Development of Weiner *et al.* Force Field Parameters Suitable for Conformational Studies of [1,4]-Benzodiazepines and Related Compounds

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A set of force field parameters capable of reproducing the preferred conformations of the biologically important [1,4]-benzodiazepines was developed for AMBER and other molecular modeling programs that utilize the Weiner *et al*. force field. Equilibrium parameters were obtained from representative model compounds found in the Cambridge Structural Database, and bond stretching and torsion potential force constants were estimated using AM1 and PM3 semiempirical Hamiltonians. Parameters obtained with the two semiempirical methods and the existing linear interpolation method are compared. Molecular mechanics and dynamic simulations showed that AM1 derived parameters, together with MNDO ESP fitted atomic charges, predicted the X-ray structure of a number of representative [1,4]-benzodiazepines within 0.01 Å, 0.8°, and 5°, from observed bond lengths, bond angles, and bond torsions, respectively.

INTRODUCTION

[1,4]-Benzodiazepines constitute an important family of compounds with diverse biological activities.[1] They are notable for targeting different central nervous system (CNS) receptors, and many [1,4]-benzodiazepines are commercially available drugs used in the treatment of anxious depression, epileptiform activity, insomnia, and other CNS related disorders.[1,2] Most of the known [1,4]-benzodiazepines have advantageous pharmacological properties, and hundreds of new structurally diverse analogues are becoming available through combinatorial chemistry.[3,4]

Other activities are related to the three-dimensional structure of these compounds and their derivatives. The preparation of a series of potent Ras farnesylation pseudopeptide inhibitors showed that [1,4]-benzodiazepine peptidomimetic derivatives have the ability to promote peptide turns.[5] In our laboratory we are exploiting this feature in the design of peptidase resistant pseudopeptide analogues of allatostatins, a family of insect neuropeptides that regulate the production of juvenile hormone in different insects,[6] representing a promising lead in the design of novel insect management agents.[7] It has been proposed that allatostatin activity is related to the adoption of a turn by the active core of the peptide, and we are currently studying analogues bearing [1,4]-benzodiazepine derivatives to test this hypothesis.

Molecular modeling can play an important role in the rational design of novel [1,4]-benzodiazepine derivatives, as has been demonstrated in the past for these and other drugs.[8,9] The process involves modeling the bioactive molecule bound to its protein receptor in order to gain insights concerning bound conformation, drug−receptor interactions, and conformational changes that may occur in the protein receptor upon binding. This information can then be used in the design of novel compounds in which favorable interactions are maximized. To examine the dynamics and energetics of these systems, several force fields for the study of biomolecular interactions have been developed.[10−15] Among them, the models of Weiner *et al*.[10,11] and Cornell *et al*.[12] are probably the best documented ones, generally included in most comercially available molecular modeling packages.[16] Although they are accurately parametrized for proteins and nucleic acids, extension of these force fields to other organic molecules is somewhat limited. To overcome this problem, a compromise can be made and a more general force field can be used. However, if the accuracy of the biomolecular models is needed, parameters for the organic ligand under study have to be calculated.[17−19] We report the development of parameters consistent with the Weiner *et al*. force field that when used together with MNDO ESP fitted atomic point charges, accurately reproduce the X-ray conformations of a number of representative [1,4]-benzodiazepines found in the Cambridge Structural Database.

PARAMETER DEVELOPMENT

The Weiner *et al*. all atom force field uses an empirical energy expression represented by the sum of several energy terms of the following form:[10,11]

$$\mathbf{E} = \sum_{\text{bonds}} K_{\text{bs}i}(l_i - l_{\text{o}i})^2 + \sum_{\text{angles}} K_{\text{ab}i}(\phi_i - \phi_{\text{o}i})^2 + \sum_{\text{dihedrals}} {}^1/_2 V_i\,[1 + \cos(n_i\varphi_i - \rho_i)] + \sum_{i<j}(A_{ij}R_{ij}^{-12} - B_{ij}R_{ij}^{-6} + q_iq_j\epsilon^{-1}R_{ij}^{-1}) + \sum_{\text{H-bonds}}(C_{ij}R_{ij}^{-12} - D_{ij}R_{ij}^{-10})$$

