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Conformational Effects of Tacticity in Poly(Vinyl Alcohol). A Molecular Mechanics and Molecular Dynamics Study of Pentane-2,4-diol and PVA Oligomers

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Molecular mechanics calculations and molecular dynamics simulations using the MM+ and AMBER (AM1 charges) force fields have been used to investigate conformational effects of chirality in the PVA monomer pentane-2,4-diol and effects of tacticity in PVA oligomers. The conformational energies are generally consistent, and in semi-quantitative agreement with conformer populations in methylene chloride derived from NMR by others. However, AMBER calculates the hydrogen-bonded conformers ca. 1 kcal mol^{-1} more stable than MM+. The calculated conformational energies for *meso*-pentane-2,4-diol decrease in the order $(a, a) < (+g, a) < (a, +g) \leq (+g, +g)$, which may be compared with the NMR derived populations 76:16:2:1. The conformational energies for the racemic form are ranked in the order $(a, -g) < (a, a)$ [MM+: $(a, -g) \cong (a, a)$] $< (+g, +g) < (+g, a) \leq (-g, -g) < (+g, -g)$, which may be compared with the NMR populations 62:23:6:5. The ordering of the conformational energies can be explained by the nature of the 1,3-interactions. The preferred hydroxyl conformation, $\chi = (H–C–O–H)$, is generally *gauche*. This conformational preference is overridden in the hydrogen-bonded conformers. Molecular molecular mechanics calculations for isotactic and syndiotactic PVA oligomers (10-monomers) suggest that the [*aaaa*] extended conformation is most stable in the isotactic case, whereas random coils are more stable than any of the investigated regular helices in the syndiotactic case. Molecular dynamics simulations at 300 K show that the isotactic isomer has a higher content of hydrogen bonded monomers (82% as compared to 43%). The high content of [*aaaa*] stretches in the isotactic oligomer gives this polymer a more non-uniform distribution of hydrophilicity around the chain axis than the syndiotactic oligomer.

Poly(vinyl alcohol) (PVA) is the only water soluble polymer with a carbon–carbon backbone that is biodegradable.[1] It is mainly used in adhesives, and as a sizing agent in textiles. Due to its relatively low toxicity and the possibility for chemical modifications in terms of cross-linking or covalent attachment of carrier molecules, it has also been probed as a possible material for microencapsulation and delivery systems.[2]

Like all vinyl polymers PVA may exist in two main tactic modifications: isotactic, where the hydroxyl groups are on the same side, and syndiotactic, where the hydroxyl groups are on alternating sides of the main chain, as illustrated below for the PVA monomer pentane-2,4-diol. In the atactic case syndiotactic and isotactic regions are averaged out over the chain.

Monomer:	*Meso*, (*R*,*S*)	Racemic, (*R*,*R*)
Polymer:	Isotactic	Syndiotactic

It is well known that tacticity may have a large effect on preferred polymer conformation and on polymer properties such as glass transition temperatures in vinyl polymers.[3,4] These effects are to a large extent dependent on the strength and nature of the 1,3-interactions that are present. In PVA the 1,3-interactions are potentially attractive because of the hydrogen-bonding possibility between the hydroxyl groups. This is in contrast to most other common vinyl polymers like poly(vinyl chloride), where steric effects and monopole and dipole terms are most decisive for the 1,3-interactions. We have used molecular mechanics calculations and molecular dynamics simulations to study the effects of tacticity on preferred conformations of the PVA monomer pentane-2,4-diol and PVA oligomers. Although this

abundant polymer has also been modelled by others,[5–7] the focus of these investigations has been to a large extent on different properties, i.e. hydrogel modelling, solid-state NMR tacticity effects studied by *ab initio* methods, and polymer miscibility studied by molecular dynamics.

Methods

The potential energy surface for the PVA monomer pentane-2,4-diol was first investigated by performing molecular mechanics calculations on (*R,R*) (racemic) and (*R,S*) (*meso*) pentane-2,4-diol using the MM+ and AMBER[8] force fields, incorporated in the molecular modelling program Hyperchem 4.5.[9] MM+ is a Hyperchem extension of the MM2 force field.[10] Models of the six unique backbone conformers for each isomer that can arise from rotations around the two C–C bonds were built with Hyperchem 4.5, installed on a Dell Pentium PC running under Windows 3.11. For each of the backbone conformers, three orientations of the hydroxyl groups (χ_1, χ_2, χ_3) were considered, corresponding to both the H–C–O–H torsion angles being $+gauche$, *anti* and $-gauche$, respectively. In conformers where hydrogen bonding was deemed possible, hydroxyl orientations that might give more linear hydrogen bonds than those considered in the general case were included in the calculations.

