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TETRAHEDRON

First Example of the Solvent Effect on Absolute Conformation of Chiral 3,3-Disubstituted 1,4-Benzodiazepin-2-ones

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Abstract: Chiral 3,3-disubstituted 1,4-benzodiazepin-2-ones (3*S*)-**7** and (3*S*)-**8** reveal solvent dependent conformational equilibria. The conformer with absolute *P*-conformation, with CH_2X (X= *p*-tosyl, Cl) group in a *pseudoaxial* (ψa) position and CH_2OAc group in a *pseudoequatorial* (ψe) position, prevails in nonpolar solvents, as shown by ^{1}H-NMR and CD spectra. For (3*S*)-**7** only a small shift of the conformational equilibrium in a polar solvent (DMSO) is observed, whereas compound (3*S*)-**8** inverts to a prevailing *M*-conformer. The inversion barrier for *M*/*P* equilibrium is estimated on the bases of TDNMR data. For compounds (3*R*)-**5** and (3*S*)-**7**, **8** the relative stability of the *M*/*P* conformers in the ground state is calculated by the MM2 method; comparison of these results with CD and ^{1}H-NMR data reveal that nonpolar solvents invert the relative stability calculated for the two conformers.

Keywords: Benzodiazepines, conformation, circular dichroism, NMR

INTRODUCTION

The solvent induced ring inversion in 1,4-benzodiazepines was observed for the first time for protonated 2,3-dihydro-1H-1,4-benzodiazepine (2*S*)-**1** by Buss *et al.*[1]. On the basis of the CD spectra the authors concluded that compound (2*S*)-**1** exists as a single *M*-conformer in the solvent mixture EtOH/MeOH, but inverts to a *P*-conformer in the solvent mixture THF/CH_2Cl_2. Conformational assignment (*M*/*P*) followed an earlier proposal;[2] it is worth noting that the same descriptor results if torsional angle (twist angle between C(5')-C(9') and C(5)-N(4) bond) is taken as the reference.[1] The authors explained the ring inversion in the nonpolar solvent mixture by the concerted effect of intramolecular hydrogen bonding between N^+-H and the carbonyl group of the side chain, and π–π stacking of the side chain aromatic ring to the phenyl ring at C(5). Both interactions are more effective in nonpolar than in polar solvents, and require a *pseudoaxial* (ψa) side chain, *i.e.* the inherently less stable conformational arrangement as shown by semiempirical PM3 calculations.[1]

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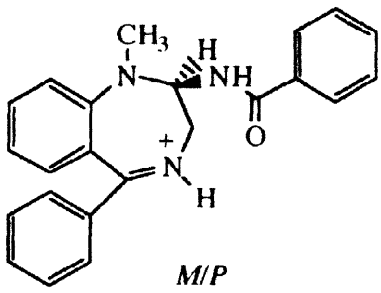
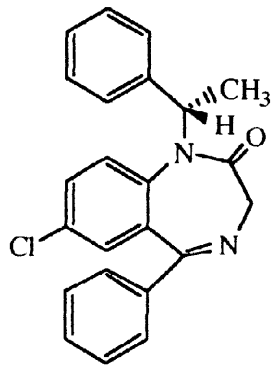


M/P

(2*S*)-**1** 100:0 (MeOH/EtOH)

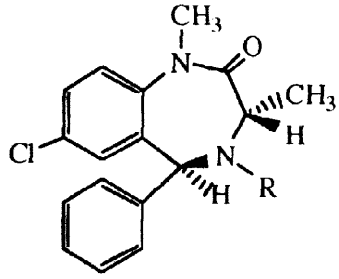
(ref. 1) 0:100 (THF/CH_2Cl_2)



M/P

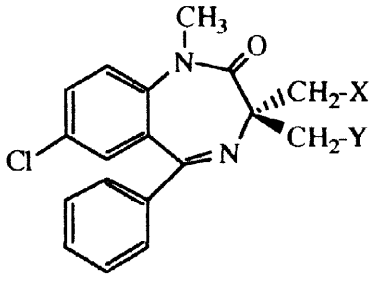
(1*S*)-**2** 45:55 ($CHCl_3$))

(ref. 3)



	R	*M/P* ($CHCl_3$)
(2*S*,3*S*)-**3**	H	100:0
(2*S*,3*S*)-**3a**	$CONH_2$	0:100

(ref. 4)



