),(17)], sharpened the lower-intensity lower-field doublet of the H(2),(3) AB-system. Relative H(2),(3) assignments are also consistent with chemical-shift values for corresponding ^{13}C nuclei [HETCOR[5] 2D n.m.r. technique]. It is noted that H(2) is the higher-field AB-doublet in spectra measured in CD_2Cl_2 or $CDCl_3$. In the minor-species, H(2),(3) appear as an AB-system in $(CD_3)_2SO$ and as an AX-system in CD_2Cl_2 (specific assignments within the pair were not made). Differentiation of diastereotopic $(C{=}O)NCH_2$ and CH_2N^+H was made by observation of vicinal coupling to N^+H for each proton in the latter geminal pair (CD_2Cl_2 solvent). The two NCH_3 groups are also diastereotopic and hence are expected to be anisochronous [two typical[6] $^3J_{CH-N^+H}$ doublets (*ca.* 5 Hz) were observed in CD_2Cl_2]. The lifetimes of the protonated species in $(CD_3)_2SO$ were short on the n.m.r. timescale, and chemical-exchange decoupling is implied by the absence of vicinal coupling to N^+-*H*. Under these conditions the two sets of N-CH_3 resonances were not resolved, a broad signal was seen. Addition of four drops of concentrated trifluoroacetic acid to the $(CD_3)_2SO$ solution afforded the expected two doublets for $N^+H(CH_3)_2$. This anisochrony is clearly the result of 'diastereotopic symmetry non-equivalence', which contradicts the statement by Kojić-Prodić that slow rotation of the bulky side chain renders the two methyl groups magnetically non-equivalent in (+)-(**1**).

† No co-ordinates were given nor were any obtainable from the Cambridge Crystallographic Data Centre.

‡ Agreement between the experimental (+)-(**1**) and ideal (*M*,2*S*,3*S*)-twist-boat values for the magnitudes and signs of five of the seven torsion angles in Table 1 is very good and discrepancies are, as expected, in the amide (ω_4) and benzo-junction (ω_6) angles.

Table 1. Selected non-hydrogen torsion angles (measured in degrees) for crystalline twist-boat (*M*,2*S*,3*S*)-(**1**) *vs.* molecular-mechanics calculated models for (*M*,2*S*,3*S*)- and (*P*,2*S*,3*S*)-diastereoisomers in twist-boat (**4**), boat (**5**), and chair (**6**) conformations [plus the boat propionyloxy model (**8**) and the (*M*,2*R*,3*S*)-*trans*-isomer twist-boat (**10**) and boat (**11**) model conformations].[a]

Structure	ω_1	ω_2	ω_3	ω_4	ω_5	ω_6	ω_7	χ_1	χ_2	χ_3	χ_4
Ideal (*M*)-twist-boat[b]	−45	−45	64	18	−75	18	64				
Cryst. (*M*,*S*,*S*)-(+)-(**1**)[c]	−42.0	−42.1	90.6	−13.3	−48.0	0.6	69.4	−168.7	−42.5	−148.2	
(*M*,*S*,*S*)-(**4**) (0.00 kcal)[d,e]	−36.9	−45.9	82.6	−0.4	−53.3	−5.7	73.0	−161.8	−47.9	−153.5	−41.6
(*P*,*S*,*S*)-(**4**) (2.25 kcal)[d,f]	37.4	42.3	−79.3	1.4	54.4	1.3	−68.1	−93.1	45.0	48.4	46.2
(*M*,*R*,*S*)-(**10**) (−0.04 kcal)[d]	−36.9	−45.4	84.9	−4.5	−52.1	−3.6	70.9	90.7	66.3	−153.9	−168.2
Ideal (*M*)-boat[b]	−31	−58	58	31	−70	0	70				
(*M*,*S*,*S*)-(**5**) (1.78 kcal)[d]	−31.6	−50.9	80.7	4.1	−55.3	4.7	70.8	−155.4	−50.9	−157.6	−47.6
(*P*,*S*,*S*)-(**5**) (0.88 kcal)[d,g]	22.8	57.4	−80.9	−4.8	54.2	6.8	−65.0	−107.9	57.7	47.4	60.7
(*P*,*S*,*S*)-(**8**) propionyloxy[h]	23.8	56.6	−81.2	−4.3	54.3	6.3	−65.4	−106.8	56.8	47.1	59.9
(*M*,*R*,*S*)-(**11**) (1.28 kcal)[d]	−29.2	−52.6	83.5	0.8	−54.2	−4.6	67.7	98.1	59.6	−157.7	−157.7
Ideal (*M*)-chair[b]	84	−64	64	−84	66	0	−66				
(*M*,*S*,*S*)-(**6**) (8.82 kcal)[d]	89.6	−47.3	−6.4	−11.0	52.8	−10.1	−64.2	−42.7	−98.1	124.4	−45.3
(*P*,*S*,*S*)-(**6**) (6.88 kcal)[d]	−93.4	48.9	8.1	10.5	−55.9	12.1	64.1	142.2	50.3	131.8	50.1

