Ab initio study of β-alanine conformers in the gas phase

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Dedicated to Professor Eusebio Juaristi on the occasion of his 55th birthday

Abstract

Twelve conformers of non-ionized β-alanine have been investigated using high level *ab-initio* methods. Geometry optimizations and frequency calculations have been performed at MP2/6-311G(d,p) and MP2/6-311++G(d,p) levels of calculation. Relative energies, rotational constants, harmonic vibrational frequencies and infrared intensities are reported. The relevance of using basis sets including diffuse functions has been supported. A factor of 0.9814 is proposed to scale the MP2/6-311++G(d,p) vibrational frequencies. The good agreement between the theoretical results and the available experimental values supports the reliability of the MP2/6-311++G(d,p) level of theory for describing the conformational behavior of molecules with internal hydrogen bonds.

Keywords: β-Alanine, conformers, MP2, scaling factor, vibrational frequencies, diffused basis set

Introduction

Amino acids exist as zwitterions in solution and in the crystalline state, stabilized by electrostatic, polarization, and H-bonding interactions with their environment.[1-4] In the gas phase, where these intermolecular interactions have no effect,, they exist as non-ionized species.**Error! Bookmark not defined.,Error! Bookmark not defined.** The study of the conformational behavior of non-ionized amino acids is important for understanding the dynamics of the peptide and protein backbones.

β-Amino acids, although much less abundant than their α partners, are also present in peptides, and in free form they show interesting pharmacological effects. They can be cyclized to β-lactams which have potential biological activity. In this respect, several methods for the synthesis of racemic β-amino acids have been developed,[5-7] and in the last few decades special attention has been paid to the preparation of enantiomerically pure compounds. Professor

Juaristi, to whom this commemorative issue is dedicated, and co-workers have made significant contributions to this field of investigation.[8-21]

Although the conformational flexibility of free, non-ionized α-amino acids is now very well established, both experimentally [22] and theoretically, [23] there is a lack of information on the β conformers. Since the experimental investigation of gaseous amino acids is quite difficult, computational chemistry could become a very useful tool providing important information on such systems.

In the present work we have chosen β-alanine because it is the simplest of the β-amino acids, therefore this molecule is sufficiently small to allow high quality calculations. The conformational behaviour of β-alanine zwitterion has been recently established by NMR spectroscopy.[24,25] It has also been investigated by post-Hartree-Fock and density functional methods (DFT).[26] However, there are very few conformational studies on the non-ionized form of β-alanine.[27-29] In reference **Error! Bookmark not defined.** it has been established that the Hartree-Fock method is not reliable enough for quantitative predictions of conformers' equilibrium, while the approaches including electron correlation (DFT, MP2 and MP4) perform remarkably well when using medium size basis sets including diffuse functions. The validity of the post Hartree-Fock methods for describing conformational behaviours has also been shown for the α amino acids.**Error! Bookmark not defined.** Accordingly, we have chosen the MP2/6-311G(d,p) and MP2/6-311++G(d,p) levels of theory for the study of the non-ionized β-alanine conformers. The previous studies on this molecule**Error! Bookmark not defined.-Error! Bookmark not defined.** were performed with no correlated methods and with non diffused basis sets.

Computational Details

All the calculations have been performed with the Gaussian 98 [30] package of programs. Relaxed scan calculations were carried out for all the torsions responsible for the non-rigidity of the molecule. They were performed trough the full 360° space with steps of 10°, using the second-order Møller-Plesset (MP2) method [31,32] and the 6-311G(d,p) and 6-311++G(d,p) basis sets. The minima structures were identified and considered identical if their energies differed by less than 10^{-5} hartree and if the root-mean-square difference of their rotational frequencies differed by less than 30 MHz. Twelve unique conformations were then fully optimized and frequency calculations were carried out, all at MP2/6-311G(d,p) and MP2/6-311++G(d,p) levels of theory. They were verified to be minima by establishing that their matrices of second derivatives (hessians) were positive definite upon diagonalization. The hessians were all determined analytically. Relative energies were calculated at 0K and 298 K. Zero point corrections (ZPE) and thermal corrections (TCE) to energy were included. The MP2/6-311G(d,p) values were corrected by using the recommended scaling factors. The ZPE and TCE values computed at MP2/6-311++G(d,p) level have not been corrected, since, to our best knowledge, there are no scaling factors reported for that level of calculation.