	X	Y	*M/P* ($CHCl_3$)
4	OH	OH	
(3*R*)-**5**	OH	$OCOCH_3$	0:100
6	$OCOCH_3$	$OCOCH_3$	
(3*S*)-**7**	O-*p*-Ts	$OCOCH_3$	15:85 32:68 (DMSO)
(3*S*)-**8**	Cl	$OCOCH_3$	30:70 70:30 (DMSO)

For centrochiral, 1-substituted 1,4-benzodiazepin-2-one (1'*S*)-**2** we observed at room temperature two diastereotopic conformations in equilibrium at ca 45:55 *P/M* ratio, governed by the (1'*S*) configuration of the chiral center in the side chain on N(1); only the *P*-conformer is present in the crystal, however.[3] Kajtar *et al.*,[4] reported, for optically pure 4,5-dihydro-1,4-benzodiazepines (3*S*,5*S*)-**3** and (3*S*,5*S*)-**3a**, that the substituent on the N(4) atom inverts the conformation from *P* in **3** to *M* in **3a**. The authors explained this inversion by strong repulsive interactions between the ureido group on N(4) and phenyl ring on C(5).

Continuing our studies of conformational effects on the enantioselectivity of enzyme catalyzed acetylation of 5-phenyl-3-hydroxyalkyl-1,4-benzodiazepin-2-ones in organic solvents,[5,6] we have prepared, starting from the prochiral 3,3-dihydroxymethyl derivative **4**, 3-acetoxymethyl-3-hydroxymethyl compound (-)-**5** in 90.2% enantiomeric excess (e.e.). By combining CD and ^{1}H-NMR data, the (3*R*) configuration was assigned to (-)-**5** in a strightforward way, and thus shows that immobilized lipase selectively acetylates the *pro-R* hydroxymethyl

group.[6] Herewith we report on enhanced conformational flexibility in 3,3-disubstituted 1,4-benzodiazepin-2-ones (-)-**7** and (+)-**8**, prepared from (-)-**5**, that leads to inversion of conformation of the later in polar solvents, as revealed by CD and ^{1}H-NMR spectroscopy. Experimental results are compared with those obtained by MM2 calculations, and some interesting discrepancies are observed. Compounds (-)-**7** and (+)-**8** discussed herewith are key intermediates in the original route to α-substituted α-amino acids and their congeners.

RESULTS AND DISCUSSION

NMR and CD study of conformational equilibrium. As indicated in the introductory section, only one conformer of 3-monosubstituted 1,4-benzodiazepin-2-ones is observed in solution.[2-4] According to the ^{1}H-NMR spectra, in $CHCl_3$-d_1 and DMSO-d_6, chiral 3,3-disubstituted derivative (-)-**5** is also present in only one and the same conformation in both solvents. For its derivatives (-)-**7** and (+)-**8**, however, solvent-dependent ^{1}H-NMR and CD spectra were observed indicating different position of equilibria between two diastereomorphic conformers. Generally, the ^{1}H-NMR signal for the *ψa* group at C(3) in 3-substituted 1,4-benzodiazepin-2-ones is shifted upfield in relation to thr *ψe* oriented group because of the strong shielding by the anistropic cone of the anellated benzene ring.[7] We therefore attempted to determine relative configuration, *i.e.* *ψa* vs. *ψe* position for the two groups in the 3,3-disubstituted chiral compounds (-)-**7** and (+)-**8** by comparison of the ^{1}H-NMR data (in $CHCl_3$-d_1) for prochiral **4** and **6**. Methylenic protons of the two CH_2OH groups in **4** are found at 3.93 ppm and 4.32 ppm, and of the two CH_2OAc groups in **6** are found at 3.80 and 4.65 ppm. Compound (-)-**7**, instead, exhibits methylenic signals for the single CH_2OAc group at 3.78 and 4.64 ppm, and for (+)-**8** the signals for the same protons appear at 3.41 and 4.23 ppm, respectively. Methylenic protons of the CH_2X group for (-)-**7** appear at 3.98 and 4.78 ppm, and for (+)-**8** at 3.83 and 4.70 ppm, Table 1, revealing an

Table 1. ^{1}H-NMR spectroscopic data for 1,4-benzodiazepin-2-ones 4-8 (in $CHCl_3$-d_1)