[a] Torsion angles are defined in the numbered diagram (**3**), except χ_4 which is defined as torsion angle H(2)–C(2)–C(3)–H(3). [b] Data from ref. 15. [c] Estimated standard deviation *ca.* 0.6° for crystalline twist-boat (*M*,2*S*,3*S*)-(**1**) (data from ref. 3). [d] Numbers in parentheses refer to molecular-mechanics-calculated energy increase relative to (*M*,*S*,*S*)-(**4**) diastereoisomer. [e] *r*(C*H* • • • *m*) non-bonded distances between methyl protons and the benzo ring centre (*m*) = 7.31, 7.50, 7.68 Å, and the respective angular deviation ∠(C*H*–*m*–*m*′) from a perpendicular line segment (*m*–*m*) to the ring centre are 36.8, 50.4, and 42.0°. [f] *r*(C*H* • • • *m*) 3.78, 4.16, and 5.36 Å and the respective ∠(C*H*–*m*–*m*′) = 7.3, 23.1, and 6.6°. [g] *r*(C*H* • • • *m*) 2.96, 4.30, and 4.51 Å and the respective ∠(C*H*–*m*–*m*′) = 15.8, 22.7, and 1.8°. [h] For propionyloxy methylene protons: *r*(C*H* • • • *m*) 2.97 and 4.55 Å, and the respective ∠(C*H*–*m*–*m*) = 13.4 and 1.2°. The corresponding values for methyl protons are 4.00, 4.97, and 5.30 Å and 43.3, 31.4, and 29.8°.

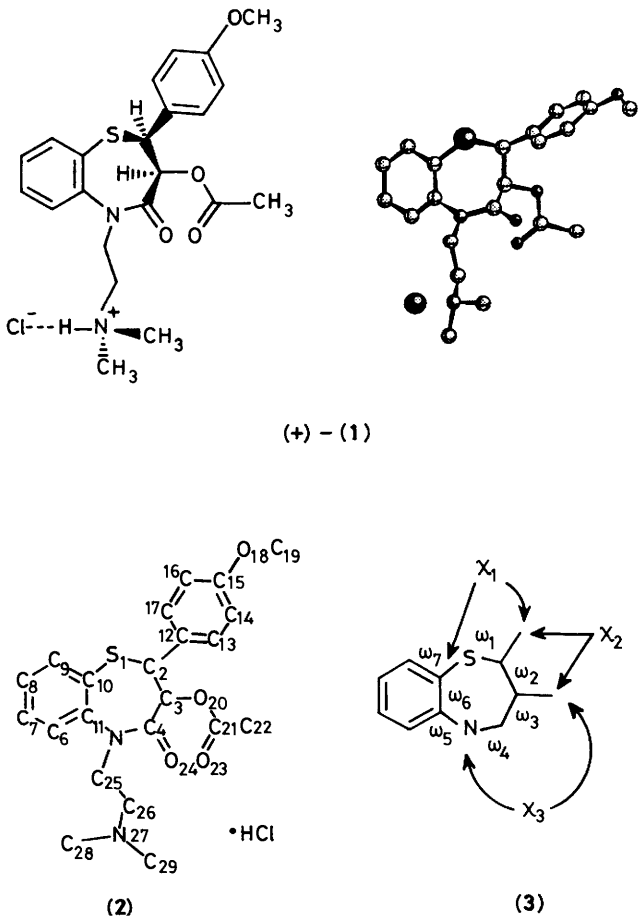


Figure 1. Structure of crystalline (+)-(**1**) (data from ref. 3).

Benzo-ring protons showed a vicinal coupling connectivity network of 7.73 ↔ 7.65 ↔ 7.42 ↔ 7.76 ppm based on 300 MHz spectrum $^3J_{HH}$ values and a COSY-90 2D-n.m.r.[7] correlation, $(CD_3)_2SO$ as solvent in both cases. Selective irradiation of H(25a) (4.14 ppm) afforded nuclear Overhauser effect (n.O.e.) enhancement for both the 7.73 ppm resonance [enabling the assignment of the H(6) terminus] and the geminal H(25b). Irradiation of H(25b), (4.43 ppm) provided an n.O.e. only for H(25a), and this suggests a side-chain conformational preference (see below).

Absorbances for (C=O)CH_3, and OCH_3 in the minor solution species were readily observed in both $(CD_3)_2SO$ and CD_2Cl_2, while that for NCH_3 was only seen in CD_2Cl_2.

Carbon-13 *N.M.R. Spectral Parameters.*—Multiplicities of ^{13}C resonances were determined by the DEPT-135[8] pulse sequence ($(CD_3)_2SO$ solvent). Assignments of protonated carbons *via* $^1J_{CH}$ were made by the HETCOR 2D-n.m.r.[5] correlation technique. Quaternary carbon resonances were assigned by $^3J_{CH}$ long-range HETCOR correlation to vicinal protons. The relative ordering of the C(6)–(11) chemical shifts were also consistent with those calculated using methylthio and acetamido substituent effects on ^{13}C resonances of mono-substituted benzenes.[9] Similarly, C(12)–(17) chemical shifts were also consistent with those calculated using methyl and methoxy substituent effects.[9] In $(CD_3)_2SO$ the two diastereotopic NCH_3 signals were coincidentally equivalent. Some minor-species ^{13}C signals were observed, but are unassigned with the exception of (C=O)CH_3 at 19.32 ppm.