The conformers were first energy-minimized with the MM+ force field using bond dipole charges, which treat the electrostatic interactions as dipole contributions. Atomic Mullikan derived charges for the optimized MM+ geometries were calculated using a single-point AM1 calculation, and the structures were then energy-minimized with the AMBER force field using a distance dependent dielectric function ($\varepsilon = r_{ij}$) and 0.5 scaling of the 1,4-non-bonded interactions. The AM1 charges were recalculated for the optimized structures, and a final AMBER energy minimization was performed. All molecular energy minimizations were performed with the Polak–Ribiere conjugate gradient method until the gradient norm was less than 0.01 kcal mol^{-1} Å^{-1}.

Regular syndiotactic and isotactic 10-monomer helices based on the three lowest energy monomer conformations found for *meso* and racemic pentane-2,4-diol were built and energy minimized with MM+. Atomic charges for the optimized MM+ geometries were calculated using a single-point AM1 calculation, and the structures were then energy minimized with the AMBER force field using the same procedure as for the monomers until the gradient norm was less than 0.1 kcal mol^{-1} Å^{-1}.

The syndiotactic [*aaaa*] and the isotactic [$-ga-ga$] helices were used as starting points for high-temperature (500 K) molecular dynamics simulations. These were performed for 100 ps after a 20 ps equlibration period, using a 1 fs step length. Coordinates were stored every 1 ps, thus producing 100 coordinate sets for analysis. Every 10th structure was selected and energy-minimized according to the MM+/AM1/AMBER protocol described above. Two low temperature (300 K) molecular dynamics simulations were then run, starting from the lowest energy syndiotactic and isotactic conformers found from the energy minimization. The molecular dynamics simulation parameters were equal to the parameters used for the high-temperature simulation.

Results and discussion

Monomers. The calculated conformational energies for *meso* and racemic pentane-2,4-diol are given in Table 1, together with NMR-derived conformer populations in methylene chloride.[11] The calculated AMBER structures are shown in Figs. 1 and 2.[12] The conformational energies are almost consistent, considering the ranking of the backbone conformers, and in good agreement with the NMR derived conformer populations. Both force fields rank the four lowest-energy *meso* conformers in the same order, $(a, a) < (+g, a) < (a, +g) \leqslant (+g, +g)$, which is in good agreement with the NMR populations 79:16:2:1. However, the ranking of the two highest-energy conformers, which are not detected by NMR, is interchanged, as MM+ predicts $(-g, +g)$ to be highest in energy, whereas AMBER predics $(+g, -g)$ to be highest in energy. The results for the racemic form show that (a, a) is 0.5 kcal mol^{-1} more stable than $(a, -g)$ according to MM+. The non-hydrogen bonded conformer (a, a) is 1.4 kcal mol^{-1} less stable according to AMBER. The latter energies are thus in best agreement with the NMR populations, which predict the hydrogen-bonded conformer to be predominant in methylene chloride (populations 63:23). This dicrepancy between MM+ and AMBER is most likely related to the treatment of hydrogen bonds, which are calculated more stable with AMBER. This can also be seen by comparing the energy differences for the two lowest *meso* isomers, which are larger with AMBER (Table 1). The ranking and similar energies of $(+g, +g)$ and $(+g, a)$, which are next in stability, is also in agreement with the NMR populations 6:5. In the racemic case both force fields rank the two highest-energy and experimentally unobserved conformers consistently: $(-g, -g) < (+g, -g)$.

The MM+ and AMBER results are also generally consistent when considering the different hydroxyl group orientations. In the non-hydrogen bonding cases the *gauche* conformers, χ_1 and χ_3, are more stable than the *anti* conformation, χ_2. When hydrogen bonding is present, which is the case for two *meso* conformers and one racemic conformer, the preference for forming hydrogen bonds usually overrides this *anti* preference (Table 1). In the racemic (a, a) conformer the O···O distance (3.4–3.5 Å) is too long for hydrogen bonding to occur. Of the five hydroxyl orientations considered, MM+ predicts four to be approximately equal in energy, whereas AMBER predicts three to be approximately equi-energetic.