Compd.	X	Y	δCH_2X	δCH_2Y
4	OH	OH	3.48 (*ψa*)	4.37 (*ψe*)
(3*R*)-5[a]	OH	$OCOCH_3$	3.94 (*ψa*)	4.23 (*ψe*)
6	$OCOCH_3$	$OCOCH_3$	3.80 (*ψa*)	4.65 (*ψe*)
			3.98 (*ψa*)	4.64 (*ψe*)
3*S*)-7[a]	*p*-Ts	$OCOCH_3$	4.78 (*ψe*)	3.78 (*ψa*)
			3.83 (*ψa*)	4.23 (*ψe*)
(3*S*)-8[a]	Cl	$OCOCH_3$	4.70 (*ψe*)	3.39 (*ψa*)

a. (3*R*)-Configuration was established for (-)-5;[6] CIP descriptor of absolute configuration changes from (3*R*) to (3*S*) for (-)-7 and (+)-8, although they posses the same three dimensional arrangement of the substituents at C(3) atom as (-)-5.

equilibrium of two conformers in solution. The ratio, of the two conformers of **7** was estimated as 85:15, and for **8** as 68:32, but no data about their absolute conformation, *M* or *P*, can be deduced from the ^{1}H-NMR spectra. More electronegative chlorine and *p*-tosyl groups (X) shift CH_2X protons to higher field than that of CH_2OAc group, but they also shift the later ones, as indicated in the Table 1. Therefore the assignment (*ψa*, *ψe*) cannot be regarded as unequivocal without additional spectroscopic data. This information is obtained from the

CD spectra, allowing determination of the prevailing conformer in solution; in Fig. 1 are presented the CD spectra of (-)-**5**, (-)-**7**, and (+)-**8** in MeCN.

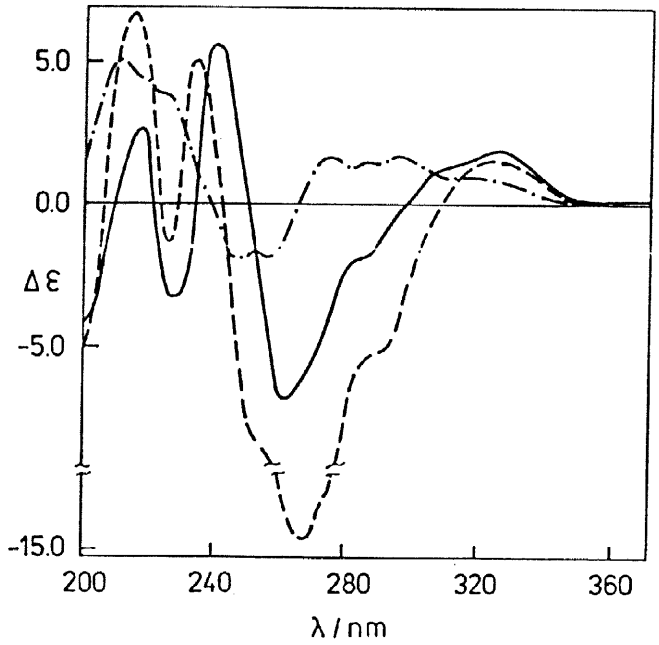


Figure 1. CD spectra of compounds (-)-**5** (--------), (-)- **7** (- - - -), (+)-**8** (- · - · - · -), in MeCN

From the strong negative Cotton effect (CE) for (-)-**5** at ca 260 nm, the prevailing *P*-conformer in solution can be unequivocally deduced.[2,4] By observing a model of the *P*-conformer of (-)-**5**, one can identify the position of the larger CH_2OAc group as ψe, and of CH_2OH group as ψa, in accord with the shifts in the NMR spectra; 4.23 ppm for CH_2OAc methylenic protons and 3.94 ppm for CH_2OH methylenic protons. Combining this data allows the (3*R*) absolute configuration to be assigned for (-)-**5**. The CD spectrum of the *p*-tosylate (-)-**7** also reveals that the 7-membered ring adopts the *P*-absolute conformation mainly, *i.e.* larger CH_2O-*p*-tosyl group is oriented in a ψa position. The CD spectrum of (+)-**8** differs from the CD of the other two congeners. Its general feature represents a relatively strong band at 250-280 nm, a less intense negative wing at 240-260 nm then a stronger one at ca 220 nm, indicating some distorsion of the benzodiazepine chromophoric system and an equilibrium of conformers. The position of the *M/P* equilibrium cannot be deduced from the CD spectra for any of these compounds. For (-)-**7** ^{1}H-NMR spectroscopy revealed a ratio of 15:85 in $CHCl_3$-d_1, which in DMSO-d_6 enhances to 32:68, with the *P*-conformer as the prevalent one. On heating (-)-**7** in the NMR tube to 50 °C in DMSO-d_6 the *M/P* ratio approaches 1:1, according to the known conformational rule that the ratio of the less stable conformer enhances with temperature.[8] These signals coalesce at 75 °C and became sharp singlets above 150 °C, where fast ring inversion takes place. Similarly, it can be concluded that (+)-**8** in $CHCl_3$ is prevalently present in the *P*-absolute conformation, *M/P* ratio is ca 30:70, but this conformation ratio changes to prevalently *M* (*M/P* 65:35) in the polar solvent DMSO.