Results and Discussion

β-Alanine shows four large amplitude vibrations responsible for the non-rigidity of the molecule. They have been presented in Figure 1 as: φ_1 (-NH$_2$ torsion), φ_2 (central C2-C5 torsion), φ_3 (-COOH torsion), and φ_4 (hydroxyl torsion). The φ variables can be identified with dihedral angles as φ_1 = H12N7C5C2, φ_2 = N7C5C2C4, φ_3 = O6C4C2C5, and φ_4 = H11O10C4C2. The torsions corresponding to variations in φ_1 and φ_4 can be interpreted as the internal rotations of tops –NH$_2$ and –OH, with respect to a fixed frame. In contrast variations in φ_2 and φ_3 involve two tops of similar weights and consequently they can hardly be considered as separated movements.
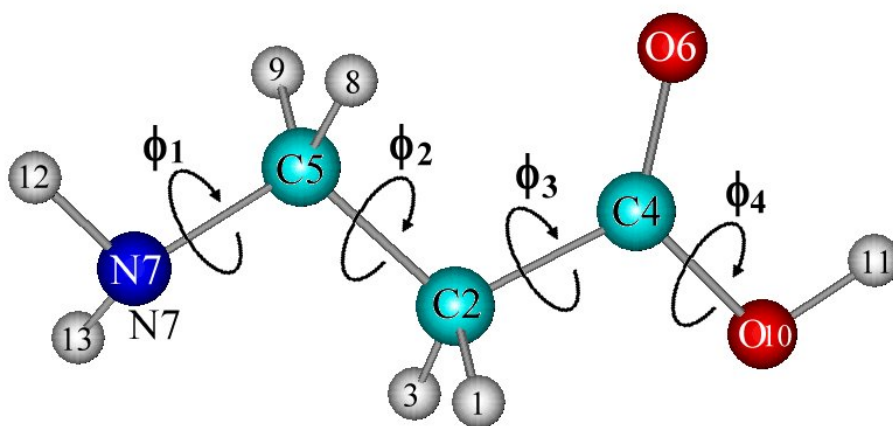

Figure 1. Atoms numbering and torsional coordinates.

Twelve different conformations were found for β-alanine by varying the torsional variables describing above (Figure 2). Their values of φ_1, φ_2, φ_3, and φ_4 are shown in Table I, as well as the energies relative to conformer I at 0K and at 298 K. The data is reported at two different levels of calculation: MP2/6-311G(d,p) and MP2/6-311++G(d,p). In order to present more accurate values the Zero Point Energy correction (ZPE) and the thermal correction to energy (TCE), they have been improved by using the scaling factors recommended by Scott and Radom.[33] at MP2/6-311G(d,p) level of theory. The MP2/6-311++G(d,p) ZPE and TCE values have not been corrected, since, to our best knowledge, there are no scaling factors reported for that level of calculation.

Table 1. MP2/6-311++G(d,p) molecular parameters defining β-alanine conformations, and energies (kcal/mol), relative to conformer *I*

