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Dynamics of *p*-Menthan-3,9-diols. A Computational Study in Aqueous and Chloroform Solutions of Two Epimers

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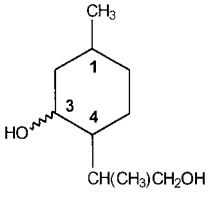
Abstract—The conformational preferences of *p*-menthan-3,9-diols in both aqueous and chloroform solutions have been investigated by molecular dynamics simulations. The effects of changing the stereochemistry at the C3 atom on the dynamics of these compounds have been studied by considering the two epimers. The results reveal a strong dependence of conformation on both the stereochemistry and the environment. In some cases the formation of an intramolecular hydrogen bond stabilises unusual conformations for the cyclohexane ring.

Introduction

The conformational preferences of substituted cyclohexane rings have long been the subject of both theoretical and experimental studies.[1] Most such studies have provided the free energy difference between equatorial and axial conformers allowing a measurement of the repulsive interaction between the substituent and the axial hydrogens when the former is in axial position. In the last years, conformational studies of cyclohexane rings bearing several bulky substituents have revealed the complex nature of the axial↔equatorial equilibrium in these compounds.[2,3] *p*-Menthan-3,9-diols are a particularly interesting family of trisubstituted cyclohexane rings. These compounds consist of a cyclohexane ring bearing methyl, hydroxyl and 1-methyl-2-hydroxy-ethyl substituents at C1, C3 and C4 carbon atoms (Scheme 1).

p-Menthan-3,9-diols are obtained from two terpenoids frequently used in the synthesis of natural products, called (−)-isopulegol and (+)-neo-isopulegol.[4] It should be emphasised that the two hydroxyl groups contained in the *p*-menthan-3,9-diols are close in the space conferring an amphiphilic character to this family of compounds. Recent studies on amphiphilic alkane-diols have pointed out their tendency to aggregate forming supramolecular systems.[5,6] For instance, bilayer-like structures have been observed for clusters of cyclohexane rings bearing two hydroxyl groups close in the space.[6]

In spite of their importance in both organic synthesis and structural chemistry, the conformational preferences of *p*-menthan-3,9-diols remain unknown. In this work we report a molecular dynamics (MD) study in both aqueous and chloroform solutions about the structure and flexibility of two epimers belonging to this family of compounds. These are the (1*R*:3*S*:4*S*:8*S*)-*p*-menthan-3,9-diol (**1**) and (1*R*:3*R*:4*S*:8*S*)-*p*-menthan-3,9-diol (**2**). It should be noted that the stereochemistry of the C3 atom may have a dramatic influence on the conformational behaviour of these compounds. The results appear useful to describe both the conformational preferences and dynamic fluctuations that might be expected for these molecules. Furthermore, the consequences of changing the stereochemistry at the C3 carbon atom are discussed.



Scheme 1. *p*-Menthan-3,9-diols.

Keywords: *p*-menthan-3,9-diol; trisubstituted cyclohexane ring; molecular dynamics study.

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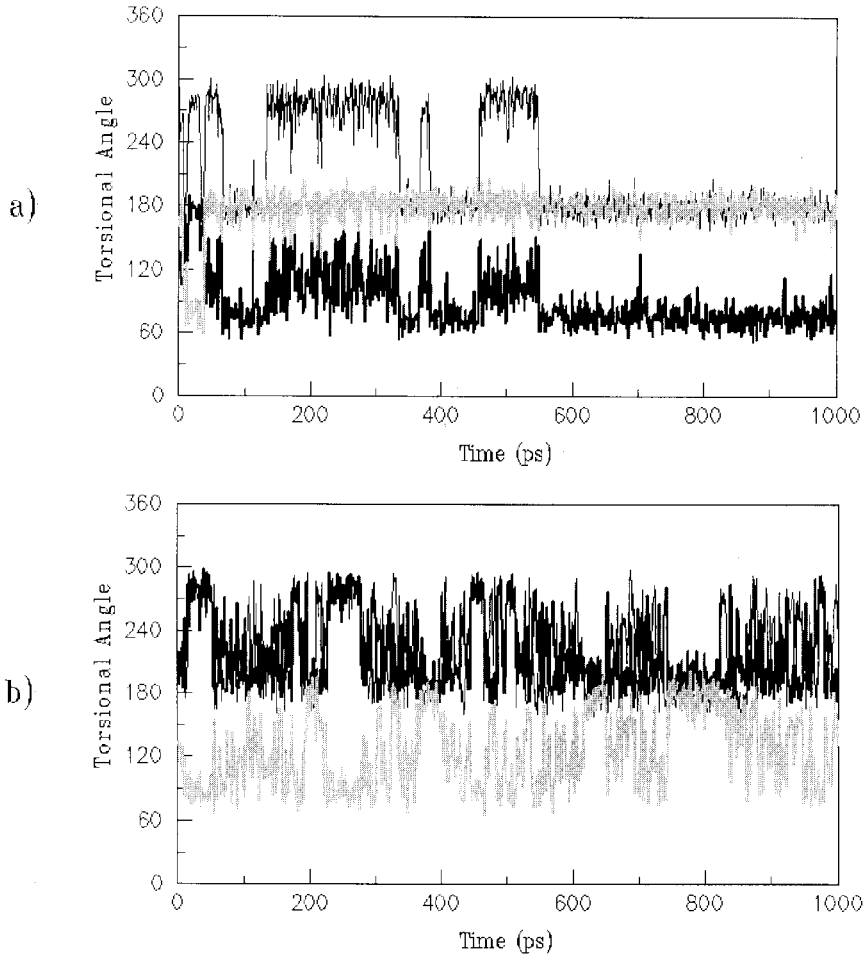


Figure 1. Trajectory plots of the torsional angles C1–C2–C3–O (thick dark line), C2–C3–C4–C8 (thick grey line) and C5–C6–C1–C7 (thin dark line) as observed for **1** (a) and **2** (b) from MD simulations in aqueous solution.

