to foresee that it will be difficult to synthesize a derivative of **1** that still possesses the same properties as **1**.

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Molecular Dynamics with Dimethyl Sulfoxide as a Solvent. Conformation of a Cyclic Hexapeptide

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Abstract: Molecular dynamics simulations including dimethyl sulfoxide (DMSO) as solvent are reported. Simulations of the pure solvent produce good agreement with the X-ray diffraction data of liquid DMSO. Simulations of the cyclic hexapeptide *cyclo*[-D-Ala-Phe^2-Val-Lys-Trp-Phe^6-] in the presence of DMSO have been carried out. The conformation of the peptide in DMSO has been well refined from NMR studies and is used as a model system. The solvent forms hydrogen bonds with backbone amide protons and the Lys side chain. However, besides this small amount of ordering close to the peptide, the solvent is randomly distributed. The radial distribution of the solvent atoms quickly approaches that of pure DMSO. The effects of the solvent on the conformational preferences of the cyclic hexapeptide are discussed.

During the last few years, the importance of molecular dynamics simulations[1-4] in the structure determination of peptides has steadily increased.[5-10] The simulations have for the most part been limited to in vacuo or incorporating water as a solvent. However, many peptides of interest are not highly soluble in water and have been studied experimentally in organic solvents such as dimethyl sulfoxide (DMSO) or chloroform ($CHCl_3$). It is of course desirable to carry out the calculations under similar conditions (i.e. same solvent) as the experimental results were obtained.

In addition, computer simulations with solvents other than water will allow for greater insight into the role of environmental factors (solvent effects) on conformation. The conformational changes induced from varying the polarity, viscosity, and ability to form hydrogen bonds can be better understood from computer simulations involving models of these different solvents.

We have reported the use of carbon tetrachloride (CCl_4) in computer simulations of a cyclic undecapeptide, cyclosporin A.[11] A comparison of molecular dynamics simulations in vacuo and in water and CCl_4 illustrated the effects of solvent on the dynamics of the molecule, conformation of side chains, and formation of hydrogen bonds.

Here we report molecular dynamics simulations with DMSO as a solvent. In a recent publication, Rao and Singh used DMSO in a series of simulations investigating the solvation of cations and anions.[12] The use of the potential parameters of these authors within the GROMOS force field[13] reproduced the structure of the solvent as determined from X-ray diffraction.[14] The solvent was then utilized in molecular dynamics simulations of a model cyclic hexapeptide.[15] The solvation of the peptide and the conformational influences of the solvent are discussed.

Methods

The molecular dynamics simulations were carried out using the GROMOS program.[13] For the parameters of DMSO, new atom types were defined for the S, O, and methyl group (CH_3) for which the united atom approach was utilized. Jorgensen has shown for methanol that using the united atom approach or including all of the atoms of the methyl group produces very similar results.[16] A similar approach was used in our simulations of cyclosporin A; the CCl_4 was simulated as a Lennard-Jones solvent using a united atom.[11] For the bond lengths and angles of DMSO the equilibrium values were taken from the structure determined from microwave spectroscopy;[17] the force constants were taken from a study of a series of cyclic sulfoxides from Allinger and Kao.[18] The charges of the atoms and nonbonded (Lennard-Jones) parameters were taken from Rao and Singh.[12]

The molecular dynamics simulations of the pure solvent were carried out for 80 ps (following a 30-ps equilibration period) using a step size of 2 fs with the application of SHAKE. A cube of volume 2.45×10^4 Å^3 containing 208 DMSO molecules was used with periodic boundary conditions and a nonbonded cutoff distance of 15 Å. The temperature and pressure were maintained at 500 K and 1 atm by the weak coupling technique.[19] A temperature relaxation time of 0.1 ps (0.01 ps during the equilibration) and an isothermal compressibility of 8.719×10^{-4} (kJ mol^{-1} nm^{-3})$^{-1}$ were used. A simulation at 300 K produced identical results. The radial distribution function was calculated following standard procedures.[20,21]