The first three terms correspond to the energy from bonded interactions. $K_{\text{bs}i}$ and $K_{\text{ab}i}$ represent the bond stretching and angle bending constants, while l_i, $l_{\text{o}i}$, ϕ_i, and $\phi_{\text{o}i}$ are bond

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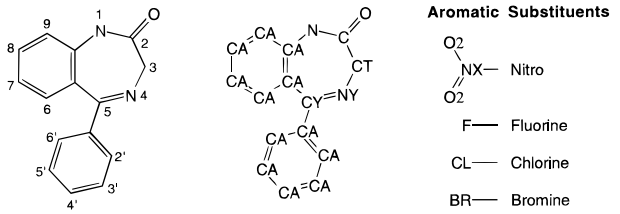

Figure 1. Chemical structure, numbering, and atom types for [1,4]-benzodiazepines.

Table 1. Atom Types and Nonbonded Parameters for [1,4]-Benzodiazepines[a]

atom type	description	R^*	ϵ	AN	AW
CY	imine sp^2 carbon	1.85	0.120	6	12.01
NY	imine sp^2 nitrogen	1.75	0.160	7	14.01
NX	nitro sp^2 nitrogen	1.75	0.160	7	14.01
F	fluorine	1.75	0.061	9	19.00
CL	chlorine	2.03	0.240	17	35.50
BR	bromine	2.18	0.320	35	79.90

[a] R^* and ϵ are van der Waals parameters. AN and AW represent atomic number and atomic weight.

length i, equilibrium bond length i, bond angle i, and equilibrium bond angle i, respectively. V_i, ρ_i, φ_i, and n_i are, respectively, the torsional potential constant, phase, torsion angle, and periodicity of bond i and describe its periodic torsional potential. The last three terms incude the nonbonded interactions. A_{ij}, B_{ij}, C_{ij}, and D_{ij} are Lennard-Jones and hydrogen bonding parameters that describe attractive and repulsive forces between nonbonded atoms and hydrogen bonding pairs. R_{ij} is the interatomic distance between atoms i and j, and q_i, q_j, and ϵ are the electrostatic charges of atom i, atom j, and the dielectric constant, respectively.

To extend the force field to [1,4]-benzodiazepines, nonbonded parameters were assigned for several new atom types not implemented in the Weiner *et al.* model. Bonded parameters K_{bs}, l_o, V, ρ, and n were calculated for all bonds containing new atoms and for bonding topologies between existing atoms not originally described in the force field.

Atom Types. Many of the atoms needed to model [1,4]-benzodiazepines are present in the Weiner *et al*. force field; however, several new atom types were necessary to represent these compounds properly. Atom types CY and NY were created to describe the imine C−N double bond. In order to mantain consistency, van der Waals and hydrogen bonding parameters for these atoms were extracted by analogy from existing sp^2 nitrogen and carbon atoms, as suggested by Kollman and co-workers.[10,11] Atom types F, Cl, and Br were needed in compounds bearing halogen substituents on the aromatic rings. van der Waals parameters for these atoms were obtained from published data.[12,20] Finally, to describe the nitro group present in several [1,4]-benzodiazepines, atom type NX was created. Nonbonded parameters for NX were taken from existing sp^2 nitrogen atoms described in the Weiner *et al.* model. The existing carboxyl and phosphate nonbonded oxygen, atom type O2, was used as oxygen atom for the nitro group. A summary of the types and nonbonded parameters for the new atoms is presented in Figure 1, Table 1, and Table 2.