| Conf.	φ_1	φ_2	φ_3	φ_4	6-311G(d,p)		6-311++G(d,p)	
					E(0K)	E(298K)	E (0 K)	E(298K)
1	79.9	64.6	141.2	3.76	0.00	0.00	0.00	0.00
2	166.1	64.4	6.15	-179.4	0.24	0.53	-0.41	-0.11
3	-62.8	63.3	11.8	-178.2	0.67	0.95	0.33	0.63
4	66.4	53.9	-122.9	-178.3	1.70	1.99	0.79	1.09
5	170.6	-60.9	-55.6	-178.9	1.70	2.03	0.87	1.20
6	175.1	-175.4	12.6	-177.9	1.87	2.31	1.08	1.54
7	-59.3	180.0	-0.09	180.0	2.04	2.48	1.52	2.03
8	166.2	57.7	-149.4	177.7	2.11	2.43	1.22	1.55
9	175.7	80.19	127.2	179.8	2.37	2.70	1.58	1.89
10	173.9	177.8	-118.5	-179.5	2.67	3.10	1.61	2.04
11	175.1	-175.4	12.6	-177.9	2.92	3.40	1.08	1.54
12	172.5	-176.2	-1.985	-1.920	7.37	7.88	6.31	6.88
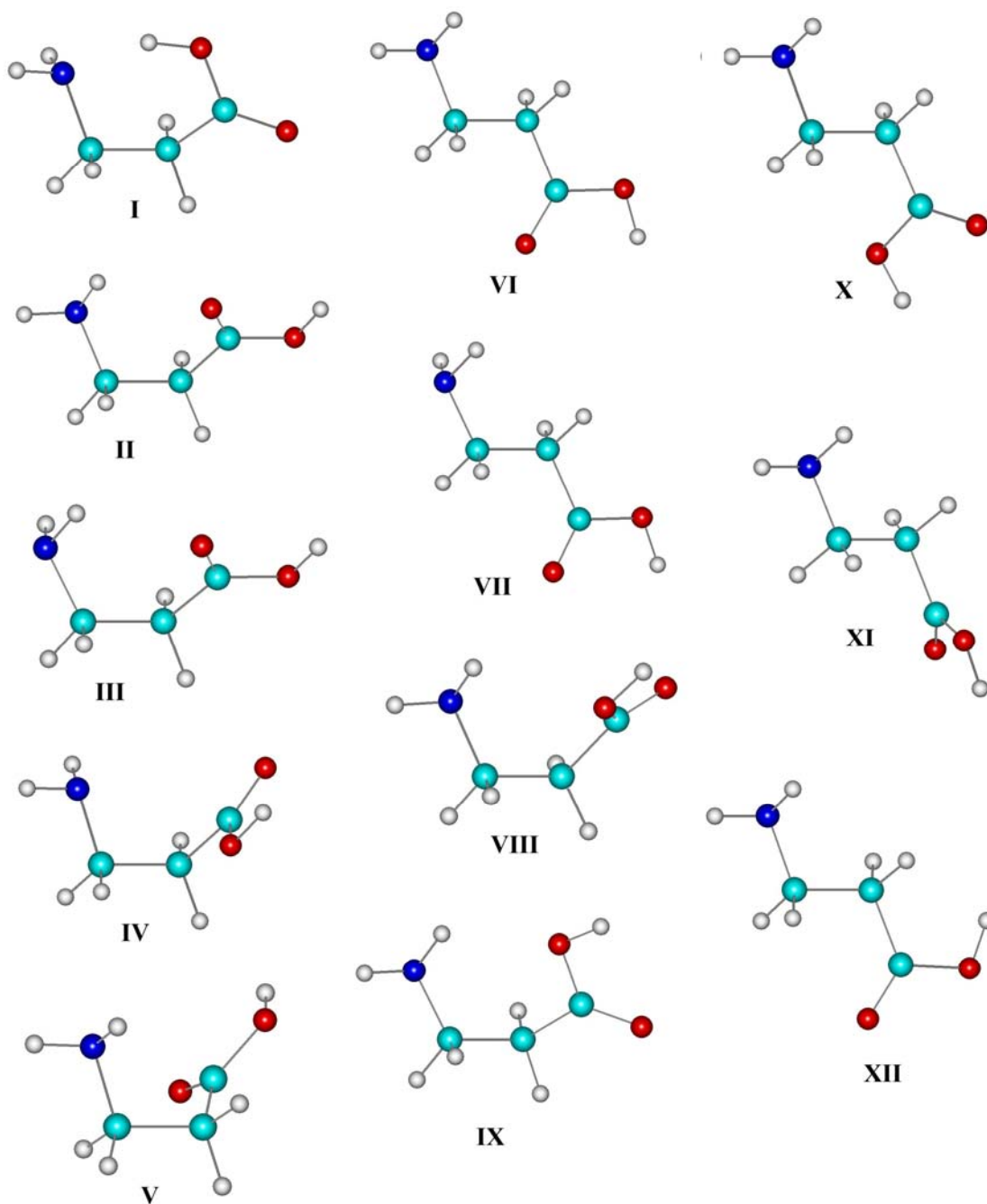
Figure 2. Conformers of β-alanine corresponding to local energy minima on the MP2/6-311G(d,p) potential energy surface.