The ranking of the conformers in terms of stability

Table 1. Calculated conformational energies (kcal mol^{-1}) for *meso* and racemic pentane-2,4-diol and NMR populations taken from the literature.[11]

Backbone conformation	MM+			AMBER			NMR
	χ_1	χ_2	χ_3	χ_1	χ_2	χ_3	
Meso isomer[a]							
(+g, +g)	1.7	3.6	1.9	3.3	4.9	3.2	1
(+g, a)	0.7	1.6	0.5	2.3	2.7	2.3	16
(+g, −g)	2.4	3.6	2.5	4.6	5.3	4.6	0
(a, +g)	1.6	2.4	1.7	2.9	3.7	3.5	2
(a, a)	0.0[c]	0.1[c]	χ_1	0.0[c]	0.4[c]	χ_1	79
(−g, +g)	3.3[c]	3.7[c]	4.2	3.8[c]	3.5[c]	χ_2	0
Racemate[b]							
(+g, +g)	1.0	1.9	0.8	2.9	3.2	2.1	6
(+g, a)	1.2	2.2	1.4	3.2	3.3	3.0	5
(+g, −g)	3.1	4.2	3.2	5.0	5.4	3.8	0
(a, a)[d]	0.1	1.4	0.5	2.3	2.1	1.4	23
(a, a)/χ_4 and χ_5	0.4	0.0		1.4	1.6		
(a, −g)	1.9[c]	1.6[c]	0.5[c]	4.4[c]	1.3[c]	0.0[c]	63
(−g, −g)	2.5	4.5	2.8	4.3	5.5	2.9	0

[a,b] The absolute energies for the ground states are (in kcal mol^{-1}): 4.10 (*meso*/MM+), −2.28 (*meso*/AMBER), 4.10 (racemate/MM+) and −2.09 (racemate/AMBER). [c] Hydrogen-bonded conformations. [d] The hydroxyl orientation χ_4 corresponds to −*gauche* and *anti*, whereas χ_5 corresponds to −*gauche* and +*gauche*.

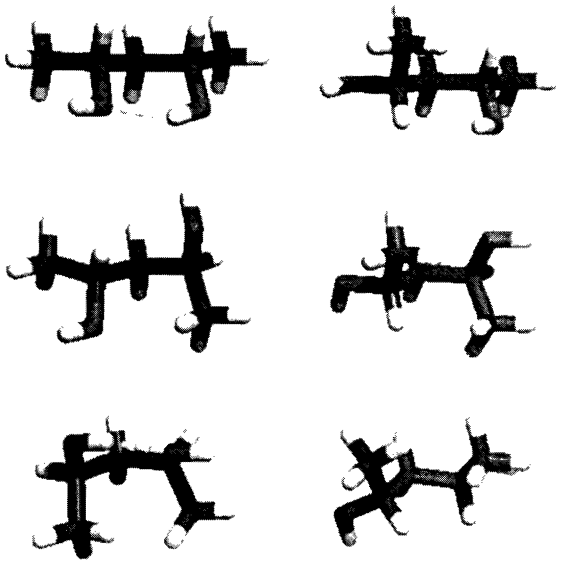

Fig. 1. Calculated *meso* pentane-2,4-diol conformers (AMBER) ranked according to energy. First row, (a, a) and (+g, a); second row, (a, +g) and (+g, +g); third row, (+g, −g) and (−g, +g).