Dynamic N.M.R. Spectroscopy and Conformational Analysis of the Two-solution Species.—Inspection of the chemical shift difference between corresponding methyl signals for the major and minor species shows that the (C=O)CH_3 group suffers the largest change in magnetic environment during the site-exchange process, Δδ 0.49 [(C=O)CH_3], *ca.* 0.06 [OCH_3], and *ca.* 0.01 ppm [NCH_3]. Variable-temperature proton-n.m.r. [300 MHz; $(CD_3)_2SO$] experiments showed dynamic behaviour. Line-shape analysis of the two (C=O)CH_3 singlets was performed on spectra recorded at four temperatures (297, 320,

Table 2. Proton-n.m.r. spectral parameters for (*P,S,S*)- and (*M,S,S*)-diastereoisomers of diltiazem hydrochloride (**1**), the propionyloxy analogue of (+)-diltiazem hydrochloride (**7**), ratio (*P,S,S*):(*M,S,S*) *ca.* 1:12 for both (**1**) and (**7**), and the *trans*-diastereoisomer (**9**).

δ_H	(*M,S,S*)-(**1**) [(*P,S,S*)-(**1**)][a]		(*M,S,S*)-(**7**) [(*P,S,S*)-(**7**)][a]	*trans*-(**9**)[a]	$J_{H,H}$	(*M,S,S*)-(**1**) [(*P,S,S*)-(**1**)][b]		(*M,S(S)*-**7**) [(*P,S,S*)-(**7**)][b]	*trans* (**9**)[b]
	$(CD_3)_2SO$	CD_2Cl_2	CD_2Cl_2	$CDCl_3$		$(CD_3)_2SO$	CD_2Cl_2	CD_2Cl_2	
H(2)	5.15 [c]	5.01 [d]	5.02 [e]	4.51	2,3	7.71(1) [4.6)]	7.72(6) [4.7]	7.75 (4)	11.0(1)
H(3)	4.99 [c]	5.10 [d]	5.11 [e]	5.02	6,7	7.8(3)[f]			
H(6)	7.73[f]	*g*	*g*	*g*	6,8	1.3(4)[f]			
H(7)	7.65[f]	*g*	*g*	*g*	7,8	7.7(3)[f]			
H(8)	7.42[f]	*g*	*g*	*g*	7,9	1.5(2)[f]			
H(9)	7.76[f]	*g*	*g*	*g*	8,9	7.8(3)[f]			
H(13)	7.38	7.37	7.37	7.01	13,14	8.77(2)	8.80(1)	8.85(7)	9.2(2)
H(14)	6.92	6.91	6.90	6.81	25a,25b	−13.7(3)	−13.56(5)	−13.56(6)	−13.9(2)
OCH_3	3.73 [3.67]	3.82 [3.77]	3.81 [3.76]	3.79	25a,26a	4.8(2)	4.91(6)	4.85(5)	5.3(2)
$(C{=}O)CH_3$	1.79 [1.30]	1.87 [1.38]	—	1.95	25a,26b	10.4(4)	10.28(9)	10.31(7)	10.1(1)
NCH (25a)	4.14	4.33	4.32	4.33	25b,26a	10.8(3)	10.55(6)	10.59(5)	10.6(2)
NCH (25b)	4.43	4.62	4.63	4.57	25b,26b	5.1(4)	5.47(8)	5.44(7)	5.1(1)
N^+CH (26a)	3.10	3.20	3.19	3.18	26a,26b	−13(1)	−12.4(1)	−12.31(8)	−12.6(2)
N^+CH (26b)	3.45	3.45	3.47	3.44	NH,26a	—	4.77	4.5	—
N^+CH_3 (a)	2.78[h]	2.87 [2.86]	2.87 [2.86]	2.88	NH,26b	—	5.69	5.93	—
N^+CH_3 (b)	2.78[h]	2.78 [2.78][i]	2.78 [2.78][i]	2.88	NH,CH_3(a)	—	4.88 [4.7]	4.86 [4.7]	—
N^+H (27)	11.3	13.0	12.5	—	$NHCH_3$(b)	—	4.89	4.87	—
$(C{=}O)CH$(a)	—	—	2.13 [1.58]	—	OCH(a), OCH(b)[j]	—	—	−16.7(1) [17.1(1)]	—
$(C{=}O)(CH$(b))	—	—	2.16 [1.69]	—	$OCH(a),CH_3$[j]	—	—	7.5(1) [7.6(1)]	—
$(C{=}O)CCH_3$	—	—	0.92 [0.61]	—	$OCH(a),CH_3$[j]	—	—	7.5(1) [7.6(1)]	—