The relative energy values in Table 1 show a discrepancy between the results obtained with the 6-311G(d,p) and the 6-311++G(d,p) basis sets. The discrepancy could be caused by the overestimation of internal hydrogen bonds when the used basis set do not include diffuse functions, which was previously pointed out by Nielsen *et al*.[Error! Bookmark not defined.] In order to

clarify that, a more detailed analysis on the possible intra-molecular interactions in β-alanine conformers is needed. Bader topological analysis [34] of the MP2/6-311G(d,p) wave functions, corresponding to all the studied conformers, were performed in order to identify and quantify all possible intra-molecular interactions (Table 2). All the hydrogen bond interactions lead to ring critical points in the corresponding conformers. The strongest internal hydrogen bond was found in conformer *I*, between H11 and N7. The interaction distance was found to be *d (7,11)* = 1.77 Å, which is the shortest distance among all the found interactions. The shortest distance and the largest value of electronic charge density (ρ) and of the Laplacian of ρ, ($\nabla^2 \rho$) at the critical points, show that the N7-H11 interaction in conformer *I* is the strongest one. This finding reinforces the hypothesis that non diffused basis set overestimate the effect of internal hydrogen bonds on the energy values. In our case this overestimation is found responsible for the prediction of conformer *I* as the most stable at MP2/6-311G(d,p) level of theory. However, there is crucial to find another way to prove that the relative energies obtained at MP2/6-311++G(d,p) are the correct ones.

Table 2. Characterization of the intra-molecular interactions found in the β-alanine conformers

Conf.	Critical Points	Atoms involved	Atomic distance	ρ	$\nabla^2 \rho$
I	*Bond*	7,11	1.769	0.049	-0.028
	Ring	7,5,2,4,10,11	-	0.018	-0.026
II	*Bond*	6,13	2.366	0.012	-0.011
	Ring	6,4,2,5,7,13	-	0.011	-0.013
III	*Bond*	6,12	2.404	0.012	-0.011
	Ring	6,4,2,5,7,12	-	0.011	-0.013
VIII	*Bond*	10,13	2.522	0.009	-0.009
	Ring	10,4,2,5,7,13	-	0.009	-0.010
IX	*Bond*	10,13	2.250	0.014	-0.014
	Ring	10,4,2,5,7,13	-	0.010	-0.014

Two conformers of β-alanine have been previously identified by McGlone and Godfrey**Error! Bookmark not defined.** by using a Stark-modulated free-expansion jet spectrometer. The authors named them β-ala(x) and β-ala(y). Hereafter we are referring to them accordingly. Their observations led to identify β-ala(x) as the lowest energy conformation. Their spectroscopic derived parameters are reported in Table 3 and have been used as reference for comparing our results. Calculations on the trideutero analogues of all the studied conformers have also been performed. The data of the non-deuterated and deuterated parent species, as well as the associated changes in the rotational constants are reported in Table 3. Since the changes in the rotational constants on deuteration are a function of the amino and hydroxyl hydrogen positions, they can be use to select which of the modeling conformers correspond to those identified in reference **Error! Bookmark not defined.**. From the agreement on the rotational constants and on their variation,

the calculated conformers corresponding to those observed by McGlone and Godfrey are: conformer *II* = β-ala(x) and conformer *I* β-ala(y). This validate the MP2/6-311++G(d,p) relative energies and reinforces the relevance of using basis set with diffuse functions, even if correlation methods are employed. Now, it seems reasonable to rely on the MP2/6-311++G(d,p) results and propose conformer *II* as the most stable one.