Atomic Charges. The molecule electrostatic potential (ESP) has to be described accurately for the assesment of inter- and intramolecular interactions. In both the Weiner *et al.* and Cornell *et al.* models this is done by placing point charges on individual atoms that reproduce the ESP surface of the molecule.[10−12] Several charge derivation methods exist, and their reliability varies. When only approximate charges are needed, the methods of Berthold and Pullman[21] or Gasteiger and Marsili[22] suffice, with the advantage that they require little computational effort. However, detailed descriptions of molecular interactions demand a higher level of theory. In the Weiner *et al.* and Cornell *et al.* models, electrostatic charges have been computed by fitting atomic point charges to ESP surfaces derived from *ab initio* calculations at the STO-3G[10,11] and 6-31G* levels,[12] respectively. It has been shown that atomic point charges fitted to ESP surfaces derived from MNDO semiempirical methods are in excellent agreement with those derived by fitting to 6-31G* ESP surfaces and are several orders of magnitude less computationally intensive than *ab initio* charges.[23,24] For this reason, and to mantain consistency with the existing charge set for aminoacids and nucleic acids, all electrostatic charges were computed by fitting atomic point charges to MNDO derived ESP surfaces.

Table 2. Hydrogen Bonding Parameters for Atom Type NY

acceptor	C	D	acceptor	C	D
H	7557	2385	HO	7557	2385
H2	4019	1409	HS	14184	3082
H3	4019	1409	HTIP	7557	2385

Bond Stretching and Angle Bending Parameters. Equilibrium bond length and angle parameters for the new bonding topologies were obtained from X-ray data available in the Cambridge Structural Database[25] and microwave data.[26] When crystallographic data were used, equilibrium parameters were obtained by averaging a significant number of experimental values for noncyclic fragments. Use of [1,4]-benzodiazepine structural data would lead to an erroneous energy in the final system due to underestimation of ring strain effects.[27]

Bond stretching constants were obtained following the method of Hopfinger and Pearlstein.[27] The quantum mechanical potential (E_{QM}) for a model compound was calculated for a bracket of bond length values around the equilibrium value. The nonbonded molecular mechanic potential (E_{MM}) was calculated in the same bond length bracket using the Weiner *et al.* force field, and the difference between E_{QM} and E_{MM}, fitted to the quadratic bond stretching expression in a least squares sense:

$$K_{bs}(l - l_o)^2 = E_{QM}(l) - E_{MM}(l)$$

Model compounds used for bond stretching parameter derivation are shown in Figure 2. AM1,[28] PM3,[29,30] and MNDO[31] semiempirical methods were evaluated for the derivation of bond constants. MNDO failed to reproduce the preferred geometries of conjugated aromatic systems and was not considered further. Both AM1 and PM3 gave higher values than expected for certain bond stretching constants, a known drawback of semiempirical Hamiltonians.[32] To solve this problem, the method decribed was applied to molecules used as standard models in the original development of the force field,[10] and the ratio between the standard and calculated values was used to scale down calculated constants in our model compounds. Acetone, *N*-methylacetamide, and methyl ethyl ether were used to scale C−C, C−N, and C−O bonds, respectively, these being the model

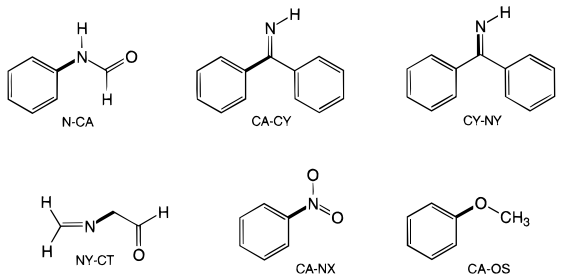

Figure 2. Model compounds used in the determination of [1,4]-benzodiazepine bond stretching constants. The bonds used for parametrization are highlighted.

Table 3. [1,4]-Benzodiazepine Bond Stretching Parameters[a]

bond	l_o (Å)	N	K_{bs} (kcal/Å^2) AM1	PM3	INT
N−CA	1.419	20	352	380	377
CA−CY	1.476	18	328	358	363
CY−NY	1.276	24	566	704	566
NY−CT	1.462	16	304	348	320
CA−F[b]	1.363	33	250	250	250
CA−CL[b]	1.741	34	257	257	257
CA−BR[b]	1.896	43	250	250	250
CA−NX	1.468	36	250	303	312
CA−NT[c]	1.390	50	360	360	360
NX−O2[c]	1.212	72	340	340	340
CA−OS[d]	1.371	59	355	365	450