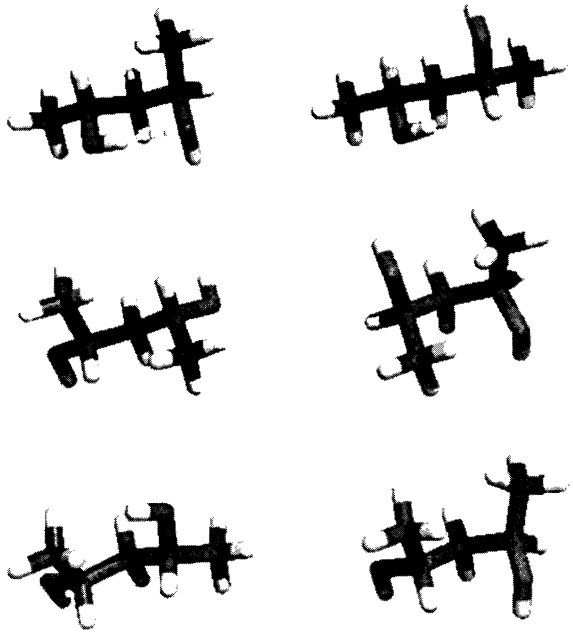

Fig. 2. Calculated racemic pentane-2,4-diol conformers (AMBER) ranked according to energy. First row, (a, −g) and (a, a); second row, (+g, +g) and (−g, −g); third row, (+g, a) and (+g, −g).

may for a large part be explained by considering which 1,3-interactions are present, as shown in Figs. 1 and 2. In the lowest-energy conformers only OH···OH hydrogen bonds are present. In the higher-energy conformers H···X interactions, which are neither strongly repulsive or attractive, are found, and in the highest energy conformers repulsive Me···Me/OH interactions are present.

Due to chirality the hydrogen bonding conformations become different in the racemate and the *meso* isomers, as shown in Figs. 1 and 2. In the *meso* isomer intramolecular hydrogen bonding is possible in the lowest-energy (a, a) conformer and in the high-energy (−g, +g) conformer. In the racemic isomer hydrogen bonding is only possible in the lowest-energy (a, −g) conformation. In all cases hydrogen bonding is achieved through six-ring formation, but the methyl groups are placed differently on the six-membered ring. In the (a, a) *meso* conformer the hydrogen-bonded six-ring places both methyl substituents in the preferred equatorial positions, whereas

both substituents are placed in axial positions in the hydrogen-bonded $(-g, +g)$ conformer. In the hydrogen-bonded racemate conformer $(a, -g)$ one methyl group is axial, whereas the other is equatorial. The absolute values of the energies show that this configuration, as expected, is less stable than the di-equatorial conformation found in the *meso* isomer.

Oligomers. The energies for the energy-minimized syndiotactic and isotactic oligomers of PVA are given in Table 2. Although the conformational searches performed are limited, no random coils are found which have lower energy than the regular extended [*aaaa*] conformer of the isotactic oligomer. In contrast to this, several random coils with lower energy than the regular helices are found in the syndiotactic case. The lowest energy conformers of each oligomer are shown in Fig. 3. The minimum energy syndiotactic conformer contains mainly stretches of (a, a) and $(a, +g)$ sequences, which were the lowest energy conformations found for the monomer.

The results from the molecular dynamics simulations underscore the results from the energy minimizations of the monomers and oligomers. Figure 4 shows histograms of the distribution of all 1,3-oxygen distances excluding the two terminal ones, found from the four molecular dynamics simulations. At high temperature (500 K) there is no large difference with regard to population of hydrogen-bonding conformers; ca. 28% of the monomers are hydrogen bonded in each case. The difference is mainly that a much larger population of longer distances (4.0–4.5 Å) is observed in the isotactic case. The 43% population of this interval corresponds mainly to population of the $(+g, a)$ monomer conformation, which is second lowest in energy. The more uniform distribution of the populations in the syndiotactic case reflects the fact that there are more monomer conformations with low energy that are accessible in this case.

At room temperature (300 K) the differences between the isotactic and syndiotactic oligomers becomes more pronounced. In the isotactic isomer 82% of the 1,3-oxygen distances correspond to hydrogen bonding distances, which is in agreement with the low minimum found for the (a, a) conformer of *meso* 2,4-pentane-2,4-diol and the regular isotactic (a, a) helix. It is also

Table 2. Calculated relative AMBER conformational energies (in kcal mol^{-1}) for regular and random coil (rc) PVA oligomers.

