Conformational Analysis of Polyacrylamide

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Summary: In this paper the dependence of the Electrostatic Potential (ESP) fitted charges, that play an important role in Molecular Mechanics (MM) calculation on the conformations, is studied. It is concluded that in order to accurately calculate the energy of one conformation, the (ESP) charges corresponding to the studied conformation must be used. Systematic search method is used to search the conformers of CH_3-CH($CONH_2$)CH_2-CH_2-$CONH_2$ which is the model compound of Polyacrylamide and 16 stable conformers are found. The most stable conformer is also obtained.

Introduction

Molecular mechanics has proved to be powerful tool for understanding the structural and energetic preferences of molecules. Using an analytical representation of the energy of a molecule as a function of internal coordinates and inter atomic distances, it is possible to reproduce or even predict conformational energy differences. A prerequisite for the reliable use of these techniques in the study of molecules is an accurate force field. Although significant progress has been made in the development of force fields to describe the energy surface of many types of compounds. Fundamental question still exist regarding the functional form of these force fields that eventually pertain to their accuracy and predictability. There is no agreement yet as the actual functional form to be used in the energy expression, and consequently, various force fields differ with respect to the values of corresponding force constants. There is not even agreement on how to treat electrostatic interactions, with a variety of representations and degrees of elaboration in use, ranging from preferentially omitting electrostatics [1], to the use of atomic charges [2-4], bond dipoles [5-6] and high order atomic multiplet moments [7].

Many potential functions are used in the molecular mechanics method, but they have many characteristics in common. They are pairwise potentials that contain non-bonded van der Waals interactions which are incorporated via a Lennard-Jones 6-12 terms and electrostatic term represented by an atom-centered monopole expression (coulomb term). Potentials which share these features include the Amber [8], Charmm [9] and Goromos [10] force fields. Similar potentials have been used by Hagler [11] and Scherage [12]. The electrostatic term is key to an accurate description of molecules in the potentials of this type. Along with 6-12 terms, it determines the intermolecular interactions. Thus, it is critically important to model the electrostatic interaction as accurately as possible. It is a difficult task to assign charges based on any type of experimental data [13], therefore they must be determined by some theoretical technique. Atomic charge is a quantity which is not rigorously defined in quantum mechanics [14]. Mulliken population analysis is a computationally simple method to extract atomic charges from approximate HF function [14], but these charges have proven unsatisfactory [15]. The second method, deriving the charges by fitting the molecular Electrostatic Potential (ESP), which is an observable quantity, has yielded much more promising results [16]. The molecular electrostatic potential may come from ab initio wave function or semiempirical wave function [17]. However, the applicability of molecular electrostatic potential derived atomic charges is seriously limited, since their computations, present in pratice several problems. One is that it becomes more difficult as the size of the molecule or the quality of the basis set increases. Another problem is that the ESP charges are dependent on the conformation of the molecule. As a rule, however, the ESP charges derived from one conformation is applied to all conformations of the same molecule

during the simulation. Apparently this can not give an accurate description of the electrostatic interaction.

In our following work, we will study the dependence of ESP charges on the conformation and its effect on the energy calculation of conformation. We will use the molecular mechanics to do conformational analysis of polyacrylamide.

Molecular mechanics theory and conformational analysis method

Molecular mechanics theory

Unlike in quantum mechanical approaches, electrons are not explicity included in molecular mechanics. This is possible due to the Born-Oppenheimer approximation, which states that electronic and nuclear motions can be uncoupled from one another and considered separately. Potential energy functions are used to describe the interactions between nuclei. With judicious parameterization, the electronic system is implicitly taken into account, therefore this is a strictly classical representation of chemical structure.

There are many molecular mechanics programs available tody. They differ in the potential energy function form and the parameterization. But they have characteristics in common. They are pairwise potentials that contains terms of the following form.

$$E = E_a + F_b + E_t + E_{vdw} + E_{elec}$$

where E_a, E_b, E_t, E_{vdw} and E_{elec} represent bond stetching, angle bending, torsional interactions, van der Waals interactions and electrostatic interactions, respectively.