[a] *N* indicates the number of experimental X-ray distances used to calculate l_o. [b] Parameters from Tripos 6.0.[c]Parameters are experimental data. [d] The INT bond stretching parameter for CA−OS was taken by analogy with the C−OH bond parameter from Weiner *et al.*[10,11]

compounds used by the Kollman group.[10] In this manner, bond parameters consistent with the existing Weiner *et al.* parameters were obtained for all relevant bonds in [1,4]-benzodiazepines. We also estimated bond constants for substituents on aromatic rings. For halogens, bond stretching parameters were taken directly from Tripos 6.0.[33] For the nitro group, experimental data existed for the N−O bond,[33] and data for the C−N bond were obtained as previously described. An experimental stretching constant was also available for the aromatic amino group.[33] All of the new bond stretching constants derived here, as well as those obtained by the linear interpolation method of Kollman (INT),[10−12] are summarized in Table 3.

The Weiner *et al.* force field has a small data table of angle bending constants, only six values being used to describe all angles involving H, N, C, and O.[10,11] To mantain consistency with the original parameter set, all angle bending constants and several equilibrium angle parameters were assigned by analogy with existing ones and are summarized in Table 4.

Torsional Potential Parameters. Together with van der Waals parameters and atomic charges, torsional potentials are the principal determinants of the relative energies of different conformers of a molecule. Accurate torsional potential parameters are thus crucial for describing the energetics and behavior of a system in dynamic simulations. An analogous approach to that taken for bond stretching parameters was followed when dihedral parameters were procured.[27] AM1 and PM3 Hamiltonians were used to calculate E_{QM} in model compounds (Figure 3) for sterically allowed rotations around the bond under study in 20° steps. The nonbonded potential E_{MM} was calculated for the same

Table 4. [1,4]-Benzodiazepine Angle Bending Parameters[a]

atoms	ϕ_o (deg)	*N*	K_{ab} (kcal/deg^2)
CA−N−C	127.2	20	50
C−CT−NY	110.4	10	63
C−CT−OH	109.5		70
CA−CA−CY	120.0		70
CA−CA−F	120.0		70
CA−CA−CL	120.0		70
CA−CA−BR	120.0		70
CA−CA−N	120.0		70
CA−CA−NT	120.0		70
CA−CA−OS	120.0		70
CA−CA−NX	120.0		70
CA−CY−CA	118.2	28	70
CA−CY−NY	122.6	24	70
CA−N−H	120.0		35
CA−N−CT	119.3	27	50
CA−NT−H2	109.5		35
CA−OS−CT	109.5		60
CA−NX−O2	118.3	52	70
CT−CT−NY	109.8	16	70
CT−NY−CY[a]	110.5		70
NY−CT−HC	109.5		35
NY−CT−OH	109.5		70
O2−NX−O2	123.5	26	70

[a] *N* indicates the number of experimental X-ray angles used in the derivation of ϕ_o. [b] Equilibrium angles are from microwave data found in ref 24.

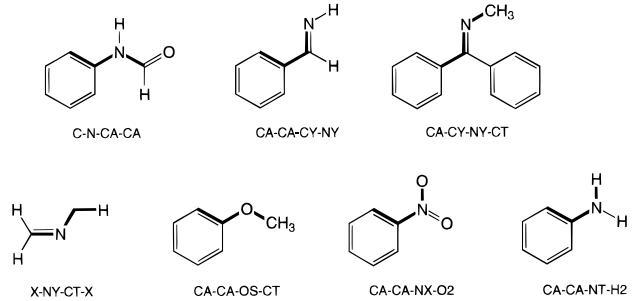

Figure 3. Model compounds used in the derivation of [1,4]-benzodiazepine torsional parameters. The dihedral angles studied are highlighted.

dihedral angle values using the Weiner *et al.* force field, and the difference, deconvoluted into a Fourier series of cosines:

$$\sum {}^1/_2 V_i [1 + \cos (n_i \varphi_i - \rho_i)] = E_{QM} - E_{MM}$$

For the bonds studied, not more than two Fourier terms were necessary to reproduce the torsional potential. In the case of the imine C−N double bond torsional parameter, we were able to scale the results with results for methylenimine, for which a torsional potential barrier of 57.5 kcal/mol has been determined.[34] The values for all new bonds are presented in Table 5, together with those obtained by Kollman's linear interpolation method (INT).[10−12]