Activation energies ($\Delta G^{\neq}$) for ring inversion of (-)-**7** and (+)-**8** can be calculated as 67.36 kJmol^{-1} and 68.62 kJmol^{-1}, respectively, and are close to the values for prochiral **4** (66.52 kJmol^{-1}) and **6** (70.29 kJmol^{-1}). A significant fragment of the temperature dependent NMR (TDNMR) spectrum of (+)-**8** is presented in Fig. 2.

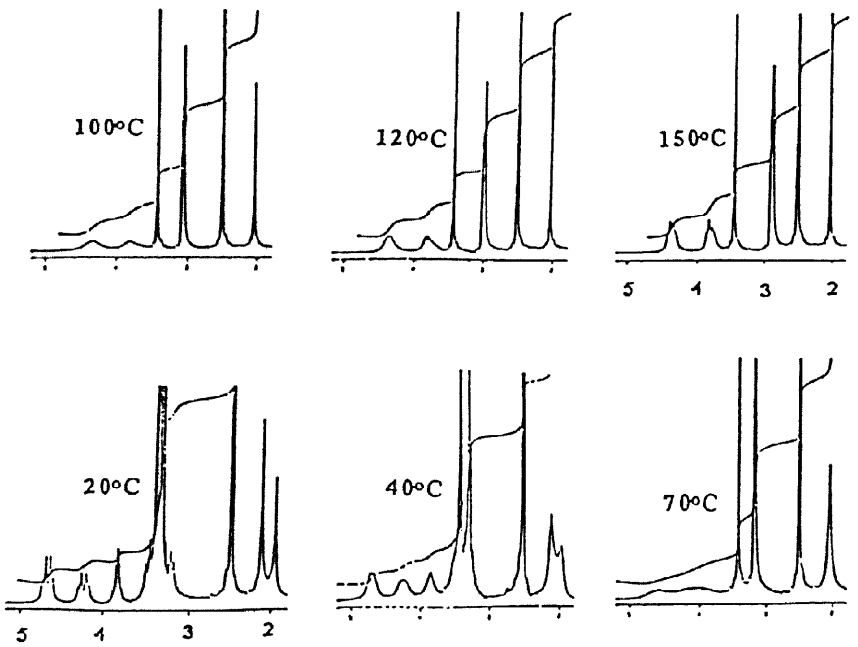


Figure 2. TDNMR Spectra of (+)-**8** in DMSO-d_6

TDNMR data reveal that the energy barrier for ring inversion of the prochiral and chiral 3,3-disubstituted 1,4-benzodiazepin-2-ones **4-8** is only 4-8 kJmol^{-1} lower than the C(3) unsubstituted congener ($\Delta G^{\neq}$ 73.64 kJmol^{-1}).[9] Relative stability of the ground states of two the conformers defines the position of the equilibrium for chiral derivatives; for prochiral ones, the two conformers are enantiomorphic. This data allows the reaction