The harmonic approximation has been the starting point for the bond stretching and angle bending term in most molecular mechanics programs, but in some programs some higher power terms are added to it. Dihedral torsions are usually represented by a finite Fourier series. A Lennard-Jones equation [18] or exponential-6 equation [19] or Morse [20] is selected to describe the van der Waals interaction. The electrostatic interactions are represented by coulomb law when atom-site charge mode is used.

In some programs, special considerations are made for hydrogen bonding [21] and additional cross terms [22] such as strech-bend and torsion-bend are also included in calculating the total energy of molecule.

In our work all the molecular mechanics calculations are carried out by using the all-atom AMBER 4.0 [23,24] in which the potential function describing the interaction of the system has the following form.

$$U_{total} = \sum_{bonds} K_r(r - r_{eq})^2 + \sum_{angles} K_\theta(\theta - \theta_{eq})^2 + \sum_{dihedrals} \frac{\nu}{2}[1 + \cos(n\phi - \gamma)]$$
$$+ \sum_{i<j} \{(\frac{A}{R^{12}_{ij}} - \frac{B}{R^6_{ij}}) + \frac{q_i q_j}{\varepsilon R_{ij}}\} + \sum_{H\text{-}bond} \{\frac{C_{ij}}{R^{12}_{ij}} - \frac{D_{ij}}{R^6_{ij}}\}$$

where r,Kr and r_{eq} are bond length, bond force parameters, and equilibrium bond length, respectively; θ, K_θ, θ_{eq} are bond angle, angle force parameter, and equilibrium angle respectively , ϕ, ν_n and γ are dihedral angle, dihedral barrier height, multiplicity, and phase, respectively. A, B, C, D are Lennard-Jones and hydrogen bonding parameters; R_{ij} is the non-bonded interatomic distance; and q_i, q_j and ε are electrostatically derived atomic charges and dielectric constant, respectively.

Conformational analysis

The conformations of a given molecular configuration are traditionally defined as the set of arrangements of its atoms in space, which can be interconverted solely by motion about single bonds [25]. Rotation about single bond is, in most instances, not free and some conformations are more stable than others. "Conformational analysis" is an analysis of the physical and chemical properties of a compound in terms of the conformation (or conformations) of the pertinent ground states, transition states, and (in the case of spectra) excited states. Stable conformations of a molecule (sometimes called conformers) correspond to local minima in the potential energy function.

Most molecules of interest to organic, bio-organic, and medicinal chemists can adopt more than one conformation. The conformations of a molecule are typically present in different amounts. Interconversion between conformations is due to internal vibrations of molecule. The molecule undergoes oscillations about each minimum, giving rise to conformational entropy. The relative populations of

the minima depend on their statistical weights, which include contributions from both the potential energy and the entropy. To perform a "conformational search" it is therefore necessary to determine those minimum energy conformations that are believed to contribute to the overall conformational partition function. This requires some means of determining the energy of any given conformation and a method for determining minima on the surface described by the potential energy function. Conformational energies are usually calculated using either quantum mechanics (often by semiempirical methods) or molecular mechanics. A variety of methods can be used to locate minima in the conformational energy surface [26]. The most general conformational searching algorithms are those that aim to identify all minima on the potential energy surface. However, as the number of minima usually increases dramatically with the number of rotatable bonds, finding all of them rapidly becomes an impossible task. It is fortunate that not all of these conformations are thermodynamically and kinetically important [27-28]. There are many techniques that are available to survey conformational spaces. The most thorough conformational search procedure is an exhaustive systematic search [29], which guarantees sampling of all region of all space. As the conformations of a molecule can, to a first approximation, be defined as those structures that differ solely by rotating about single bonds. An obvious way to perform a conformtional search is to systematically increment each single bond through 360°C, thereby generating all possible combinations of torsional angles. Such an algorithm is called a grid search. It is usual to then minimize each structure to find the associated minimum energy conformation. In this way all the minima can be found, but the size of molecule to which this straightforward algorithm can be applied is fairly limited. Suppose the angular increment is θ and that there are n rotatable bonds in the molecule. The number of conformations generated is therefore $(360/\theta)_n$. Most of the heuristic search methods employed to sample conformational space are based either on molecular dynamics and/or Monte Carlo techniques with the most popular being simulated annealing [30-33] and Monte Carlo with energy minimization [33-35]. Some other interesting heuristic search techniques include the diffusion equation method [36-37] and an approximate solution of the imaginary time Schrodinger equation via a mobile basis set [38].