Improper Torsions. Although out of plane bending contributions are not explicitly considered in the potential energy equation, they are included by the Weiner *et al.* force field as improper torsions in the periodic torsional energy term.[10,11] They are sometimes needed to mantain substituent planarity around certain atoms, such as sp^2 carbonyl carbons and amide nitrogens. In [1,4]-benzodiazepines only two new improper torsions need to be included to properly describe sp^2 imine carbons and aromatic amide nitrogens. Due to their similarities with the existing sp^2 carbonyl carbon and amide nitrogen, parameters from these atoms were used to

Table 5. Torsional Parameters for [1,4]-Benzodiazepines[a]

parameter	$V_{1/2}$	$V_{2/2}$	$V_{3/2}$	ρ_1 ($n = 1$)	ρ_2 ($n = 2$)	ρ_3 ($n = 3$)
			AM1			
C−N−CA−CA	0.37	2.30		0.0	180.0	
CA−CA−CY−NY		2.85			180.0	
CA−CY−NY−CT		28.7			180.0	
CA−CA−OS−CT		1.89			180.0	
CA−CA−NX−O2		1.38			180.0	
CA−CA−NT−H2		0.73			120.0	
X−NY−CT−X			0.34			0.0
			PM3			
C−N−CA−CA	0.31	3.16		0.0	180.0	
CA−CA−CY−NY		1.70			180.0	
CA−CY−NY−CT		29.8			180.0	
CA−CA−OS−CT		1.45			180.0	
CA−CA−NX−O2		0.22			180.0	
CA−CA−NT−H2		1.19			120.0	
X−NY−CT−X			0.27			0.0
			INT			
X−N−CA−X		1.32			180.0	
X−CA−CY−X		2.05			180.0	
X−CY−NY−X		29.0			180.0	
X−CA−NX−X		0.00			180.0	
X−CA−NT−X		2.59			120.0	
X−NY−CT−X			0.00			0.0
			Impropers			
X−X−CY−NY		10.5			180.0	
X−X−N−CA		1.0			180.0	

[a] Torsional constants (V) are in kilocalories per mole, and phases (ρ) are in degrees. The periodicity of the bond (n) is also indicated.

represent the improper torsional energy of imine carbons and aromatic amide nitrogens, respectively, and are listed together with torsional parameters in Table 5.

General Considerations. All molecular modeling and semiempirical molecular orbital calculations were performed using SYBYL 6.3 (Tripos Associates Inc. St. Loius, MO) running on a Silicon Graphics Indigo R4000 workstation. All AM1, PM3, and MNDO semiempirical calculations were performed through the interface to MOPAC 6.0[35] provided in SYBYL, using the PRECISE option. Net atomic point charges were obtained by computing the MNDO ESP surface and fitting it to expectation values on Connolly surfaces at 1.4, 1.6, 1.8, and 2.0 times the van der Waals radii, as described by Kollman.[23] Charges on sets of electronically equivalent atoms were substituted by the average charge of the set. Geometries used in charge calculation of model fragments were optimized with the same semiempirical method used for parameter derivation, while X-ray geometries with optimized hydrogen coordinates were used for [1,4]-benzodiazepines. A distance dependent dielectric constant ($\epsilon = R_{ij}$) was used to simulate solvent effects in all force field calculations. As was done in the derivation of atomic point charges, equilibrium geometries used in bond stretching and torsional barrier parameter derivation were optimized with AM1 or PM3 Hamiltonians, depending on the method used to obtain the quantum mechanical potential, E_{QM}. Molecular mechanic nonbonded potentials were calculated with the Kollman all atom force field, SYBYL's implementation of the Weiner *et al.* all atom force field, considering all atoms of the molecule for nonbonded interactions (nonbonded cutoff = 99 Å). An energy gradient below 0.05 kcal/mol was employed as termination criteria in all energy minimizations. Parameters from linear interpolation were calculated with the online WWW service provided by the Institute of Medical Biology, University of Tromsø (http://atf1.fagmed.uit.no/farma/ampar.html),[36] using X-ray derived equilibrium parameters as input. Comparison, superposition, and root mean square deviation (RMSD) calculation of structure sets were done with software previously developed in our laboratory.[37] A copy of the new parameter set can be obtained from the authors at gmoyna@cbnmr.chem.tamu.edu.