To examine the effects of the organic solvent on peptide conformation, a simulation of a model hexapeptide, cyclo[-D-Ala^1-Phe^2-Val^3-Lys^4-

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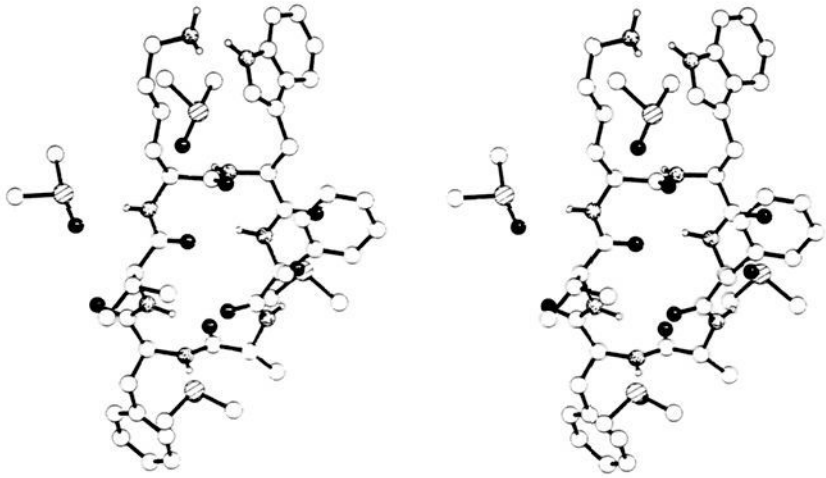

Figure 1. Stereoplot of VDA008 from molecular dynamics simulation in DMSO after 50 ps with application of NOE constraints. The DMSO molecules which form intermolecular hydrogen bonds are included.

Trp[5]-Phe[6]-], VDA008,[15] was carried out. The peptide was placed in the middle of a truncated octahedron and soaked with DMSO. A volume of 1.47×10^4 Å^3 required the addition of 120 DMSO molecules. For the simulation of the peptide in DMSO one additional parameter is required. The GROMOS program does not contain an explicit hydrogen bond term, but utilizes a balance of the Lennard-Jones and Coulombic parameters to obtain the correct distance and geometry of hydrogen bonds. For simulations involving water, the repulsive portion of the Lennard-Jones term for the oxygen of the solvent and that for the polar atoms of the solute are increased to obtain correct hydrogen bonds.[13] For DMSO, the repulsive part of the Lennard-Jones term of the oxygen of DMSO was also increased to a value of 500 (kcal·Å^{12}/mol)$^{-1/2}$ for intermolecular interactions with polar atoms of the solute.[22] This produced distances of approximately 2.85 Å between the oxygen of DMSO and nitrogen of amides in good agreement with the distance (2.83 Å) measured by X-ray analysis of peptides with DMSO present.[23]

Two molecular dynamics simulations with different starting structures were carried out. The first simulation (simulation 1) started with the structure from a previous study derived from in vacuo simulations with the application of NOE and dihedral constraints.[15] There are two β-turns within the cyclic hexapeptide, a βII′ about D-Ala-Phe and a βII about Lys-Trp. In addition, the side chains of Phe[2], Trp, and Phe[6] were set to values of −60, −60, and 180°, respectively. These side chain torsions have been determined experimentally from the diastereotopically assigned β protons using homo- and heteronuclear coupling constants.[15] For Phe[2] and Trp −60° is the predominant rotamer with populations of 81 and 69%, respectively, with the remainder of the population equally distributed between the 180° and 60° rotamers. In contrast, the side chain of Phe[6] was determined to be 28 and 53% −60° and 180°, respectively.