Methods

Energy minimisation and molecular dynamics simulations were carried out using the program package AMBER 4.0.[7,8] The energy of a molecule is described by simple potential energy functions comprising stretch, bend, torsional, van der Waals and electrostatic interactions. The force-field parameters that were used in this work were taken from a previous study,[9] in which the *p*-menthan-3,9-diols were parameterised explicitly using quantum mechanical calculations. The initial geometries of **1** and **2** were obtained by energy minimisation in the gas-phase.[9]

The molecules were placed in the centre of equilibrated boxes of water and chloroform molecules having a density of 1.00 and 1.48 g/mL, respectively. The solvent molecules that overlapped the *p*-menthan-3,9-diols were discarded. The resulting systems had dimensions of 17.17×16.11×15.24 $Å^3$ and 25.60×25.60×25.60 $Å^3$, and contained 121 water molecules and 125 chloroform molecules, respectively. The water molecules were described by the TIP3 model[10] whereas the OPLS model was used for the chloroform molecules.[11] Periodic boundary conditions were applied using the nearest image convention. We updated the list of nonbonding interactions every 25 steps, and imposed an 8 Å cutoff for these interactions. Accordingly, the simulation boxes are large enough to mimic a dilute solution. The SHAKE algorithm[12] was used to constrain bond lengths of the solvent molecules to their equilibrium values.

After initial energy minimisation of the whole system, the MD simulations were begun with initial velocities set to zero. The systems were coupled to a thermal bath using the algorithm developed by Berendsen et al.[13] which applied a velocity scaling at each step. The system was heated to 300 K in 25 ps using a temperature coupling parameter of 0.2 ps in a constant volume simulation. The time step was 0.001 ps, and the coordinates were stored every 1000 steps. Each simulation was run for a total of 1000 ps after 25 ps of equilibration. However, in order ensure that the simulations are long enough, a MD of 4000 ps was run for **1** in aqueous solution. The results were almost identical to those discussed below indicating that the configurational space of small solutes, like those studied in the present work, can be correctly sampled by trajectories of 1000 ps. Furthermore, pilot simulations of 500 ps were performed for **1** considering solvent boxes larger than those described above, i.e. increasing the number of solvent molecules. No significant change was obtained in

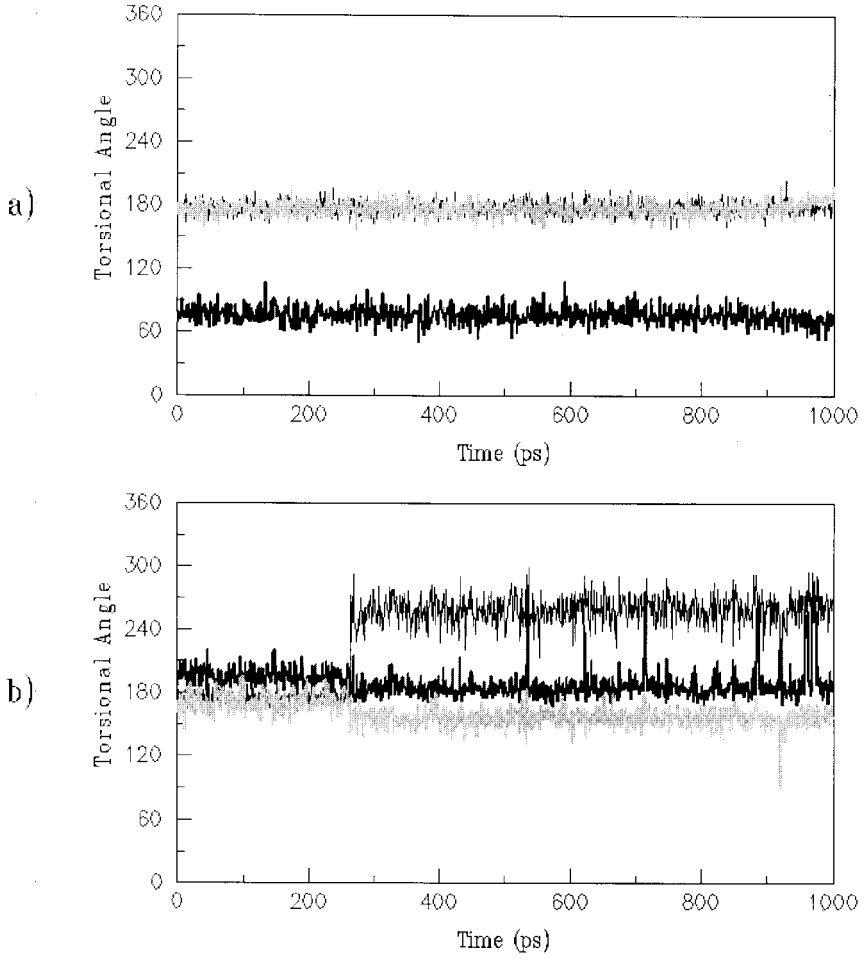


Figure 2. Trajectory plots of the torsional angles C1–C2–C3–O (thick dark line), C2–C3–C4–C8 (thick grey line) and C5–C6–C1–C7 (thin dark line) as observed for **1** (a) and **2** (b) from MD simulations in chloroform solution.

the results indicating that the dimensions selected for the present simulations are right.