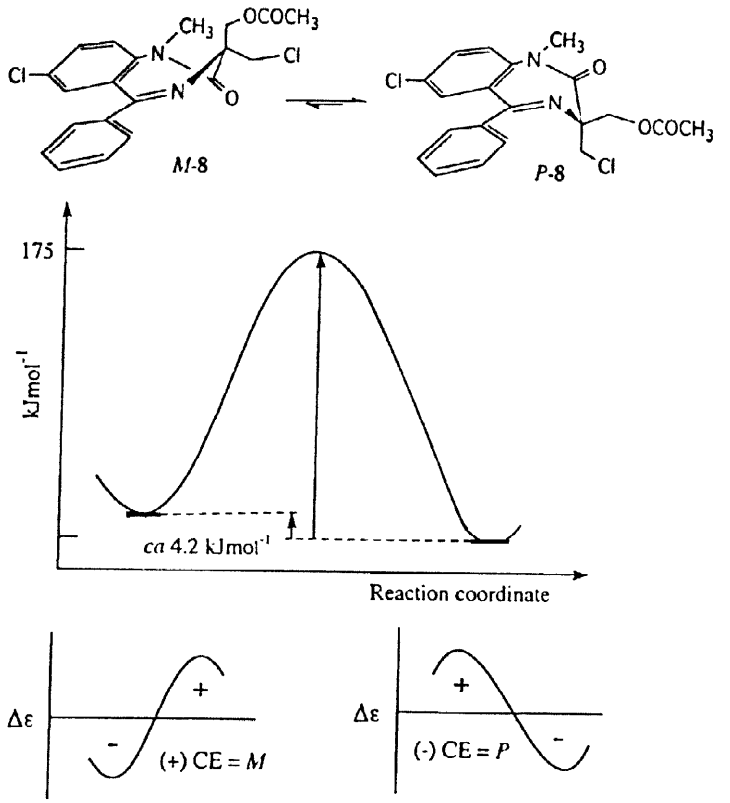


Figure 3. Reaction coordinate and conformational equilibrium *M*-**8** == *P*-**8**, in $CHCl_3$-d_1

coordinate diagram for the ring-inversion process of (3*S*)-**8** as in Fig. 3 to be constructed. On the NMR time-scale, inversion of the 3-substituted and 3,3-disubstituted derivatives of 1,4-benzodiazepin-2-ones proceeds at similar frequency; it is the position of equilibrium that distinguishes these two classes of compounds. In the former it is completely shifted to the ψe conformer, whereas in the later, in some cases, high ratio of the ψa conformer is present.

Solvent-dependent conformational equilibria observed in the NMR spectra of (+)-**8** in $CHCl_3$-d_1 and DMSO-d_6, are qualitatively reflected by the CD spectra in four solvents of different polarity, Fig. 4. After the inflection point at 312 nm, a positive band in nonpolar solvents changes to a very weak negative band in DMSO (at lower wavelength, transparency of all solvents but dioxane is low), confirming the shift of the equilibrium towards the *M*-conformer in the first three solvents and inversion to the prevailing *M*-conformer in DMSO.

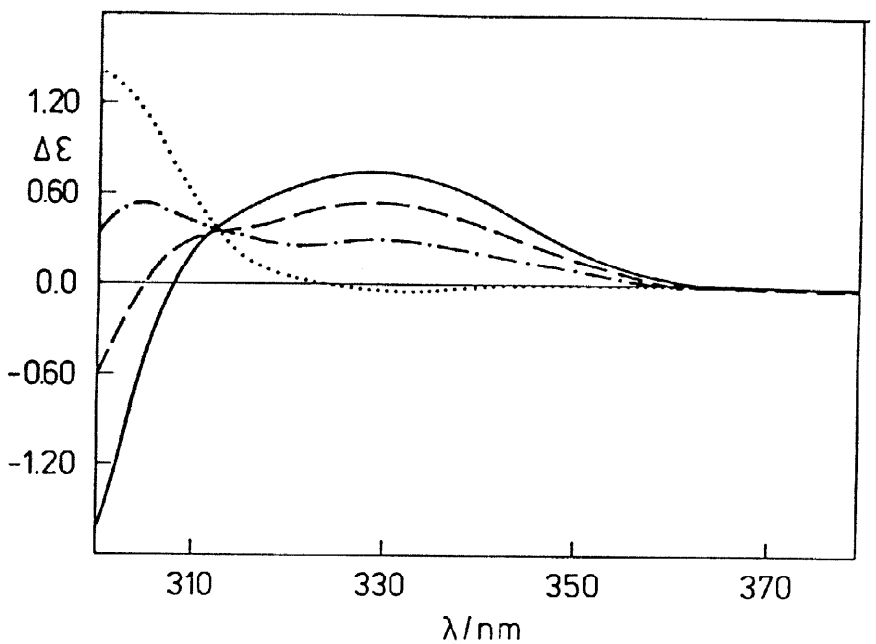


Figure 4. CD spectra (in the 300-350 nm region) of (+)-**8** in; dioxane , (--------), $CHCl_3$ (- - -), CH_2Cl_2 (- · - · - · -), and DMSO (.....).

In the addition to the spectroscopic data, conformational analysis, using molecular mechanics calculations, were performed for (3*R*)-**5**, (3*S*)-**7** and (3*S*)-**8** revealing the relative stability of *M*- and *P*-boat conformers. For each, *M*- and *P*- conformer, several conformational minima were found depend on the dihedral angles N(4)-C(3)-C(3')-X and N(4)-C(3)-C(3')-OAc. The global minima energies obtained for two conformations are presented in Table 2.