The starting structure for the second simulation (simulation 2) was "randomized" by application of forcing potentials to all of the ϕ and ψ torsions (as well as the χ_1 of Phe[2], Trp, and Phe[6]) to 180°. Because such an extended conformation cannot exist for a cyclic hexapeptide, energy minimization with weak forcing potentials on these torsions generates high-energy structures with a relatively random distribution of dihedrals. For the study here it was only necessary to create a structure well removed from the conformation found in solution.

The molecular dynamics simulations with the peptide were initiated following standard methods using a step size of 2 fs with SHAKE at 1000 K for 5 ps. The temperature was then reduced to 300 K and the system allowed to come to equilibrium for 5 ps. The next 50 ps of simulation were used for the analysis. During this 60 ps of simulation, force constants of 2000 kJ mol^{-1} nm^{-2} were applied for the 18 proton–proton distances measured.[15] For simulation 1, the NOE force constants were removed and the simulation continued for 200 ps. All computer simulations were carried out on Silicon Graphics 4D/240SX and 4D/70GTB computers.

(22) This increase in the repulsive portion of the Lennard-Jones term is in conjunction with the standard increases for the polar atoms of the solute utilized by GROMOS (e.g. the term for the nitrogen of an amide is 636 and 950 [kcal·Å^{12}/mol]$^{-1/2}$ for solute–solute interactions and solute–solvent interactions, respectively).

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Table I. Selected Dihedral Torsions of the Starting Structures and Averages from Molecular Dynamic Simulations of VDA008 in Dimethyl Sulfoxide

torsion		simulation 1			simulation 2	
		starting	NOE	free	starting	NOE
D-Ala	ϕ	63.3	69.1	62.2	116.2	70.1
	ψ	−126.5	−110.2	−121.3	−133.8	−114.6
Phe[2]	ϕ	−74.8	−83.9	−90.7	−149.9	−79.6
	ψ	−2.4	−27.7	−8.6	168.6	−29.8
	χ_1	−61.2	−72.4	−67.1	−146.9	−174.3
Val	ϕ	−129.5	−101.6	−108.5	113.4	−103.2
	ψ	170.7	164.2	175.2	−59.5	170.9
Lys	ϕ	−59.6	−32.4	−46.0	−179.5	−33.3
	ψ	124.7	105.6	114.5	146.8	106.5
	χ_1	−67.1	−166.1	−170.2	87.3	−76.2
Trp	ϕ	80.8	66.7	72.1	165.3	51.6
	ψ	−4.2	−6.1	−34.4	151.8	7.2
	χ_1	−65.8	−51.3	−58.9	−138.3	57.9
Phe[6]	ϕ	−176.1	−136.7	−123.8	33.9	−141.5
	ψ	126.6	98.6	125.5	44.8	95.8
	χ_1	159.5	−63.1	−66.5	−166.5	−171.9

Results and Discussion

Radial distribution functions (rdfs) show the variation of the distribution of atoms of the solvent from a random orientation. The usefulness of the rdfs in the development of potential parameters has been illustrated.[20,21] The rdfs for all of the intermolecular atom pairs of DMSO were calculated from the atomic trajectories during the molecular dynamics simulations. The distance of the first maximum of the rdfs and the shape of the peaks are in agreement with both the X-ray structure and the simulations of Rao and Singh.[12]

Selected torsions from the two molecular dynamics simulations with VDA008 in DMSO are listed in Table I. During the first simulation the conformation of the peptide is maintained; there is not a large deviation of the torsion values from the starting conformation, especially true when the NOEs are applied. The exceptions are two transitions involving side chains: Lys goes from predominantly −60° to 180° and Phe[6] from 180° to −60°.

Continuing the simulation, without the application of the NOEs, there are small variations of the torsions, but for the most part the overall structure of two β-turns is maintained: the backbone torsions are close to the standardly defined values for such turn structures.[24] There are no further transitions of the side chain torsions. The two 10-membered intramolecular hydrogen bonds associated with the two β-turns are also maintained during the simulation. The observed intramolecular hydrogen bonds are listed in Table II.