[a] Downfield from $SiMe_4$, 200 MHz for (**1**) and (**7**) unless noted otherwise: [300 MHz for (**9**)], corresponding δ value for the minor species (*P,S,S*)-diastereoisomer given in square brackets; major:minor ratio *ca.* 12:1 for both (**1**) and (**7**). [b] Standard deviations (Hz) in parentheses; corresponding *J*-value for the minor-species (*P,S,S*)-diastereoisomer given in square brackets. [c] Two unassigned minor species H(2),(3) doublets at 5.26 and 5.24 ppm [d] Two unassigned minor species H(2),(3) doublets at 5.28 and 5.02 ppm [e] Two unassigned minor species H(2),(3) absorbances at *ca.* 5.32 and ca. 5.06 ppm. [f] From the corresponding 300 MHz spectrum. [g] Aromatic protons were not assigned. [h] Broadened singlet, two doublets seen upon addition of 4 drops concentrated trifluoroacetic acid. [i] According to the integration, minor *N*-methyl absorbance is hidden by that of the major species. [j] Coupling involving propionyloxy diastereotopic methylene proton(s) in (**7**).

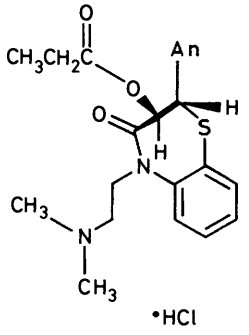
Table 3. Carbon-13 n.m.r. spectral parameters for the (*M,S,S*)-diltiazem hydrochloride (**1**) major species in $(CD_3)_2SO$.

Carbon	δ_C[a]	Coupling	*n*	$^nJ_{C,H}$[b]/Hz
C(2)	53.07	C(2)–H(2)	1	149.44(6)
C(3)	70.32	C(2)–H(3)	2	4.28(6)
C(4)	166.91	C(3)–H(2)	2	4.5(1)
C(6)	124.44	C(3)–H(3)	1	151.6(1)
C(7)	131.41	C(6)–H(6)	1	162.84(1)
C(8)	127.84	C(6)–H(8)	3	8.12(1)
C(9)	135.15	C(7)–H(7)	1	164.20(1)
C(10)	127.16	C(7)–H(9)	3	8.28(1)
C(11)	144.23	C(8)–H(6)	3	7.2(6)
C(12)	126.48	C(8)–H(8)	1	165.4(6)
C(13),(17)	130.61	C(9)–H(7)	3	7.7(5)
C(14),(16)	113.46	C(9)–H(9)	1	166.5(5)
C(15)	159.13	C(10)–H(6)	3	6.1(9)
C(19)	55.05	C(10)–H(8)	3	9.2(8)
C(21)	168.87	C(13)–H(2)	1	6.1(6)
C(22)	20.02	C(13)–H(13)	1	158.1(4)
C(25)	52.47	C(13)–H(17)	3	6.1(6)
C(26)	43.54	C(14)–H(13)	2	4.2(1)
C(27)	41.96[c]	C(14)–H(14)	1	159.5(1)
C(28)	41.96[c]	C(19)–CH_3	1	144.42(1)
		C(22)–CH_3	1	129.9(6)

[a] ppm downfield from $SiMe_4$, 50 MHz; minor (*P,S,S*)-species absorbances found at 168.24, 131.22, 129.34, 78.81, 44.36, and 19.32 ppm, major:minor ratio *ca.* 12:1 from the proton-n.m.r. spectrum. [b] Values in Hz (standard deviation given in parentheses) taken from proton-undecoupled spectrum. [c] Diastereotopic carbon atoms are coincidentally equivalent.

340, and 360 K) using the CLATUX program.[10,11] The mean of the four $\Delta G^{\ddagger}$ values for the diastereoisomerization process in the temperature range 297–360 K was found to be 17.2(1) kcal mol^{-1}. The enthalpy and entropy contributions were not calculated.

Molecular-mechanics-calculated structures were made using the 'MMX87'[12] program (an adaptation of Allinger's 'MM2'[13] program combined with 'MMP1'[14] π-subroutines) to provide models for various conformations of (+)-(2*S*,3*S*)-(**1**). In these models, a methyl group was used in place of the dimethylaminoethyl side-chain. Using the sign of the S(1)–C(2)–C(3)–C(4) torsion angle (ω_2) as descriptors, (*P,S,S*)-and (*M,S,S*)-diastereoisomers are formed by inversion of the heptagonal ring. In the ring-inversion process, the signs of all heptagonal-ring torsion angles are reversed. Ring inversion results in a reversal of the substituent orientation [*e.g.* the 4-methoxyphenyl and acetoxy groups on C(2),(3)]. For example, axial 2-(4-methoxyphenyl) and equatorial 3-acetoxy orientations in the crystalline twist-boat (*M*,2*S*,3*S*)-(**1**) are converted by ring-inversion into equatorial and axial orientations in the corresponding (*P,S,S*)-twist-boat diastereoisomer (see Figure 2). Three heptagonal-ring conformation families were considered: twist-boat (**4**), boat (**5**), and chair (**6**), and (*P*,2*S*,3*S*)- and (*M*,2*S*,3*S*)-diastereoisomeric models were calculated for each conformational type, see Table 1. The conformer definitions are based on similarities to the ideal torsion-angle values[15] also listed in Table 1. Similar heptagonal-ring geometries for both the crystalline twist-boat (*M*,2*S*,3*S*)-(**1**) molecule and the calculated (*M,S,S*)-(**4**) twist-boat model compound are implied by the tabulated data. In the series of six molecular-mechanics models, the (*M,S,S*)-(**4**) structure was calculated to be of lowest energy. Both chair-conformational models (**6**) were found to be of highest energy [*ca.* 7–9 kcal higher than (*M,S,S*)-(**4**)] of the series of six examples. In these two chair models (**6**), the ring-junction torsion angle S(1)–C(10)–C(11)–N(5) and the amide torsion angle C(3)–C(4)–N(5)–C(11) are both twisted *ca.* 10.9(9)° out of ideal planarity.