According to the total energy content, *M*-conformers, with CH_2X group in a ψe position are more stable than those with the same group in a ψa position, i.e. their relative stabilities are opposite to those found in nonpolar solvents. For (-)-**5**, stabilization of the *M*-conformer reaches the value of 13.8 $kJmol^{-1}$ and reflects hydrogen bonding between hydroxymethyl group and amide oxygen, Fig 5. However, when hydrogen bonding is not present the energy of the same conformer reaches the value of 96.6 $kJmol^{-1}$ which is higher than the total energy of the global minimum of the *P*-conformer. The total energy of the minima with in the *P*-conformer alter very little (4 $kJmol^{-1}$)

Table 2. Selected angles and total energy (Etot, in kJmol^{-1}) for two conformers of the compounds **5**, **7** and **8**

Compd.	Angle N(4)-C(3)-C(3')-X	Angle N(4)-C(3)-C(3')-OAc	E_{tot}	E_{tot} (M–P)
M-(3*R*)-**5**	58	−176	81.6	
				-13.8
P-(3*R*)-**5**	168	178	95.4	
M-3*S*)-**7**	−60	−177	105.0	
				-5.8
P-(3*S*)-**7**	49	179	110.9	
M-(3*S*)-**8**	−66	173	107.1	
				-5.4
P-(3*S*)-**8**	175	−55	112.5	

For (3*S*)-**7** and (3*S*)-**8** the energy difference in favour of the *M*-conformer diminishes to 5.8 kJmol^{-1} and 5.4 kJmol^{-1} respectively. Stabilization of *M*-**7** over *P*-**7** presumably rises from π–π interactions of the *p*-tosyl on C(3) and the 5-phenyl group. The overlap is not ideal but the average distance (3.5 Å) is within Waals contact distance.[10] Interaction of π–π type is less effective between the annelated ring and the *ψa* oriented *p*-tosyl group due to steric crowding. Replacement of the hydroxy group by a chlorine destroys hydrogen-bonding in (3*S*)-**8** and predominant stabilization of the *M*-conformer is no longer expected. Conformational analysis gave several energetically close minima for the both conformers ranging from 107-118 kJmol^{-1} for the *M*-conformer and 112-128 kJmol^{-1} for the *P*-conformer. The highest energy minima were obtained when the chlorine or acethoxy group entered the cone of the benzodiazepine ring. This overlap in energy minima obtained for the gaseous state reveals that external influence, like solvent, determines the favourable conformer.

Specific conformational mobility and sensitivity of (-)-**7** and (+)-**8** to the medium could be explained by the solvent effect on the repulsive interaction of the electronegative substituent within the anisotropic cone of the anellated aromatic ring when the CH_2X group is present in the *ψa* position. Since the solvent is involved in any conformational equilibrium, polar groups being only slightly solvated in nonpolar solvents seem "smaller" and therefore more easily present in *axial* position; in the solvent of high polarity, inversion of *P*- to *M*-conformers occurs.

In conclusion, we have presented the first example of a solvent dependent conformational equilibrium for chiral 3,3-disubstituted 1,4-benzodiazepin-2-one, and also rationalized the effect of the solvent. Compounds (3*S*)-**7** and (3*S*)-**8** in nonpolar solvents are prevalently in the *P*-absolute conformation, characterized by (-) CE band (couplet) at ca 260 nm. Consequently, their CH_2X roup is in the *ψe* position. ^{1}H-NMR spectra in the polar solvent (DMSO) reveal enhanced *M*/*P* ratio for (3*S*)-**7**; for (3*S*)-**8** it even inverts. The higher ratio of the *P*-conformer in less polar solvents can be explained by the stronger repulsive interaction of the *ψa* substituent within the anisotropic cone of the anellated ring, an effect which is not properly reflected in the MM2 calculations.