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Table II. Stable Intramolecular Hydrogen Bonds Observed during the Molecular Dynamics Simulation of VDA008 with and without NOE Restraints in Dimethyl Sulfoxide (Simulation 1)[a]

atoms		turn	distance	angle	percentage[b]
NOE:					
Val NH	Phe^6 O	βII	3.06	158	56.8
Phe^6 NH	Val O	βII′	2.84	161	76.0
Phe^6 NH	Lys O	γ	2.78	154	3.2
Free:					
Val NH	Phe^6 O	βII	3.09	156	62.4
Phe^6 NH	Val O	βII′	2.84	161	58.4
Phe^6 NH	Lys O	γ	2.75	156	17.6

[a] A stable hydrogen bond has a distance of less than 3.2 Å between N and O and an N-H-O angle of greater than 150°. The distance is in Å, the angle in deg. [b] Percentage of the simulation that the hydrogen bond is observed.

Table III. Stable Intermolecular Hydrogen Bonds between Peptide and Solvent Observed during the Molecular Dynamics Simulation of VDA008 with and without NOE Restraints in Dimethyl Sulfoxide (Simulation 1)[a]

atoms		distance	angle	percentage[b]
NOE:				
D-Ala NH	Sol^{24} O	2.85	158	62.7
D-Ala NH	Sol^{68} O	2.92	163	10.7
Phe^2 NH	Sol^{61} O	2.83	160	78.0
Val NH	Sol^{61} O	3.13	152	14.0
Lys NH	Sol^{41} O	2.82	158	70.7
Trp NH	Sol^{90} O	2.92	163	77.3
free:				
D-Ala NH	Sol^{68} O	2.86	164	81.3
Phe^2 NH	Sol^{61} O	2.91	160	80.0
Val NH	Sol^{61} O	3.09	151	8.7
Lys NH	Sol^{41} O	2.83	163	82.0
Trp NH	Sol^{90} O	2.92	163	80.7

[a] A stable hydrogen bond has a distance of less than 3.2 Å between N (solute) and O (solvent) and an N-H-O angle of greater than 150°. The distance is in Å, the angle in deg. [b] Percentage of the simulation that the hydrogen bond is observed.

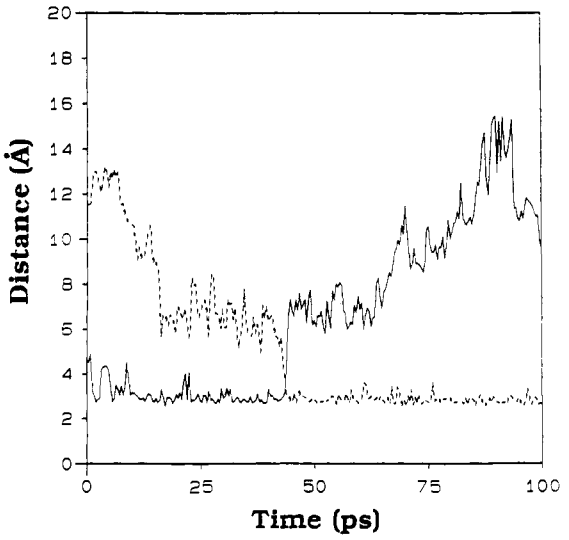

Figure 2. Plot of the displacement of a DMSO molecule forming an intermolecular hydrogen bond with the amide of D-Ala. The distance between the amide nitrogen and oxygen of DMSO is plotted for DMSO 24 (solid) and DMSO 68 (dashed).