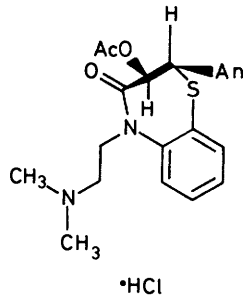


(7)

Pseudorotation barriers for the boat family of conformations (boat $\rightleftharpoons$ twist-boat) are considered to be very low in energy.[15] This pseudorotation process does not involve ring-inversion since the signs of all torsion angles remain invariant [*e.g.* compare the (*M*,*S*,*S*)-(**4**) and (*M*,*S*,*S*)-(**5**) models in Table 1]. Hence, the twist-boat (*P*,*S*,*S*)-(**4**) and boat (*P*,*S*,*S*)-(**5**) conformations, for example, are expected to be in rapid equilibrium. In both these (*P*,*S*,*S*)-boat-family conformations, the $(C{=}O)CH_3$ methyl protons are located almost directly above the centre of the benzo ring as a result of the axial-like acetoxy orientation, see Table 1 footnotes *e*–*g*. The relatively large 0.49 ppm shift upfield for $(C{=}O)CH_3$ methyl protons in the minor species suggests a [(*M*,*S*,*S*) $\rightleftharpoons$ (*P*,*S*,*S*)] diastereoisomerization mechanism involving a heptagonal-ring-inversion process between boat-family conformations. Such a process could involve [(*M*,*S*,*S*)-(**4**) $\rightleftharpoons$ (*P*,*S*,*S*)-(**5**)] (see Figure 2), based upon the molecular-mechanics energy differences listed in Table 1. The 0.88 kcal calculated energy difference is in very good accord with the *ca.* 12:1 equilibrium ratio noted for the two diastereoisomeric species in solution. In such a process, the minor-species $(C{=}O)CH_3$ methyl protons are expected to be fairly strongly shielded (relative to those in the major species) as they reside within the shielding cone of the anisotropic benzo-ring (see Figure 3). It is noted that the two substituents at C(2),(3) in the major-species are located in the less sterically hindered *exo* region of the 1,5-benzothiazepine-ring system while those in the minor species fall within the more hindered *endo* region.

The propionyloxy analogue (+)-(**7**) of (+)-diltiazem·HCl was examined to investigate further the existence of a minor species with a (*P*,*S*,*S*)-boat (twist-boat) conformation in solution. The ^1H n.m.r. spectrum (CD_2Cl_2) of (+)-(**7**) shows major and minor species in a ratio similar to that noted for (+)-(**1**). In the above hypothesis the propionyloxy methylene protons are also expected to reside directly above the benzo ring centre in (*P*,*S*,*S*)-boat (twist-boat) structures. Larger angular deviations [$\angle$(C*H*–*m*–*m*)] from the perpendicular line segment (*m*–*m*′) to the benzo ring centre (*m*) for the methyl protons should result in less efficient shielding, see Table 1 footnote *h* and Figure 4. As expected, greater shielding was observed for the minor-species propionyloxy methylene protons. The $(C{=}O)CH_2CH_3$ diastereotopic methylene protons in the minor species were shifted 0.55 and 0.47 ppm upfield from corresponding nuclei in the major species, while the minor-species $(C{=}O)CH_2CH_3$ methyl protons were shifted only 0.31 p.p.m. upfield from their major-species counterparts.

Altona and co-workers[16] have shown that relative orientations and electronegativities of X,Y-substituents in –CH(X)–CH(Y)– segments modified the Karplus[17] relationship between vicinal coupling constants and dihedral angles. Different vicinal $^3J_{H(2)H(3)}$ coupling constants were observed for the two solution-species. For example, in $(CD_3)_2SO$ the value was 7.7(1) Hz for the solution major-species, while a smaller, 4.6(1) Hz, value was observed for the minor-species. As noted before, the methoxyphenyl and acetoxy moieties are, respectively, axially and equatorially disposed in both calculated (*M*,*S*,*S*)-twist-boat-(**4**) and (*M*,*S*,*S*)-boat (**5**) major-species models. Using Altona's empirical generalization of the Karplus equation,[16] the respective $^3J_{H(2)H(3)}$ coupling constants for these two models are calculated to be 6.3 and 5.4 Hz. Similar calculations were performed for the corresponding (*P*,*S*,*S*)-twist-boat-(**4**) [$^3J_{H(2)H(3)}$ 3.3 Hz] and (*P*,*S*,*S*)-boat-(**5**), (1.4 Hz) minor-species models in which the methoxyphenyl and acetoxy moieties are now, respectively, equatorial and axial. The calculated values for the (*P*,*S*,*S*)-boat-family conformations are smaller than those for the (*M*,*S*,*S*)-models. The values for $^3J_{H(2)H(3)}$ observed for the major- and minor-species in solution are in reasonable accord with those calculated by Altona's general equation. More significantly, the trend of change is the same as that calculated.