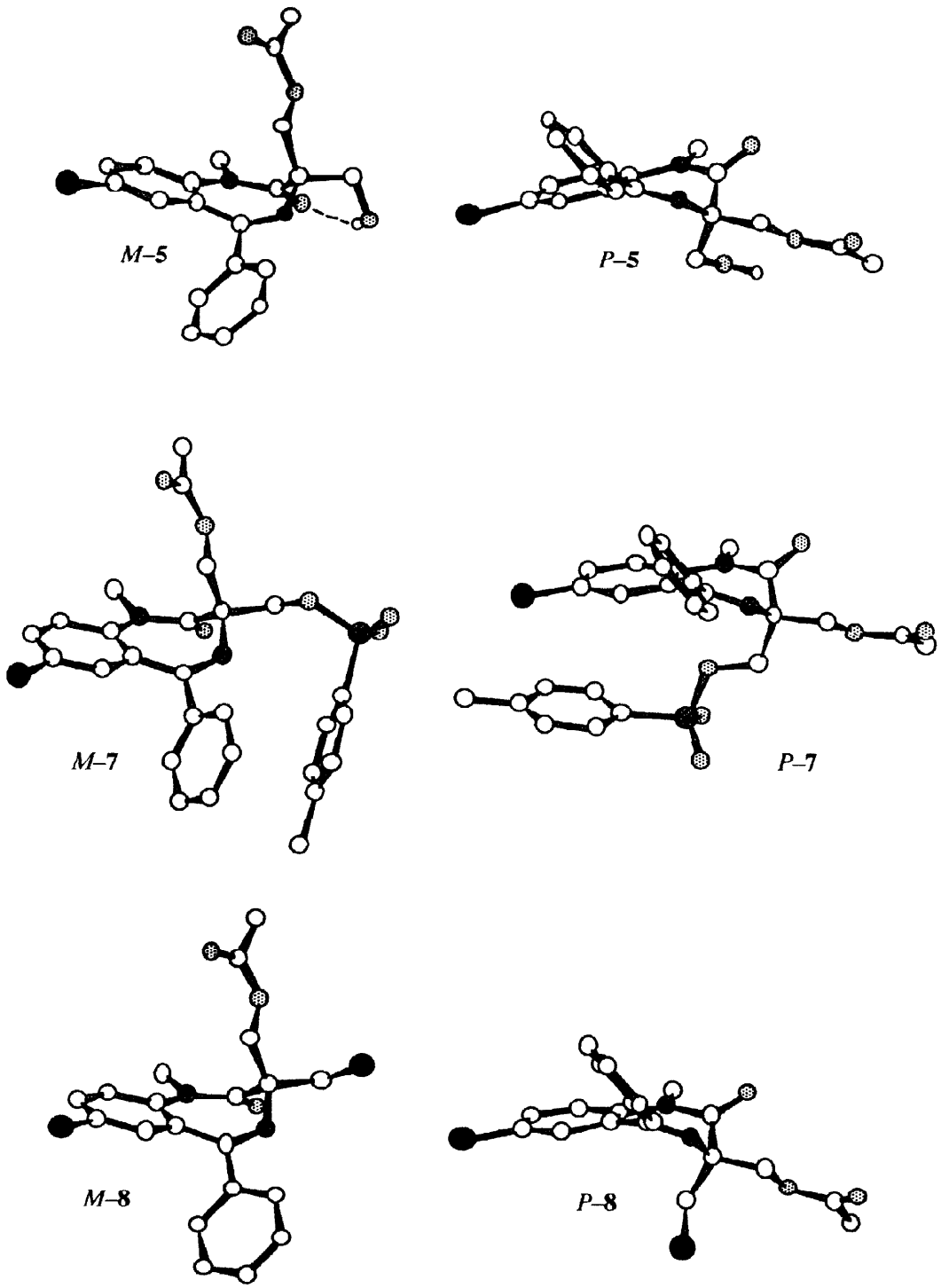


Figure 5. Ball and stick presentation of MM2 calculated minimum energy conformations of *M*-(3*R*)-**5**, *P*-(3*R*)-**5**, and of *M*-(3*S*)-**7**,**8** and *P*-(3*S*)-**7**,**8**.

EXPERIMENTAL

General remarks. ^{1}H- and ^{13}C-NMR spectra were recorded on Varian Gemini XL 300 spectrometer for $CDCl_3$ solutions, δ in ppm relative to TMS as internal reference, and *J* in Hz, IR spectra were recorded on Perkin Elmer 297 spectrometer for KBr pellets. Melting points were determined on Electrothermal Melting Point Apparatus and were not corrected. Optical rotations were measured on an Optical Activity AA-10 Automatic Polarimeter in a 1 dm cell; concentrations are given in g/100 ml. CD spectra were recorded on Jobin-Yvon instrument; calculated for 100% opt. purity. HPLC analyses were performed on HP 1050 chromatograph with C18 RP (Supelco, 250 x 4.6 mm) reverse phase column; separation was monitored by HP 1050 UV detector set up at 254 nm and connected to HP 3396A integrator. Chiral column Chiralcel OD (from Diacel Co.) was used in this work. During usual work-up all organic extracts were dried over Na_2SO_4 or $MgSO_4$ and evaporated *in vacuo* on a Büchi rotavapor. Preparation of 3,3-dihydroxymethyl-1,4-benzodiazepin-2-one, its kinetic resolution to (-)-**5** by the immobilized lipase Novozyme 435, and bis-acetylation to **6** are described in ref. 6.