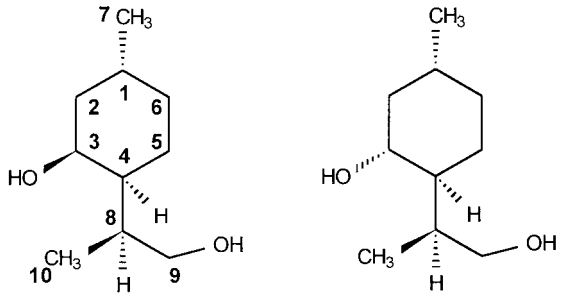
Results and Discussion

Conformation of the cyclohexane ring

Figs. 1 and 2 represent the variation with time of the torsional angles C1–C2–C3–O, C2–C3–C4–C8 and C5–C6–C1–C7 obtained during the MD simulations performed in water and chloroform, respectively. As can be seen, the two compounds present a larger conformational flexibility in water than in chloroform.

In compound **1** the substituents attached to C3 and C4 are *cis* to one another, both of them being *trans* with respect to the methyl group attached to C1 (Scheme 2). According to this, the most favoured conformation for **1** in water corresponds to a chair conformation in which the methyl and 1-methyl-2-hydroxy-ethyl substituents are in equatorial position whereas the hydroxyl substituent remains in an axial position. It is worth noting that the ring evolves occasionally towards a twist conformation in which the substituents attached to C3 and C4 present an equatorial position. This twist conformation remains stable short periods of time.

Simulations in chloroform solution (Fig. 2a) predict a chair conformation, identical to that observed in water, as the most stable in the organic solution. However, the most important feature exhibited by Fig. 2a is the absence of conformational transitions. Thus, the chair conformation, which is displayed in Fig. 3, remains stable throughout the simulation. We have performed MD simulations in both water and chloroform of the second chair conformation



1 **2**

Scheme 2.

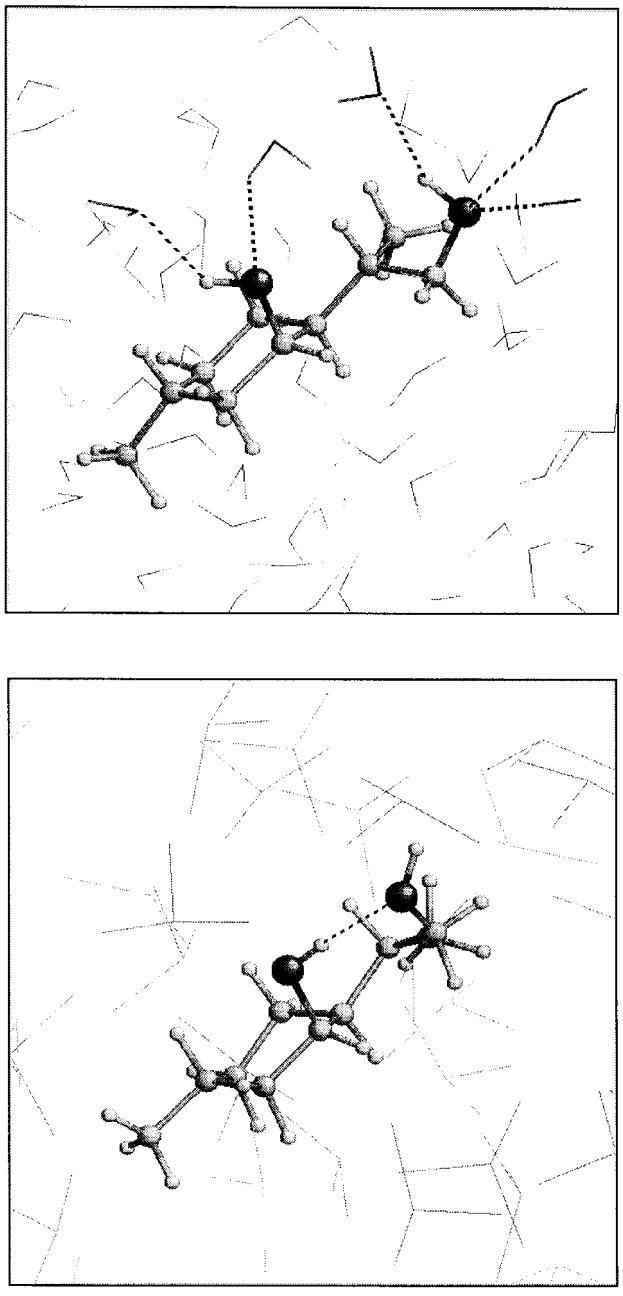


Figure 3. View of the chair conformation obtained for **1** in aqueous (top) and chloroform (bottom) solutions. Intermolecular hydrogen bonding interactions between the hydroxyl groups of the solute and the water solvent molecules are indicated by dashed lines.