The formation of solute-solvent hydrogen bonds is important in the stabilization of the conformation during the simulations. The intermolecular hydrogen bonds observed during the molecular dynamics simulations are listed in Table III. Four hydrogen bonds are observed for a majority of the NOE restrained simulation: the amides of D-Ala, Phe^2, Lys, and Trp from intermolecular hydrogen bonds with the oxygen of solvent molecules. In Figure 1, the structure after 50 ps of restrained dynamics is shown with

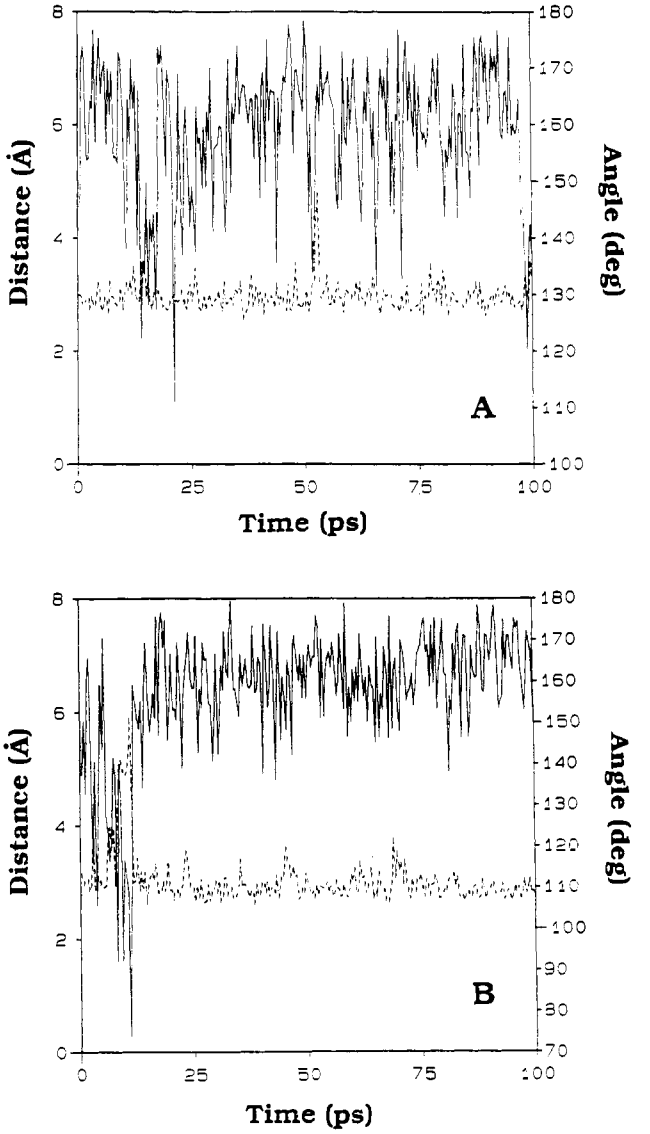

Figure 3. Plot illustrating intermolecular hydrogen bonds between solute and solvent. The distances between the amide nitrogen of the peptide and the oxygen of DMSO (dashed line) and the angle formed by atoms NH-O (solid line) during molecular dynamics simulations of VDA008 in DMSO (simulation 1) are shown for (A) Phe^2 NH-DMSO 61 and (B) Lys NH-DMSO 41.

the four DMSO molecules involved in hydrogen bonds. In the conformation with the two β-turns, each of these four amide protons are oriented away from the 18-membered cyclic ring system. In addition, the intermolecular hydrogen bonds involving the amides of D-Ala and Lys force the carbonyls of Val and Phe^6 to be directed inward, toward the ring system (assuming a trans orientation about the peptide bond) and therefore stabilized the two β-turns. It has been claimed previously that the conformations of cyclic peptides are not stabilized by intramolecular hydrogen bonds but by stronger hydrogen bonds to the solvent.[25] Similar solute-solvent interactions are important in protein conformation and stability.[26,27]

Three of the intermolecular hydrogen bonds are maintained during the complete simulation, with and without the application of the NOEs (Table III). The DMSO molecule forming the hydrogen bond with the amide of Ala is displaced by another