Conformation	Isotactic	Syndiotactic
[*aaaa*]	0.0	7.3
[$+ga+ga+ga+ga$]	22.1	
[$a-ga-ga-ga-$g]		6.0
[$+g+g+g+g$]	28.0	14.4
rc1	17.9	0.0
rc2	21.0	2.9
rc3	16.0	9.1
rc4	19.4	8.9
rc5	21.4	5.8
rc6	14.5	6.6
rc7	19.8	2.8
rc8	13.2	5.8
rc9	17.2	9.5
rc10	18.1	3.4

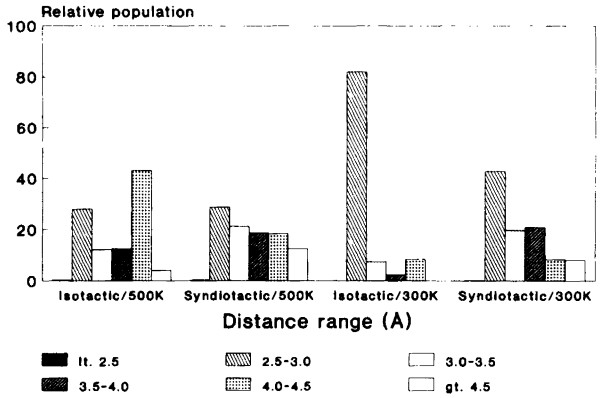

Fig. 4. Relative population of 1,3-oxygen distances found in isotactic and syndiotactic PVA at two (300 and 500 K) molecular dynamics simulation temperatures.

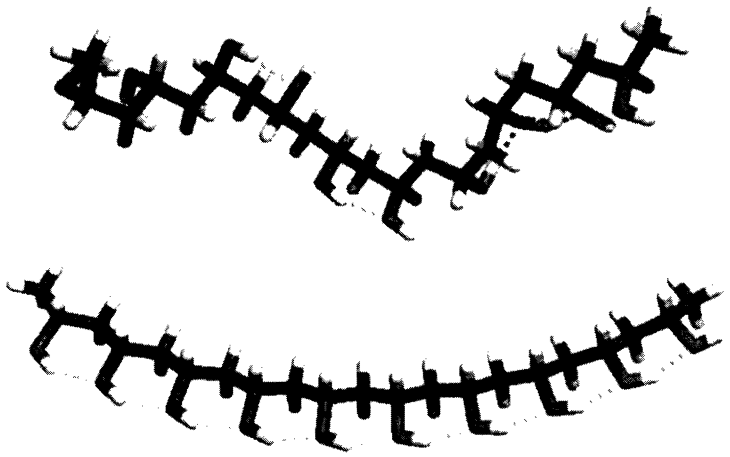

Fig. 3. Calculated lowest-energy conformers for syndiotactic (above) and isotactic (below) PVA oligomers.

compares well with the 79% population found from NMR. Correspondingly the percentage of longer distances, which correspond to conformers other than (*a*, *a*), is reduced substantially as compared to the 500 K simulation. The (+*g*, *a*) and (+*g*, +*g*) monomer conformations, (4.0–4.5 Å bin) and the (*a*, +*g*) monomer conformation (3.0–3.5 Å bin) have the populations 8% and 7%, respectively, as compared to the NMR populations 17% and 2%.

In the syndiotactic case 43% of the distances correspond to a hydrogen-bonding (*a*, −*g*) monomer conformation at room temperature. This is comparable to the 63% NMR population. The relatively high percentage (20% and 21%) of intermediate 1,3-oxygen distances (3–0–3.5 and 3.5–4.0 Å) corresponds mainly to population of (*a*, *a*) conformers, which have a 23% NMR population. The population of 4.0–4.5 Å distances, corresponding to (+*g*, *a*) is 8% (NMR: 5%), and the >4.5 Å distance range, which corresponds to the (+*g*, +*g*) monomer conformation, achieves an 8% population (NMR: 6%).

Differences between the syndiotactic and isotactic oligomers can also be demonstrated by considering the distribution of end-to-end distances as shown in Fig. 5. At high temperature the distribution of distances is almost similar, with a maximum in the 15–20 Å range. At room temperature distances greater than 20 Å are found most frequently for the isotactic isomer, corresponding to long *anti* stretches. The syndiotactic oligomer populates all distance ranges from 5 Å, with increasing populations, in agreement with the easier accessability of the kinked conformations (*a*, −*g*) and (+*g*, +*g*).