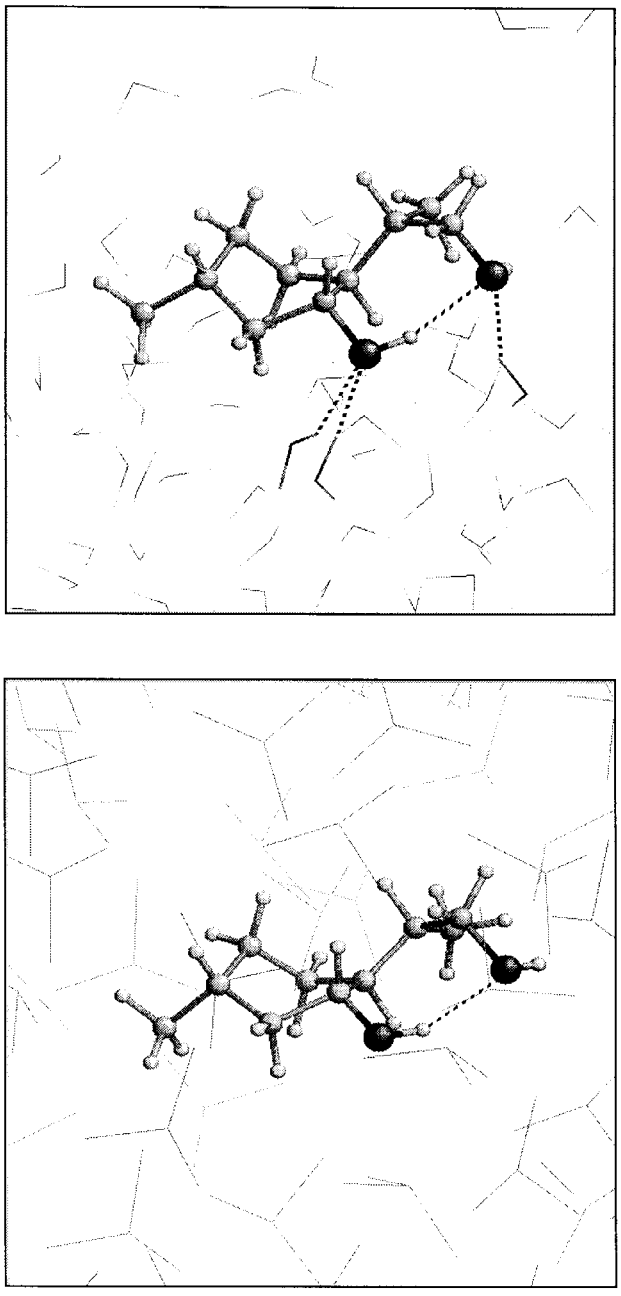


Figure 4. View of the most stable conformation obtained for **2** in aqueous (top) and chloroform (bottom) solutions. Intermolecular hydrogen bonding interactions between the hydroxyl groups of the solute and the water solvent molecules and the intramolecular hydrogen bond between the two hydroxyl groups are indicated by dashed lines.

for **1**, i.e. that with the methyl and 1-methyl-2-hydroxyethyl substituents in the axial positions. An analysis of the energies (data not shown) points out that the conformation displayed in Fig. 3 is several kcal/mol more stable than the latter, as it was expected.

In compound **2** the three substituents of the cyclohexane ring are all either axial or equatorial depending on the conformation of the ring (Scheme 2). Fig. 1b indicates that in aqueous solution a twist conformation with the three substituents in axial position is the most populated one. This twist becomes into a chair conformation at intervals of about 50–100 ps. However, the latter conformation transforms again into the former one in a few picoseconds. This is a surprising result since a chair conformation with the three substituents in equatorial position was expected as the most stable. However, a similar anomalous conformational behaviour has been also found in sterically crowded all-*trans*-alkylcyclohexanes.[14] In this case the stabilisation of the axial position is also encouraged by the formation of an intramolecular hydrogen bond. A detailed inspection of Fig. 1b shows fast and frequent conformational changes between the conformations, i.e. twist and chair, with the substituents in axial position and the chair conformation with the three substituents in equatorial position. Thus, a