(9)

The ^1H spectral parameters of the *trans*-analogue (**9**) of (±)-diltiazem hydrochloride are given in Table 2 for the purpose of comparison. As opposed to the *cis*-isomer (**1**), only one species is apparent in the ^1H n.m.r. spectrum of (**9**). The typical antiperiplanar 11.0(1) Hz value of $^3J_{H(2)H(3)}$ is consistent with either of the molecular-mechanics-calculated models twist-boat (*M*,*R*,*S*)-and (*P*,*S*,*R*)-(**10**) or boat (*M*,*R*,*S*)- and (*P*,*S*,*R*)-(**11**) (torsion angles defining the models are listed in Table 1). The antiperiplanar arrangement between H(2),(3) precludes the heptagonal-ring inverted (*M*,*S*,*R*)- and (*P*,*R*,*S*)-twist-boat (boat) models in which the two methine protons are diequatorially disposed. As in the case of the *cis*-isomers (**4**) and (**5**), the twist- boat *trans*-analogue was calculated to be lower in energy *vis-à-vis* the boat conformation. Again, using Altona's empirical generalization of the Karplus equation,[16] the respective $^3J_{H(2)H(3)}$ coupling constants for the two above-mentioned models (**10**) and (**11**) are calculated to be 10.1 and 10.7 Hz and thus are consistent with the experimental value.

Solution Conformation of the Side Chain.—The measurement of all four vicinal coupling constants in the dimethylene portion of the diltiazem hydrochloride side chain enables one to identify the major rotamer for the major solution species C(25)–C(26) bond. Inspection of Table 2 shows that H(25a) is coupled to H(26a) and H(26b) by *ca.* 4.9 and *ca.* 10.4 Hz vicinal coupling constants, respectively. These weighted time-averaged values suggest a synclinal (*gauche*) relationship between H(25a),(26a) and an antiperiplanar disposition between H(25a),(26b), based upon Karplus[17] relationships. A similar analysis for the other protons clearly suggests that the antiperiplanar rotamer (**12**) is the prime contributor to the time-averaged structure. Using averaged *gauche* and antiperiplanar coupling constants, the

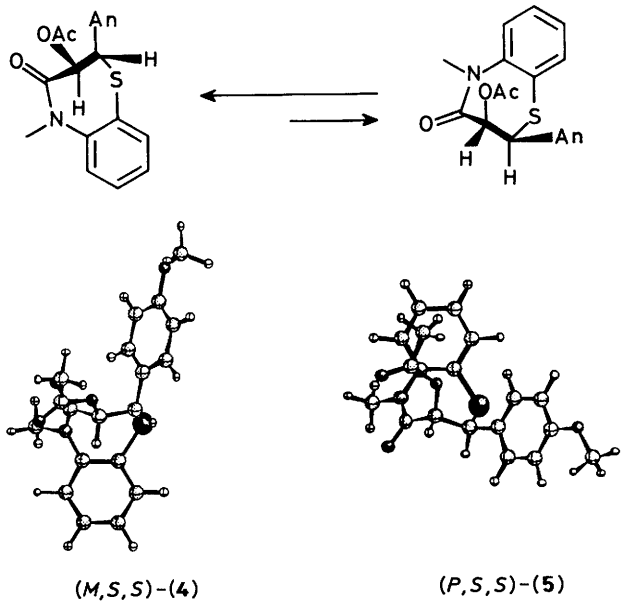
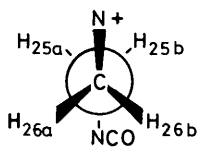
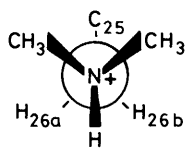


Figure 2. Interconversion of (*P*,2*S*,3*S*)- and (*M*,2*S*,3*S*)-diastereoisomeric conformations interchanges the axial and equatorial orientations of ring-substituents.

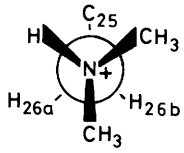
ratio between the antiperiplanar rotamer (**12**) and the two non-equivalent *gauche* conformations was estimated[18] to be *ca.* 4:1 [in both $(CD_3)_2SO$ and CD_2Cl_2]. The presence of the same major rotamer antiperiplanar-(**12**) was also found for side chain of the *trans*-analogue (**9**). While the conformation about the C(25)–C(26) bond for crystalline (*M*,*S*,*S*)-(**1**) is also antiperiplanar (**12**),[3] there is a difference in the C(26)–N^+ bond conformation in CD_2Cl_2 solution *vs.* the solid state. The magnitudes of the two similar but different $^3J_{NHH(26a)}$, $^3J_{NHH(26b)}$ coupling constants point to synclinal (*gauche*) dihedral angles between NH and *both* H(26a,b), *i.e.* a *gauche–gauche* conformation (**13**) in CD_2Cl_2, while the C(26)–N^+ conformation is antiperiplanar–*gauche*[3] (**14**) in crystalline (*M*,*S*,*S*)-(**1**).