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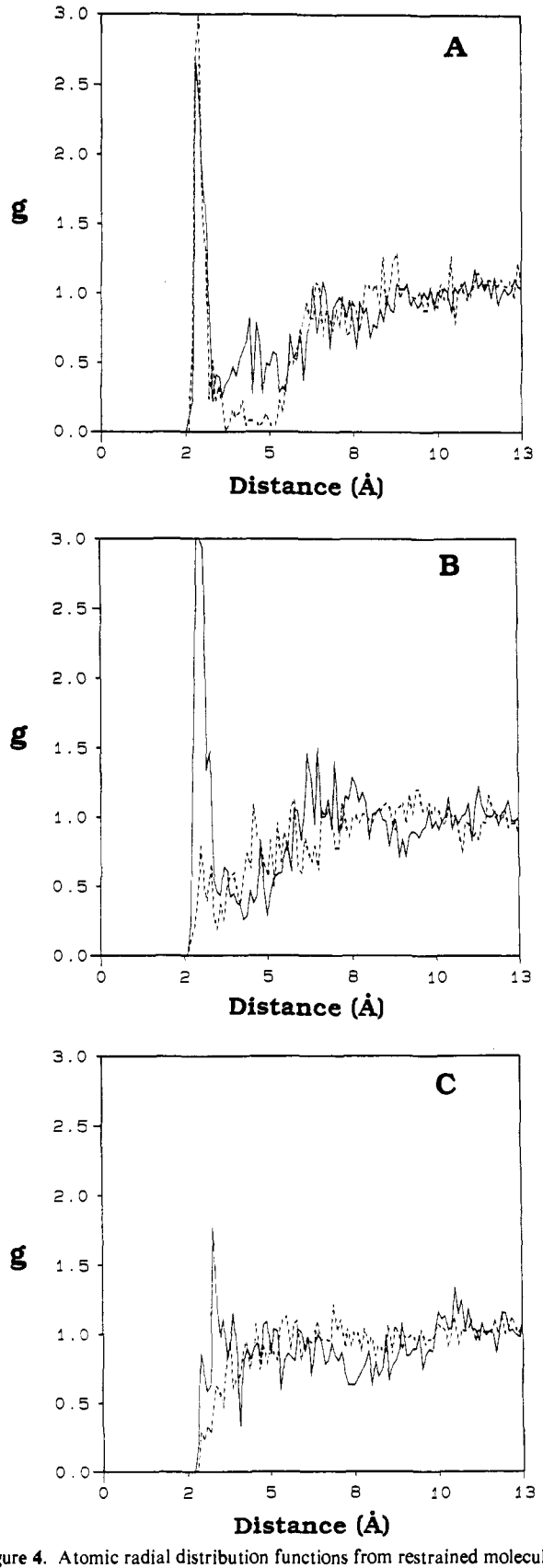

Figure 4. Atomic radial distribution functions from restrained molecular dynamics simulation of VDA008 in DMSO (simulation 1) calculated for the oxygen of DMSO and selected atoms from the peptide: (A) Ala NH (solid), Trp NH (dashed); (B) Lys NZ (solid), Trp NE1 (dashed); (C) Phe CZ (averaged over both Phe's solid), Ala CB (dashed).

DMSO molecule. The exchanging of the solvent molecules occurs at approximately 44 ps into the simulation and is illustrated in Figure 2.