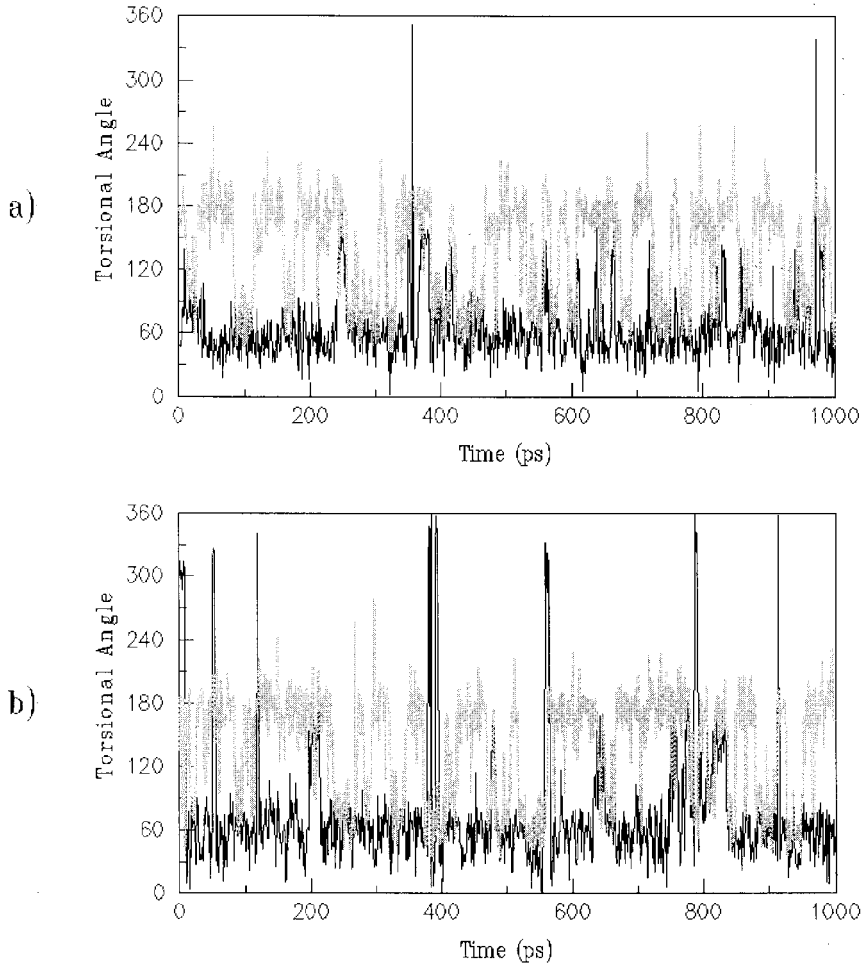


Figure 5. Trajectory plots of the torsional angles C3–C4–C8–C9 (dark line) and C4–C8–C9–O (grey line) as observed for **1** (a) and **2** (b) from MD simulations in aqueous solution.

large number of visits to the latter conformation is detected although the time that the molecule spends in it is very small.

A different conformational behaviour is obtained in chloroform solution. In this case, the ring moves towards a twist conformation in which the methyl is in axial position whereas the hydroxyl and 1-methyl-2-hydroxy-ethyl are in equatorial position. This twist conformation remains stable along all the simulation. The same conformation is reached when the simulation starts from a chair with the three substituents in axial position. Since the intramolecular hydrogen bond can be formed in both the chair and twist conformations, the high stability of the latter conformation has been entirely associated to the solvent effects. Fig. 4 shows a snapshot with the most stable conformation of **2** in water and chloroform, respectively.

Conformation of the substituents

The dihedral angles C3–C4–C8–C9 and C4–C8–C9–O have been used to describe the conformational preferences of the 1-methyl-2-hydroxy-ethyl substituent. The evolution of these parameters with the simulation time in water and chloroform is displayed in Figs. 5 and 6, respectively. As can be seen, the conformational preferences of the dihedral angle C3–C4–C8–C9 are very similar for the two epimers in the two solvents. Thus, the *gauche*$^+$ is the predominant conformation, which avoids steric clashes between the 1-methyl-2-hydroxy-ethyl substituent and the cyclohexane ring.

On the other hand, the dihedral angle C4–C8–C9–O can adopt different conformations depending on both the solvent and the compound. Thus, the conformational preferences of this parameter are led by the formation of hydrogen bonding interactions which can be either intra or intermolecular in water and only intramolecular in chloroform. The different conformational transitions detected along the simulations are in all cases related with changes in the hydrogen bonding patterns.

The analysis of the hydroxyl group shows a very different behavior depending on the solvent. Figs. 7 and 8 display the trajectory of the dihedral angles C2–C3–O–H and C8–C9–O–H in water and chloroform, respectively. It can be seen that in water such dihedral angles show a large conformational flexibility for the two compounds. This flexibility is related with the continuous formation and breaking of both intra and intermolecular hydrogen bonds. A very different behaviour is obtained in chloroform solution since in this case hydrogen bonds between the solute and the solvent are