PARAMETER VALIDATION

Three sets of parameters for [1,4]-bezodiazepines were derived, two from AM1 and PM3 semiempirical methods and one using the linear interpolation method. A strategy similar to that used in the validation of the Tripos force field was followed.[33] To evaluate the ability of each parameter set in predicting the observed conformations of [1,4]-benzodiazepines, the sets were independently used to minimize the energy of a series of these compounds for which X-ray structural data was available.[25] For each parameter set, every structure of the series was minimized, and the RMSD for all heavy atoms between minimized and experimental structures was calculated. The RMSD values obtained within each parameter set were then averaged, yielding $RMSD_{av}$. Smaller values of $RMSD_{av}$ indicate a better agreement between experimental and calculated structures. The values obtained for a set of 30 [1,4]-benzodiazepines were 0.091, 0.095, and 0.096 Å for parameters derived using AM1, PM3, and linear interpolation, respectively. As a reference, the same calculations were performed with Tripos 6.0 general use force field,[33] obtaining an $RMSD_{av}$ of 0.140 Å. It is evident that any of the three parameter sets reported here predicts the experimental structures of [1,4]-bezodiazepines more precisely than a more general force field. Among the three new sets, structures minimized with parameters developed using the AM1 semiempirical had, on average, the smallest deviation from experimental structures, and these parameters were therefore chosen to complement the existing parameter set for modeling [1,4]-bezodiazepines with the Weiner *et al.* force field.

Deviations from experimental geometries of structures calculated with the new parameter set were then studied. Geometrical parameters that determine the three-dimensional structure of the seven-membered ring of [1,4]-benzodiazepines were analyzed. The average deviations between experimental and calculated bond lengths, bond angles, and dihedral angles described by the new parameter set were, respectively, 0.01 Å, 0.8°, and 5° for the set of 30 [1,4]-benzodiazepines studied. These results are summarized in Table 6, together with deviations observed for four particular cases involving the medicinally important [1,4]-benzodiazepines shown in Figure 4. The excellent agreement between calculated and experimental structures for these cases can be seen in Figure 5, where their X-ray and calculated structures are superimposed.

Finally, the new set of parameters was tested in dynamic simulations. It has been reported that the seven-membered ring of [1,4]-bezodiazepines can exist as two interconvertible conformers.[38] When no substituents are present at the C-3 position, the two forms are mirror images, indicating the prochiral nature of these compounds. It is desirable that the force field parameters used to model [1,4]-bezodiazepines not only reproduces faithfully their X-ray structure, but also

Table 6. Deviations from Experimental Bond Lengths, Bond Angles, and Dihedral Angles for Structures Calculated using AM1 Derived Parameters[a]

molecule	av	diazepam (Valium)	prazepam (Demetrin)	oxazepam (Praxiten)	flunitrazepam (Rohypnol)
			CSD Refcode		
RMSD (Å)		DIZPAM10	PRAZAM	OXAPAM10	CAGWUC
	0.091	0.077	0.123	0.054	0.047
			Distances (Å)		
N−CA	0.010	0.001	0.009	0.015	0.016
CA−CY	0.014	0.000	0.005	0.016	0.019
CY−NY	0.005	0.000	0.008	0.006	0.000
NY−CT	0.009	0.003	0.011	0.005	0.025
			Angles (deg)		
C−N−CA	0.94	1.33	0.23	0.18	0.95
N−CA−CA	0.34	0.03	0.80	0.17	0.09
CA−CA−CY	0.60	0.41	0.07	0.25	0.17
CA−CY−CA	1.44	2.77	0.75	0.99	1.87
CA−CY−NY	0.22	0.85	0.68	1.48	0.05
CY−NY−CT	0.26	1.24	0.75	1.13	0.30
NY−CT−C	1.60	0.52	1.11	3.75	0.23
			Torsions (deg)		
C−N−CA−CA	5.3	10.2	3.5	4.6	4.9
CA−CA−CY−NY	3.9	5.6	5.7	5.0	3.9
CA−CY−NY−CT	4.1	5.3	1.4	3.8	2.0
CY−NY−CT−C	4.7	4.3	2.8	7.1	3.5

[a] The absolute value of the deviations was used for the calculation of the averages.