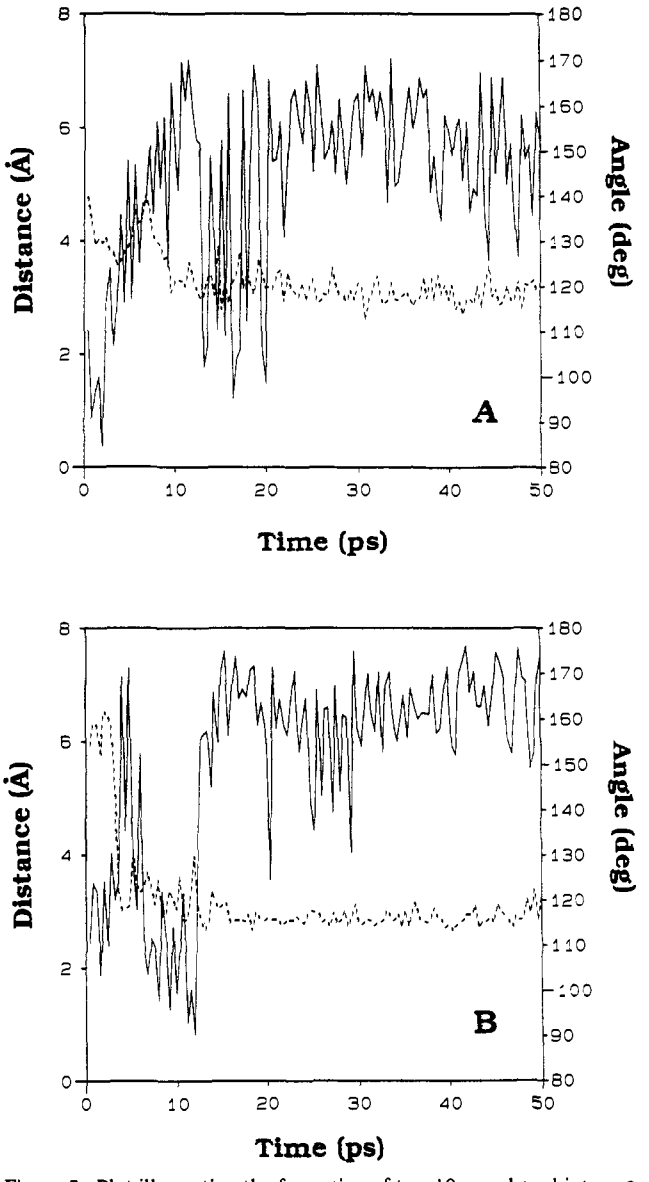

Figure 5. Plot illustrating the formation of two 10-membered intramolecular hydrogen bonds characteristic of β-turns during molecular dynamics simulations of VDA008 in DMSO (simulation 2). The distance between amide nitrogen and carbonyl oxygen (dashed) and the angle formed by atoms NH–O (solid) is plotted for (A) Val NH–Phe^6 O and (B) Phe^6 NH–Val O.

There is only a small variation of the distance between the nitrogen and oxygen atoms within the intermolecular hydrogen bonds. The average length between the nitrogen of the amide and oxygen of the solvent, when involved in a hydrogen bond, is 2.87 Å (recall that the nonbonding parameters of the solvent were adjusted to produce this value). However, there is a large variation in the angle formed by the nitrogen and proton of the amide and oxygen of DMSO as is illustrated in Figure 3. The average of the angle is approximately 160° when involved in a hydrogen bond. Very similar average angles are found for intramolecular hydrogen bonds (see Table II) and for intermolecular hydrogen bonds involving the oxygen of water.[27]

It has been well-established that temperature coefficients of amide protons provide an estimate of the strength of intramolecular hydrogen bonds.[28] Along the same lines the temperature coefficients should provide information on the strength of intermolecular hydrogen bonds and can therefore be compared with the results here. The temperature coefficients for the amides not involved in intramolecular hydrogen bonds are 5.6, 5.4, 2.8, and 4.0 (-ppb/K) for D-Ala, Phe^2, Lys, and Trp, respectively.[15] The tentative agreement with the results from the simulation is relatively good. The largest coefficient is for the D-Ala amide which