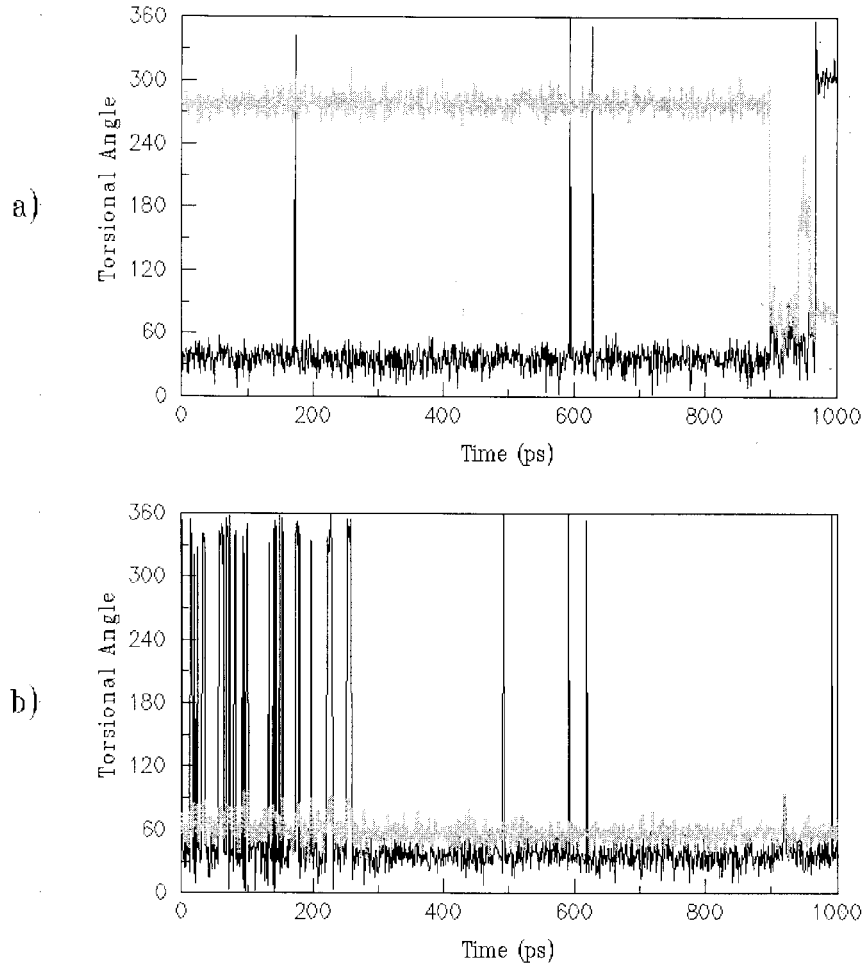


Figure 6. Trajectory plots of the torsional angles C3–C4–C8–C9 (dark line) and C4–C8–C9–O (grey line) as observed for **1** (a) and **2** (b) from MD simulations in aqueous solution.

not possible. Accordingly, clear conformational preferences are displayed by the two dihedral angles, which are related to the intramolecular hydrogen bond between the two hydroxyl groups.

The predominant conformation for C2–C3–O–H corresponds to the *trans* for the two compounds whereas the most populated conformer for C8–C9–O–H is the *skew*$^-$ and *gauche*$^+$ for **1** and **2**, respectively. This difference depends obviously on the stereochemistry at C3. It is interesting to note that a conformational transition occurs for **1** at the last steps of the simulation. Thus, the dihedral angle C8–C9–O–H changes from *skew*$^-$ to *gauche*$^+$. Similarly, for **2** there is a conformational transition around 200 ps in which the diehdral angle C8–C9–O–H changes from *gauche*$^+$ to *gauche*$^-$. Both transitions are related with a swap in hydrogen bonding pattern. Thus, the two hydroxyl groups interchange their donor and acceptor roles.

Comparison of the MD results with those obtained previously from a systematic conformational search using energy minimisation methods[9] reveals a reasonable agreement. Thus, similar conformations were predicted for the cyclohexane ring by both MD and energy minimisation. The lowest energy minimum of **1** was the chair conformation, whereas almost identical energies were predicted for the chair and twist conformations of **2**. Nevertheless, conformational studies based on energy minimisation methods present a serious drawback. This is that both thermal effects and entropic contributions are usually not considered, and therefore the conformational flexibility is systematically underestimated. Accordingly, our previous study on **1** and **2** was not able to predict the large conformational flexibility of the substituents.[9] This means that many of the conformers obtained along MD simulations were not characterised as minimum energy conformations.

Intramolecular hydrogen bond

The hydrogen bond between the two hydroxyl groups was assumed if the OH···H distance is smaller than 2.5 Å. Table 1 lists the maximum life-time for this interaction (τ_{hb}) and the maximum time without forming it (τ_{free}). As can be seen the two compounds show a common behaviour in chloroform, the intramolecular hydrogen bond being present throughout the simulation. A different situation appears in aqueous solution where only one of the compounds displays the intramolecular hydrogen bond. Thus, the hydroxyl groups of **1** only form hydrogen bonds with the solvent, being able to act as either donors or acceptors. Conversely, **2** presents both intra and intermolecular hydrogen bonds. It is worth noting that in this case τ_{hb} does not exceed a few