Table 3. MP2/6-311++G(d,p) rotational constants (GHz)

Conf.	A	B	C	Δ (A)	Δ (B)	Δ (C)
β-ala(x)[a]	7.268	2.335	1.987			
d_3- β-ala(x)[a]	7.003	2.145	1.835	0.264	0.190	0.151
β-ala(y)[a]	7.177	2.500	1.982			
d_3- β-ala(y)[a]	6.805	2.330	1.866	0.372	0.169	0.116
I	7.172	2.513	1.993			
d_3-I	6.804	2.342	1.876	0.368	0.171	0.117
II	7.159	2.363	2.011			
d_3-II	6.889	2.168	1.857	0.270	0.195	0.154
III	6.982	2.313	2.005			
d_3-III	6.584	2.147	1.887	0.398	0.166	0.119
IV	5.742	2.486	2.354			
d_3-IV	5.373	2.293	2.182	0.369	0.193	0.172
V	5.825	2.435	2.296			
d_3-V	5.499	2.237	2.114	0.326	0.198	0.182
VI	9.195	1.858	1.585			
d_3-VI	8.933	1.678	1.449	0.263	0.179	0.136
VII	9.184	1.834	1.571			
d_3-VII	8.933	1.678	1.449	0.252	0.156	0.122
VIII	6.321	2.433	2.200			
d_3-VIII	5.884	2.279	2.047	0.437	0.154	0.153
IX	7.168	2.405	1.938			
d_3-IX	6.664	2.253	1.806	0.503	0.151	0.132
X	8.465	1.895	1.668			
d_3-X	8.032	1.731	1.527	0.433	0.164	0.141
XI	9.195	1.858	1.585			
d_3-XI	8.932	1.678	1.449	0.263	0.179	0.136
XII	9.045	1.859	1.580			
d_3-XII	8.405	1.706	1.456	0.641	0.153	0.124

[a] Reference **Error! Bookmark not defined.**.

As it has been previously established, the *ab-initio* vibrational frequencies (ω) are typically larger than the fundamentals (υ) observed experimentally.[35] A major source of this disagreement

is the neglect of anharmonicity effects in the theoretical treatment. Other causes are the incomplete incorporation of electron correlation and the use of finite basis set. However, the overestimation of *ab-initio* vibrational frequencies is relatively uniform, and consequently frequency scaling factors are often applied. Scott and Radom[Error! Bookmark not defined.] recommend a scaling factor of 0.9496 for the MP2/6-311G(d,p) vibrational frequencies. However, there is no scaling factor recommended for frequencies computed at MP2/6-311++G(d,p). Analyzing the MP2/6-311G(d,p) scaled frequencies together with the MP2/6-311++G(d,p) harmonic frequencies of all the studied conformers, a scaling factor of 0.9814 has been used in the present work to correct the latter ones. The information contained in the MP2/6-311++G(d,p) theoretical vibrational frequencies and infrared intensities reported in Table IV, for the six most stable conformers of β-alanine, could help on the interpretation of experimental investigation of the gas-phase vibrational spectrum of this amino acid.

The results summarized in Table 4 show that there are some normal modes which do not change significantly from one conformer to another. The band corresponding to ω_{26} (-C=O stretching) appears as the most intense one in all conformers but *I*, and its frequency changes very little among them, from 1777 (*II*, *III*) to 1805 (*XII*) cm^{-1}. However, some normal modes with high IR intensities shift considerably. For example the modes involving the –OH group. In conformer *I* the mode corresponding to the –OH stretching (ω_{31}) shifts towards lower frequencies in about 450 cm^{-1}, been the highest intensity vibration of this conformer, while the peak of the –OH torsion (ω_{13}) shifts towards higher frequencies in about 350 cm^{-1}. These changes can be explained by the strong intra-molecular hydrogen bond in conformer *I*, involving the hydrogen atom in the –OH group. High intensity normal modes whose frequency does not change from one conformer to another should serve as indicators of the presence of β-alanine, while characteristic shifts should help identification of β-alanine conformers.