(**12**)

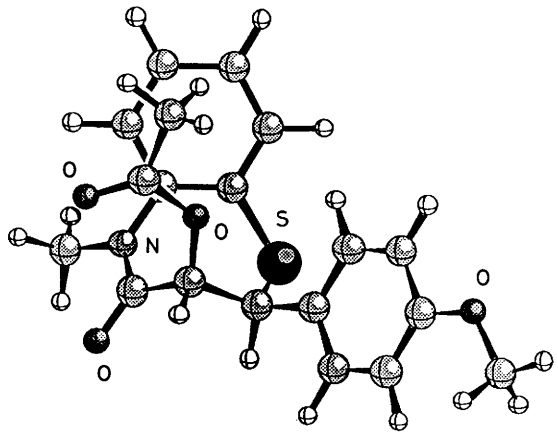


(**13**)

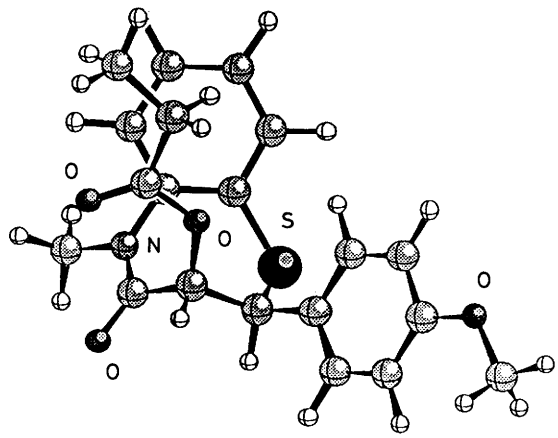


(**14**)

In conclusion, a comparison of n.m.r. spectroscopic parameters for both solution species of diltiazem hydrochloride shows that those for the major diastereoisomer are fully consistent with the (*M*,2*S*,3*S*)-twist-boat heptagonal-ring conformation noted in the solid state. Dissolution of crystalline



(*P*,*S*,*S*)-(**5**)



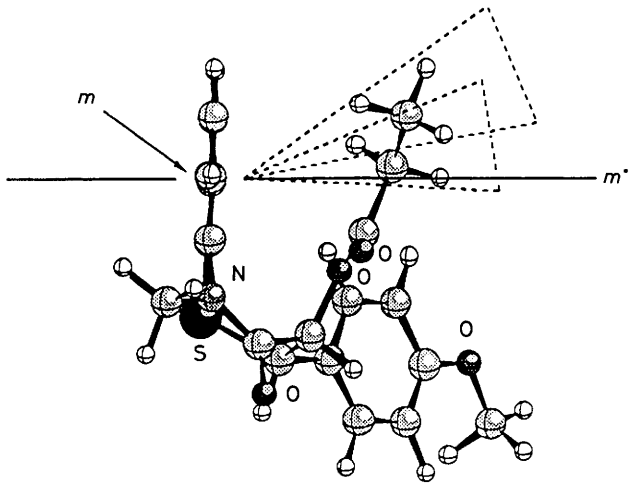
(*P*,*S*,*S*)-(**8**)

Figure 3. Calculated putative (*P*,2*S*,3*S*)-(**5**) and (*P*,2*S*,3*S*)-(**8**) models for the solution minor species showing the respective axially oriented acetoxy and propionyloxy groups above the benzo-ring.

diltiazem hydrochloride (+)-(**1**) results in diastereoisomerization to form a minor species the stereochemistry of which appears to be the 1,5-benzothiazepine-ring-inverted (*P*,2*S*,3*S*)-boat (twist-boat) analogue.

Experimental

(+)-Diltiazem hydrochloride (2,3-*cis*), its racemic 2,3-*trans* isomer, and the 3-propionyloxy-2,3-*cis* analogue were prepared by literature methods[19] and supplied by Abic Ltd. (Israel). N.m.r. spectra (4.7 T) were recorded at 200.1 (^{1}H) and 50.3 MHz (^{13}C) on a Bruker WP-200-SY Fourier-transform spectrometer. ^{1}H n.m.r. (7.05 T) and n.O.e. difference spectra were recorded at 300.1 MHz on a Bruker AM-300 Fourier-transform spectrometer. The broad-band proton-decoupling technique was utilized for routine ^{13}C n.m.r. spectra, with deuteriated solvent as an internal lock, and residual CH_2Cl_2 absorbances as internal secondary reference for CD_2Cl_2 or $SiMe_4$ as internal standard for $(CD_3)_2SO$ solutions. Line-shape analysis of dynamic n.m.r. spectra were performed on an Apple-III microcomputer using an adaptation[12] of the CLATUX program for n.m.r. lineshapes for classical two-site exchange.[11] Heterocorrelation[6] 2D-n.m.r. spectra utilizing $^1J_{CH}$ coupling were performed with Δ_1 and Δ_2 delays of 0.0037 and 0.0022 s,