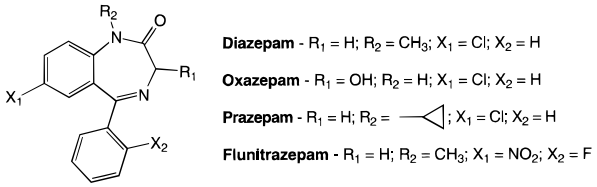

Figure 4. Chemical structures of diazepam, oxazepam, prazepam, and flunitrazepam.

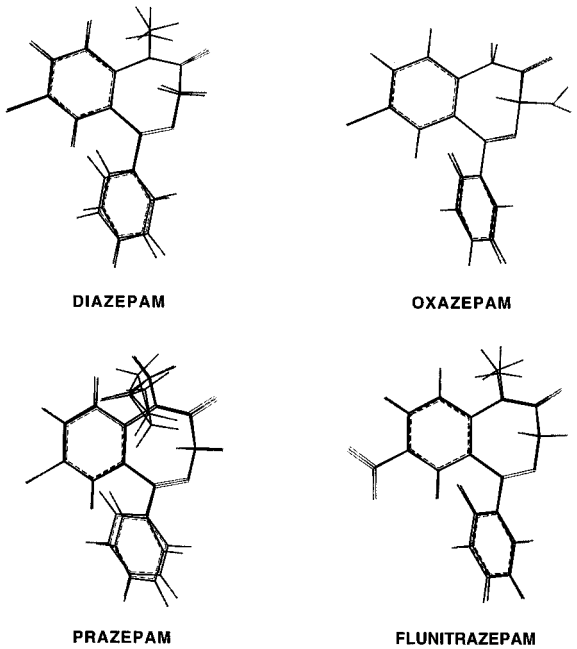

Figure 5. Superposition of X-ray and minimized structures for the [1,4]-benzodiazepines discussed in the text.

describes this dynamic behavior. To investigate this, the four compounds presented in the previous section were subjected to simulated annealing,[39,40] a molecular dynamics technique used for conformational searching, using the new parameter set. The simulated annealing experiments consisted of 20 cycles of heating at 800 K for 1000 fs and exponential annealing to 200 K for 1000 fs, followed by energy minimization of the annealed structures. In all cases, both conformations of the seven-membered ring were found, indicating that the new parameter set gives the dynamic simulations enough freedom to sample adequately all the conformational space available to the studied molecules. Cases with no substitution at C-3 had no ΔE between the two conformers, as expected for pseudoenantiomers. For oxazepam, which bears a hydroxyl substituent at the C-3 position, the pseudoequatorial conformation was energetically favored by 5.2 kcal/mol. Although no experimental data exist, the calculated ΔE is consistent with NMR experiments[41] which indicate the presence of a single oxazepam isomer in solution at 300 K, and thus a ΔE for the ring inversion higher than 4 kcal/mol at this temperature.

CONCLUSION

Although a higher level of theory has been used in the development of Weiner *et al.* force field parameters for other compounds,[42] the set derived from semiempirical methods presented here predicts the experimental conformations of [1,4]-benzodiazepines with accuracy. Simulated annealing experiments also show that the new parameter set does not constrain the stuctures during dynamic simulations and permits a thorough sampling of the conformational space available to them. Although not suitable for the prediction of heats of formation or vibrational frequencies, the parameters reported here should be useful for conformational studies involving [1,4]-benzodiazepines, with the advantage that these compounds can now be modeled together with proteins and nucleic acids. The reliability of the new parameter set will be thoroughly tested in conformational studies of [1,4]-benzodiazepine peptidomimetics of allatostatin neuropeptides, and the results of these investigations will be reported in due course.

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