Table 4. MP2/6-311++G(d,p) vibrational frequencies (cm^{-1}) and infrared intensities (km/mol) corresponding to the six most stable conformers of β-alanine

	I		II		III		IV		V		VI	
	ω	I	ω	I	ω	I	ω	I	ω	I	ω	I
1	86	0.5	51	1.7	44	0.2	73	1.3	47	2.6	44	3.0
2	203	6.0	149	1.7	144	1.7	121	2.7	124	1.0	107	2.3
3	273	8.1	240	12.0	229	3.1	225	12.8	218	18.1	177	3.7
4	329	5.8	292	48.0	329	46.5	276	20.8	267	20.3	249	45.1
5	402	13.1	363	7.0	353	11.7	396	1.8	397	1.3	373	2.5
6	486	9.6	485	42.8	491	17.8	460	2.2	448	8.2	445	16.7
7	568	3.1	509	28.8	512	40.5	552	50.2	550	44.7	509	41.7
8	690	7.5	616	34.2	613	20.6	590	92.8	616	83.0	624	80.9
9	812	12.5	633	74.9	634	80.1	691	35.6	704	46.9	637	41.1
10	869	51.4	805	5.8	791	28.8	805	60.1	806	64.4	793	20.7
11	915	23.4	867	71.0	854	173.6	846	65.2	850	62.9	861	94.1
12	952	30.6	896	49.2	878	30.4	906	11.6	907	8.1	896	17.4
13	982	84.0	950	6.0	934	3.4	973	4.6	973	6.6	993	15.6
14	1016	13.5	1061	20.9	1030	22.5	1012	37.6	1023	8.8	1066	39.9
15	1083	6.0	1114	41.3	1114	58.8	1089	54.7	1094	42.5	1102	66.7
16	1137	11.0	1126	176.0	1123	148.6	1116	52.2	1116	94.6	1131	140.2
17	1232	89.2	1196	101.7	1185	86.9	1207	139.6	1191	167.6	1171	71.6
18	1281	15.6	1222	3.5	1242	20.7	1252	9.9	1256	12.8	1250	14.9
19	1302	5.8	1295	7.1	1292	5.3	1302	9.4	1291	1.2	1289	2.2
20	1358	7.5	1341	4.8	1372	33.5	1325	25.0	1322	11.6	1322	1.9
21	1407	8.9	1398	66.4	1385	5.4	1376	34.4	1398	71.9	1376	58.7
22	1449	13.4	1420	33.8	1403	54.2	1415	12.2	1409	12.1	1434	61.9
23	1470	233.2	1435	17.8	1439	17.4	1459	14.9	1464	14.2	1450	9.2
24	1501	5.1	1491	3.0	1474	5.7	1504	2.0	1501	4.8	1504	1.0
25	1615	31.2	1622	61.9	1629	26.3	1624	33.8	1623	31.9	1629	33.8
26	1788	374.9	1777	237.5	1777	249.7	1789	292.9	1787	268.2	1781	262.6
27	3013	45.2	2991	51.4	3020	7.9	2979	70.5	2983	67.4	2989	46.4
28	3020	5.7	3033	7.7	3040	30.3	3042	9.0	3042	9.5	3034	6.6
29	3080	16.7	3074	23.3	3074	6.1	3085	5.8	3084	5.4	3078	0.7
30	3110	5.4	3094	5.1	3099	17.5	3109	14.5	3107	14.2	3096	17.7
31	3290	792.7	3482	2.4	3479	1.3	3473	0.5	3475	0.5	3473	0.3
32	3469	0.8	3575	10.1	3579	7.9	3571	5.0	3573	5.1	3568	3.6
33	3562	12.4	3731	75.4	3728	74.6	3737	76.9	3726	70.4	3731	74.1

Conclusions

Twelve different conformers of gaseous β-alanine were identified. The minima structures have been considered identical if their energies differ by less than 10^{-5} hartree and if the root-mean-square difference of their rotational frequencies differ by less than 30 MHz.

Geometry optimizations and frequency calculations have been performed at MP2/6-311G(d,p) and MP2/6-311++G(d,p) levels of calculation. The relevance of using basis sets including diffuse functions to correctly predict the relative energies of the conformers has been supported.

Relative energies, rotational constants, harmonic vibrational frequencies and infrared intensities are reported. A factor of 0.9814 is proposed to scale MP2/6-311++G(d,p) vibrational frequencies.

The good agreement between the theoretical results and the available experimental values supports the reliability of the MP2/6-311++G(d,p) level of theory for describing the conformational behavior of molecules with internal hydrogen bonds.

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