(*P*,*S*,*S*)-(**8**)

Figure 4. Edge-on view through the benzo-ring of the (*P*,2*S*,3*S*)-(**8**) model showing smaller angular deviations [$\angle(CH\text{–}m\text{–}m')$] for the propionyloxy methylene protons relative to the *m*–*m'* perpendicular line segment through the benzo-ring centre, *vs.* larger values for the adjacent methyl protons.

respectively, and the corresponding values for long-range $^{n}J_{CH}$ coupling were 0.045 and 0.030s. Molecular-mechanics calculations were performed on a MicroVAX-II computer under MicroVMS V4.5 using the MMX87[13] program (an adaptation of Allinger's MM2[14] program incorporated with MMP1[15] π-subroutines for localized π-electron systems).

Acknowledgements

This article is dedicated to Professor Kurt Mislow (Princeton University) on the occasion of his retirement. The authors would like to express their thanks to Dr. Hugo Gottlieb (Bar-Ilan University) for recording ambient and variable temperature ^{1}H n.m.r. spectra at 7.05 T, and for stimulating discussions. Appreciation is also given to Dr. Michael A. Bernstein (Merck Frosst Canada Inc.) for enabling us to perform the long-range HETCOR and n.O.e. difference spectra at 7.05 T, and for warm hospitality extended to R. G. during summer 1988. Gratitude is also expressed to Prof. Daniel Kost (Ben Gurion University of the Negev) for providing the Apple III adaptation of Binsch's CLATUX Program for n.m.r. Lineshapes. Thanks are also given to the Kreitman Family Endowment Fund, Ben Gurion University of the Negev, for the purchase of a Bruker WP-200 FT n.m.r. spectrometer.

References

1 H. Inoue, S. Takeo, M. Kawazu, and H. Kugita, *Yakugaku Zasshi*, 1973, **93**, 729.
2 M. Windholz, ed., 'Merck Index,' 10th edn., Rahway NJ, 1983, p. 466 and references therein.
3 B. Kojić-Prodić, Z. Ruzić-Toros, V. Sunjić, E. Decorte, and F. Moimas, *Helv. Chim. Acta*, 1984, **67**, 916.
4 R. S. Cahn, C. Ingold, and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, 1966, **5**, 385.
5 (*a*) A. Bax, *J. Magn. Reson.*, 1983, **53**, 517; (*b*) A. Bax in 'Topics in Carbon-13 N.M.R. Spectroscopy,' ed. G. C. Levy, Wiley, New York, 1984, vol. 4, pp. 197–238.
6 (*a*) R. Glaser, S. Cohen, D. Donnell, and I. Agranat, *J. Pharm. Sci.*, 1986, **75**, 772; (*b*) R. Glaser, Q.-J. Peng, and A. S. Perlin, *J. Org. Chem.*, 1988, **53**, 2172.
7 A. Bax and R. Freeman, *J. Magn. Reson.*, 1981, **44**, 542.
8 D. M. Doddrell, D. T. Pegg, and M. R. Bendall, *J. Magn. Reson.* 1982, **48**, 323.
9 Atta-ur-Rahman, 'Nuclear Magnetic Resonance—Basic Principles,' Springer-Verlag, New York, 1986, pp. 156–161.
10 G. Binsch, *Top. Stereochem.*, 1968, *3*, 97.
11 D. Kost, CLATUX Program Adapted to an Apple-III Microcomputer,' personal communication.
12 MMX87, Serena Software Inc., Bloomington, Indiana.
13 (*a*) N. L. Allinger and Y. H. Yuh, *QCPE*, program No. 395; (*b*) N. L. Allinger, *J. Am. Chem. Soc.*, 1977, **99**, 8127.
14 N. L. Allinger and J. T. Sprague, *J. Am. Chem. Soc.*, 1973, **95**, 3893.
15 J. Dale, 'Stereochemistry and Conformational Analysis,' 'Universitetsforlaget–Verlag Chemie, Oslo–New York, 1978, pp. 191–195.
16 C. A. G. Haasnoot, F. A. A. M. de Leeuw, and C. Altona, *Tetrahedron*, 1980, **36**, 2783.
17 (*a*) M. Karplus, *J. Chem. Phys.*, 1959, **30**, 11; (*b*) *J. Am. Chem. Soc.*, 1963, **85**, 2870.
18 R. J. Abraham, L. J. Kricka, and A. Ledwith, *J. Chem. Soc., Perkin Trans. 2*, 1974, 1648.
19 (*a*) H. Kugita, H. Inoue, M. Ikezaki, M. Konda, and M. Takeo, *Chem. Pharm. Bull. (Tokyo)*, 1970, **18**, 2284; (*b*) *ibid.*, 1971, **19**, 595; (*c*) H. Kugita, H. Inoue, M. Ikezaki, and S. Takeo, *ibid.*, 1970, **18**, 2028.

Received 17*th October* 1988; *Paper* 8/02519C