exchanges DMSO molecules during the simulation (Figure 2). In addition, Lys which has the lowest temperature coefficient and shows a very stable intermolecular hydrogen bond with a small average length (2.82 Å) during the simulation. However, the dynamics do not differentiate the intermolecular hydrogen bonds involving the Phe[2] and Trp amides and illustrate a rather stable hydrogen bond for Phe[2] which has a temperature coefficient only slightly smaller than D-Ala. It is not too surprising that a "clear-cut" trend is not observed: There are many factors that affect the chemical shift of amides and their variation with temperature. For the most part, the chemical shift of amide protons involved in intermolecular hydrogen bonds is downfield of the protons involved in intramolecular hydrogen bonds, indicating that the solvent induces greater deshielding and maybe forms stronger hydrogen bonds. It therefore seems reasonable to use both the chemical shift and the temperature coefficient as a rough estimate for the strength of intermolecular hydrogen bonds. For some cyclic peptides (for example *cyclo*[-D-Pro-Phe-Thr-Lys-Trp-Phe-]) there is a direct correlation between the chemical shift of the amides and their temperature coefficient.[10] However, for VDA008 this is not the case. Currently a series of cyclic peptides with well-determined experimental structures are being simulated in DMSO to further investigate the interaction between amide protons and the solvent.

Besides the orientation of the solvent molecules to form the intermolecular hydrogen bonds, there is only a small amount of ordering of the solvent. The rdfs between the solute and solvent, shown in Figure 4, quickly approach a value of one indicating a random orientation of solvent. The rdfs for the amides involved in intermolecular hydrogen bonds (Figure 4A) show a sharp peak which integrates to one solvent molecule and then approaches 1 after approximately 6 Å. The slow approach to a random orientation (from approximately 3.5–6 Å in Figure 4A) is caused by the exclusion of the solvent by the peptide, which was not taken into consideration in the calculation of the rdf. As for the solvation of the side chains, the Lys ^{6}NZ has a rdf (Figure 4B) very similar to that of the amides involved in hydrogen bonds. This is in contrast to the indole nitrogen of Trp (NE1) which shows absolutely no ordering of solvent molecules. As to be expected the rdfs of Ala (CB) and the two Phe (CZ) side chains also show no ordering of solvent (Figure 4C), both quickly rising to a value of 1 after approximately 4 Å.

The lack of a solvation sphere about the peptide is quite different from that found for simulations of peptide molecules with water as a solvent.[29] It was reported that a hydration sphere of up to 8 Å is formed around the charged end groups of the peptide. This difference is reasonable since DMSO can only be an acceptor of hydrogen bonds and therefore does not favor the formation of further structure as commonly found in water.

The second simulation of VDA008 in DMSO was carried out to explore if the viscosity of the organic solvent is too great for conformational changes to take place on the time scale of molecular dynamics simulations. The starting structure and the average torsions after 50 ps of molecular dynamics are listed in Table I. The experimental conformation containing the two β-turns was indeed adopted after 50 ps of molecular dynamics. The root-mean-square difference of the backbone atoms between the structures after 50 ps from simulations 1 and 2 is 0.20 Å. The experimental structure is obtained at approximately 21 ps into the simulation. The onset of the structure is illustrated by following the formation of the two 10-membered hydrogen bonds associated with the two β-turns. As shown in Figure 5, the Val NH-Phe^{6} O and Phe^{6} NH-Val O hydrogen bonds are formed at approximately 21 and 14 ps into the simulation, respectively. This simulation shows that the peptide can undergo conformational changes (largely to satisfy the experimental constraints) during the simulation in a relatively short time span.

Conclusions

A cyclic hexapeptide which has been extensively examined by NMR spectroscopy was examined by molecular dynamics simulations in DMSO. Intermolecular hydrogen bonds are formed between the solvent and backbone amide protons and the Lys side chain. These intermolecular hydrogen bonds stabilize the conformation found experimentally: the experimental structure is stable even without the application of the NOE derived restraints. Starting from a random structure and with the application of the NOEs, the peptide quickly adopts the conformation found experimentally. Besides the ordering of DMSO molecules close to the peptide to form hydrogen bonds, the solvent adopts a random orientation, quickly approaching that of pure DMSO. The calculations also provide insight into the interaction of the solvent with side chains, particularly the lack of a hydrogen bridge for the Trp indole NH proton.

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Registry No. DMSO, 67-68-5; VDA008, 127819-53-8.