(-)-3-Acetoxymethyl-5-phenyl-7-chloro-3-(tosyloxymethyl)-1-methyl-2,3-dihydro-1H-1,4-benzodiazepin-2-one ((-)-7). To the solution of (-)-**5** (0.38 g, 1.0 mmol) in pyridine (5.0 ml), stirred and cooled to 3 °C, was added over 1 h freshly crystallized *p*-TsCl (0.31 g, 1.6 mmol). Then reaction flask was deposited for 72 h in a refrigirator, and the reaction was followed by TLC using dichloromethane/EtOAc (9.0:1.0) as eluent. Water was added (10.0 ml), and the reaction mixture was extracted with dichloromethane (3x15 ml), organic extracts were washed with 10% aq. HCl (3x15 ml), then with saturated sodium bicarbonate solution (3x15 ml), and water (3x15 ml). Usual workup and chromatography on silicagel column with dichloromethane/EtOAc (9.0:1.0) as eluent afforded (-)-**7** (425 mg, 79.3%) as a crystalline solid, $[\alpha]_D$ -121.4 (c 0.85 in THF), mp. 89-92 °C. IR (KBr): 1710, 1630 (w), 1230, 1030, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.89 (s, 3H), 2.44 (s, 3H), 3.38 (s, 3H), 3.78 (d, J 11.5 Hz, 1H), 3.98 (d, J 11.3 Hz, 1H), 4.64 (d, J 10.0 Hz, 1H), 4.78 (d, J 10.0 Hz, 1H), 7.17-7.93 (m, 8H). ^{13}C-NMR ($CDCl_3$): 20.17, 21.37, 36.67, 56.94, 67.87, 72.27, 123.20, 128.14, 128.25, 128.37, 128.87, 129.01, 129.13, 129.45, 129.69, 129.75, 130.55, 131.01, 132.06, 138.41, 167.46, 168.66, 170.18. Anal. for $C_{27}H_{25}N_2SO_6Cl$ (541.01): Calcd.: C 59.94, H 4.66, N 5.18. Found: C 60.04, H 4.58, N 5.14.

(+)-3-Acetoxymethyl-5-phenyl-7-chloro-3-chloromethyl-1-methyl-2,3-dihydro-1H-1,4-benzodiazepin-2-one ((+)-8). Triphenylphosphine (0.45 g, 1.75 mmol) dissolved in dichloromethane (10.0 ml) was added in small portions over 15 min at 0 °C to hexachlorodimethylcarbonate (0.2 g, 0.67 mmol). After 30 min stirring the solution was evaporated to dryness and to the solid colourless residue was added a solution of compound (-)-**5** (0.61 g, 1.6 mmol) in dichloromethane (5.0 ml). Stirring was continued for 20 h at 45 °C. After usual workup, the crude product was purified by column chromatography with dichloromethane/acetone (9.0:1.0). Crystallization from n-hexane afforded (+)-**8** as colourless crystals (0.41 g, 64.3%), $[\alpha]_D$ +27.6 (c 1.7 in THF), m.p. 99-101 °C. IR (KBr): 3450 (broad, w), 1745, 1670, 1610 (w), 1220, 855, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.95 (s, 3H), 2.12 (s, 3H), 3.39 (dd, J 8.4 Hz, 2H), 3..41 (s, 3H), 3.83 (s, 2H), 4.23 (dd, J 10 Hz, 2H), 4.70 (dd, J 8.8 Hz, 2H). ^{13}C-NMR ($CDCl_3$): 20.40, 36.93, 50.37, 57.37, 66.07, 103.66, 123.16, 128.40, 129.55, 129.75, 130.64, 131.03, 132.07, 141.33, 167.44, 189.07, 194.48. Anal. for $C_{20}H_{18}N_2O_3Cl_2$ (405.28): Calcd.: C 59.27, H 4.48, N 6.91. Found: C 59.41, H 4.59, N 6.84.

MM2 Calculations were performed using ChemOffice Ultra 4.5, *CambridgeSoft Corp.*, Massachusetts (USA), Serial # 496311. The convergence criteria for the gradient of the potential energy surface (RMS gradient) was set to 0.1.

From the coalescence temperature T_c, determined by TDNMR, k_c and $\Delta G^{\neq}$ values for ring-inversion were calculated.[11]

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