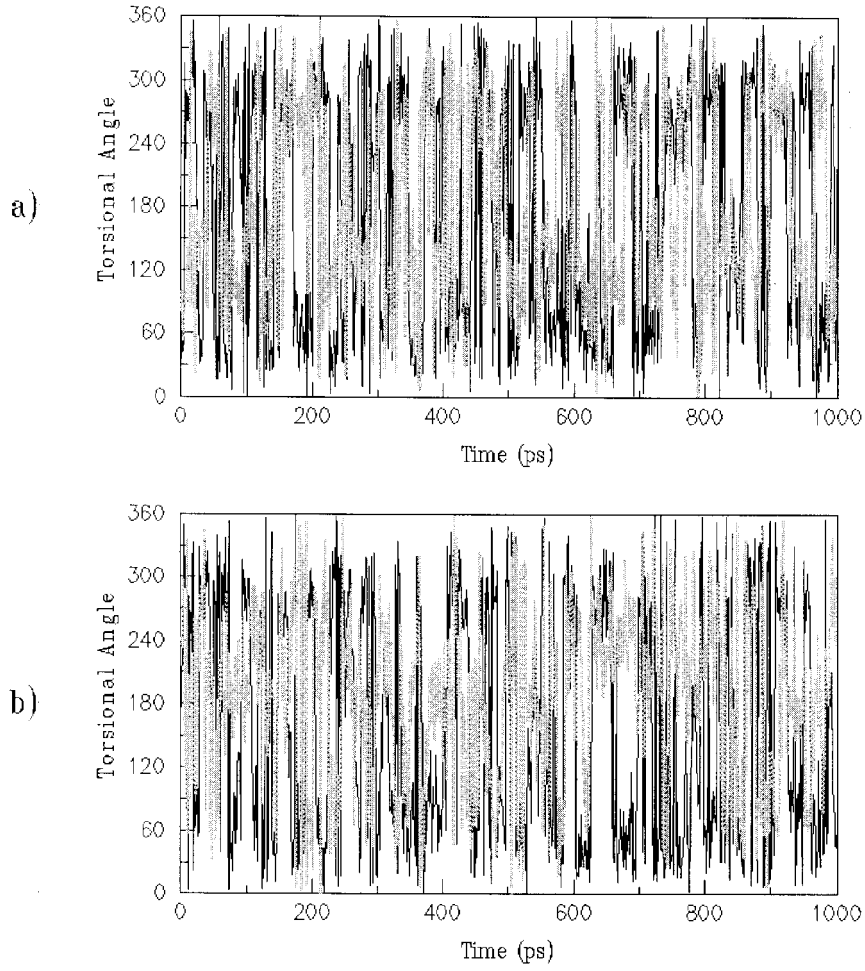


Figure 7. Trajectory plots of the torsional angles C8–C9–O–H (dark line) and C2–C3–O–H (grey line) as observed for **1** (a) and **2** (b) from MD simulations in aqueous solution.

tenth picoseconds. Furthermore, the most frequent hydrogen bonding pattern corresponds to C3–OH···O–C9 indicating that the hydroxyl group attached to C3 prefers to act as a donor. According to these results, it can be concluded that the formation of the intramolecular hydrogen bond depends on the solvent, displaying very long life-times in chloroform. Conversely, in water there is a competition with the solvent molecules and its existence depends on the stereochemistry of the compound.

In the course of a detailed experimental study about the structure of *p*-menthan-3,9-diols, the existence of an intramolecular hydrogen bond in **1** and **2** was investigated by ^{1}H NMR spectroscopy.[15] Spectra of both compounds in deuterated chloroform exhibited an intramolecular interaction involving the hydroxyl groups. For **2** the signal associated to such interaction remains unaltered upon the addition of water indicating that the hydrogen bond is stable in both polar and non-polar environments. A very different behaviour was observed for **1** after adding the polar solvent. Thus, in this case it was hard to detect the signal due to the fast exchange with the water molecules. These experimental results, which will be included in a forthcoming paper,[16] concur with the MD predictions described in this work.

Conclusions

MD simulations in both aqueous and chloroform solutions were performed for two epimers belonging to the family of *p*-menthan-3,9-diols. These are the (1*R*:3*S*:4*S*:8*S*)-*p*-menthan-3,9-diol (**1**) and (1*R*:3*R*:4*S*:8*S*)-*p*-menthan-3,9-diol (**2**), which are constituted by a trisubstituted cyclohexane ring with two hydroxyl groups close in the space. The results indicate that the stereochemistry and the nature of the solvent seem to have a strong influence on the conformational preferences of both the cyclohexane ring and the substituents. A chair conformation with the substituents attached to C1 and C4 in equatorial position and the substituent at C3 in axial position was obtained for **1** as the most stable in water and chloroform. On the other hand, the most populated structure of **2** in aqueous solution corresponds to a twist conformation with the three susbstituents in axial position. This conformation is stabilised by the formation of an intramolecular hydrogen bond between the two hydroxyl groups. In chloroform solution an evolution towards another twist conformation is observed. This conformation remains stable along all the simulation by the favourable interactions with the solvent molecules.