The results of the AMBER molecular dynamics simulations of isotactic and syndiotactic PVA oligomers are seen to reflect well the calculated potential energy surfaces for the PVA monomer, pentane-2,4-diol. The results are also in semi-quantitative agreement with NMR derived populations for the monomer in methylene chloride. They show distinct differences with regard to the preferred secondary structure of the chains. For the isotactic isomer the strong preference for the extended hydrogen bonded (*a*, *a*) monomer conformer at room temperature is manifested as a 82% population. In contrast, the syndiotactic oligomer has a 43% population of hydrogen bonded monomers, which in this case corresponds to the (*a*, −*g*) conformation. Thus, syndiotacticity leads to more kinks in the secondary structure and less intramolecular hydrogen bonding as compared to the isotactic case.

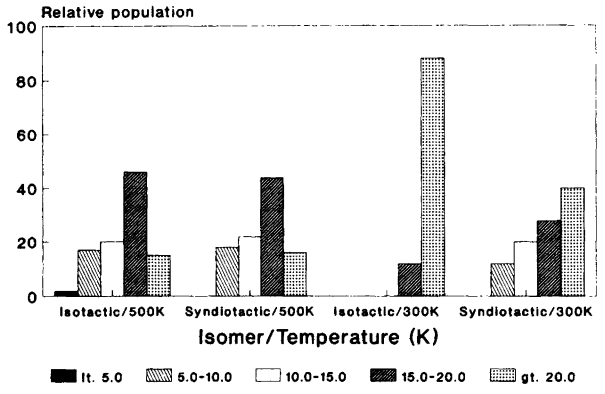

Fig. 5. Relative population of end-to-end distances found in isotactic and syndiotactic PVA at two (300 and 500 K) molecular dynamics simulation temperatures.

The conformational differences between isotactic and syndiotactic PVA demonstrated by these *in vacuo* calculations may not reflect the situation in water. This is indicated by the NMR results, which suggest that the populations of *meso* and racemic hydrogen-bonded monomer conformations are reduced to 18% and 9%, respectively. However, it can be pointed out that the higher content of intramolecular hydrogen bonding in isotactic PVA might expectedly lead to less water solubility for this conformer. Furthermore, the predominance of the hydrogen bonded (*a*, *a*) monomer conformation gives the chain axis a mainly hydrophillic side where the hydroxyl groups are located, and a more hydrophobic side comprising the methylene groups. Expectedly this might increase the likelihood for hydrophobic assosiation of neighbouring chains in longer PVA polymers. In the syndiotactic isomer the hydrophillic hydroxyl groups are more evenly distributed around the chain axis, and less frequently hydrogen bonded to neighbouring hydroxyl groups. This would expectedly promote water solubility and decrease the likelihood for hydrophobic interactions between neighbouring chains. The more uneven distribution of hydrophilicity in isotactic PVA as compared to syndiotactic PVA may also be of relevance for toxicity problems and applications of such polymers in encapsulation and delivery systems.

References

1. Swift, G. *Polymer Degradation and Stability 45* (1994) 215.
2. Korsmeyer, R. W. and Peppas, N. A. *J. Membr. Sci. 9* (1981) 211.
3. Bicarano, J. *Prediction of Polymer Properties*, 2nd Edn., Marcel Dekker, New York 1996, pp 180–182.
4. Dale, J. *Stereokjemi og konformasjonsanalyse*, Universitesforlaget, Oslo 1975.
5. Tamai, Y., Tanaka, H. and Nakanashi, K. *Macromolecules 29* (1996) 6761.
6. Imashiro, F. and Obara, S. *Macromolecules 28* (1995) 2840.
7. Deshpande, D. D. *Polym. Sci. 2* (1994) 698.
8. Weiner, S. J., Kollman, P. A., Nguyen, D. T. and Case, D. A. *J. Comput. Chem. 7* (1986) 2308.
9. *Hyperchem 4.5*, Hypercube, Inc. 419 Philip Street, Waterloo, Ontario N2L 3X2 Canada.
10. Allinger, N. L. *J. Am. Chem. Soc. 99* (1977) 8127.
11. Moritani, T. and Fujiwara, Y. *J. Chem. Phys. 59* (1973) 1175.
12. The pictures were made using the shareware programs Povchem 1.0, POV-Ray 2.0 and Lview 3.1 downloaded from the Internet.

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