Regarding to conformational preferences of the substituents,

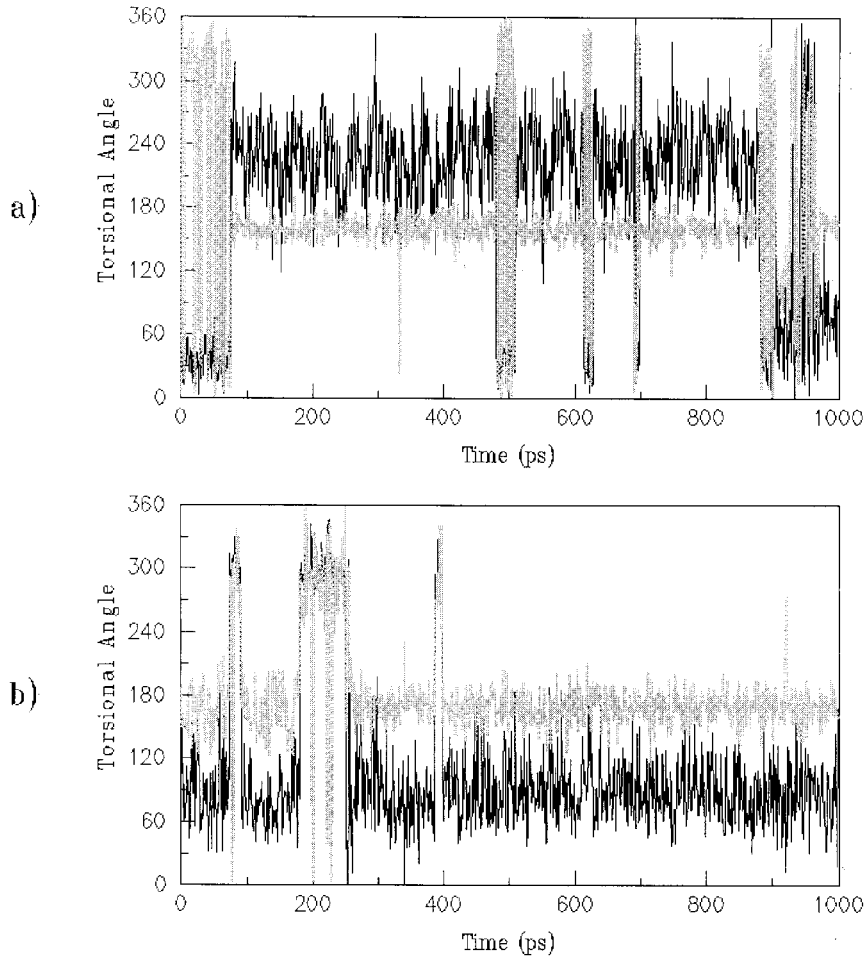


Figure 8. Trajectory plots of the torsional angles C8–C9–O–H (dark line) and C2–C3–O–H (grey line) as observed for **1** (a) and **2** (b) from MD simulations in chloroform solution.

it was observed that they mainly depend on the type of hydrogen bond formed by the hydroxyl groups. Two types of hydrogen bonds can be formed in aqueous solution: intramolecular (between the two hydroxyl groups) and intermolecular (between a hydroxyl group and the solvent molecules). Accordingly, a large conformational flexibility was observed in this solvent. The number of conformational transitions is drastically reduced in chloroform solution since in this solvent only the intramolecular hydrogen bond is possible. Thus, the scarce number of conformational transitions observed in chloroform is related with change in the donor and acceptor roles.

Table 1. Maximum life-time for the intramolecular hydrogen bond (τ_{hb}, in ps) and maximum time without forming any type of hydrogen bonding interaction (τ_{free}, in ps) in water and chloroform for the two investigated compounds

Compound	Solvent	H-bond pattern	τ_{hb}	τ_{free}
1	Water	C3–OH···O–C9	0	4
	Water	C9–OH···O–C3	0	6
	Chloroform	C3–OH···O–C9	76	89
	Chloroform	C9–OH···O–C3	24	207
2	Water	C3–OH···O–C9	27	3
	Water	C9–OH···O–C3	2	4
	Chloroform	C3–OH···O–C9	89	8
	Chloroform	C9–OH···O–C3	6	883

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References

1. (a) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Wiley: New York, 1965. (b) Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis*; Wiley: New York, 1991.
2. (a) Antunez, S.; Juaristi, E. *J. Org. Chem.* **1996**, *61*, 6465. (b) Saiz, E.; Guzman, J.; Iglesias, M. T.; Riande, E. *J. Phys. Chem.* **1996**, *100*, 18345. (c) León, S.; Martínez de Ilarduya, A.; Alemán, C.; Muñoz-Guerra, S. *J. Phys. Chem. A* **1997**, *101*, 4208. (d) Perrin, C. L.; Fabian, M. A.; Rivero, A. *J. Am. Chem. Soc.* **1997**, *101*, 4208.

3. *Conformational Behavior of Six-Membered Rings: Analysis, Dynamics and Stereoelectronic Effects*, Juaristi, E., Ed.; VCH: New York, 1995.
4. Dev, S. *Terpenoids Handbook*, CRC: Boca Raton: Florida, 1985.
5. Foerster, G.; Brezesinski, G.; Neumann, S.; Tschierske, C.; Zaschke, H.; Kuschel, F. *Mol. Cryst. Liq. Cryst.* **1990**, *193*, 121.
6. Friedemann, R.; Naumann, S. *J. Mol. Struct. (Theochem)* **1997**, *398*, 405.
7. Weiner, S. J.; Kollman, P. A.; Nguyen, D. T.; Case, D. A. *J. Comput. Chem.* **1986**, *7*, 230.
8. Pearlman, D. A.; Case, D. A.; Caldwell, J. W.; Ross, W. S.; Cheatham, T. E., III; Ferguson, D. M.; Seibel, G. L.; Singh, U. C.; Weiner, P. K.; Kollman, P. A. AMBER 4.1, University of California, San Francisco, 1995.
9. Namba, A. M.; León, S.; da Silva, G. V. J.; Alemán, C. Submitted for publication.
10. Jorgensen, W. L. *J. Chem. Phys.* **1977**, *77*, 4156.
11. Jorgensen, W. L.; Briggs, J. M.; Contreras, M. L. *J. Phys. Chem.* **1990**, *94*, 1683.
12. Ryckaert, J.-P.; Ciccotti, G.; Berendsen, H. J. C. *J. Comput. Phys.* **1977**, *23*, 327.
13. Berendsen, H. J. C.; Postma, J. P. M.; van Gunsteren, W. F.; DiNola, A.; Haak, J. R. *J. Chem. Phys.* **1984**, *81*, 3684.
14. Golan, O.; Goren, Z.; Biali, S. E. *J. Am. Chem. Soc.* **1990**, *112*, 9300.
15. ^{1}H NMR spectra were obtained on a Bruker DPX 300 spectrometer operating at 300.13 MHz. Samples were prepared by dissolving ca. 10 mg of *p*-menthan-3,9-diol in 0.5 mL of deuterated chloroform containing 0.3% (v/v) of TMS as an internal reference. For each compound, after recording the first spectrum, two drops of water were added and the sample shaken throughout and a second spectrum was recorded. The experiments were run at room temperature.
16. Namba, A. M.; da Silva, G. V. J. In preparation.