Method employed

System

In order to study the conformation dependent properties of polyacrylamide we use its monomer CH_3 - CH_2 - $CO(NH_2)$ and dimer CH_3 - $CH(CONH_2)$- CH_2 - CH_2 - $CO(NH_2)$ to model it. The conformations of the monomer and the dimer are explored in torsion angle phase space by rotating systematically about their single bonds.

Conformational search procedure

In our study we use the systematic search method to sample the potential energy surface of the monomer and the dimer using molecular mechanics method. The angular increment, we take, is 30°.

Atomic charges calculation

The Atom-centered point charges for the force field calculation are determined using the AM1 [39] semiempirical method followed by Electrostatic Potential (ESP) calculations fitting expectation values on a Connolly surface [40] using MOPAC 6.0 package [41].

Energy calculation and minimization

We use the Amber force field method (AMBER 4.0) package to calculate the energy and do minimzation of the systematically generated conformations.

Results and Discussion

A schematic representative of the initial conformations characterized for CH_3-CH_2-$CONH_2$ and CH_3-$CH(CONH_2)$-CH_2-CH_2-$CONH_2$ are shown in Figure 1.

Where the number is the index number used in culculations. The structure parameters of the initial conformations for the monomer and dimer are listed in Table-1 and 2, where the bond lengths and bond angles are not listed because the changes of their values are not significant in different conformers.

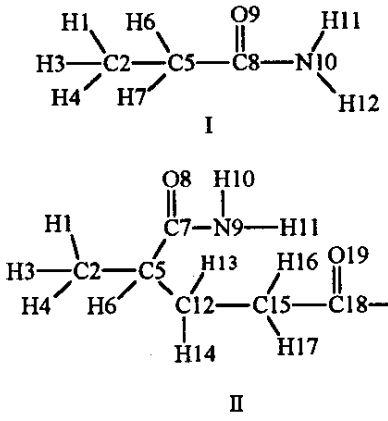

Fig. 1: Schematic representation of conformations for CH_3 - CH_2 - $CONH_2$ (I) and CH_3 - $CH(CONH_2)$ - CH_2 - CH_2 -$CONH_2$ (II)

Table-1: Torsional angles of the initial conformation for I.

Dihedral	Value	Dihedral	Value
H6-C5-C2-H	60.97	N10-C8-C5-C2	-177.52
H7-C5-C2-H	179.58	H11-N10-C8-C5	179.99
H8-C5-C2-H	-59.68	H12-N10-C8-C5	0.09
09-C8-C5-C	2.54		

Table-2: Torsional angles of the initial conformation for II

Dihedral	Value	Dihedral	Value
H6-C5-C2-H1	-171.10	H14-C12-C5-C2	-176.40
C7-C5-C2-H1	-53.64	C15-C12-C5-C2	-55.81
O8-C7-C5-C2	116.76	H16-C15-C12-C5	-156.73
N9-C7-C5-C2	-64.12	H17-C15-C12-C5	-39.42
H10-N9-C7-C5	3.44	C18-C15-C12-C5	84.89
H11-N9-C7-C5	179.23	O19-C18-C15-C1	21.85
C12-C5-C2-H1	71.42	N20-C18-C15-C1	-159.40
H13-C12-C5-C2	66.46	H21-N20-C18-C1	-177.33
		H22-N20-C18-C1	-0.18

Dependence of atomic charges on conformation and its effect on conformation energy

To show how the ESP atomic charges depend on the conformation we have calculated the ESP charges for different conformations of compound I generated by rotating the torsional angles H1-C2-C5-Y (Y=H6,H7,C8) ϕ°. The calculated values are listed in Table-3.

From Table-3 we can see that the ESP charges depend on the conformations greatly. In the

Table-3: ESP atomic charges of compound 1 for its different conformations

Atom/ϕ	0°	30°	60°	90°	120°	150°	180°
H1	0.1217	0.1454	0.1563	0.1432	0.1110	0.1236	0.1310
C2	-0.3707	-0.4292	-0.4865	-0.4233	-0.3342	-0.4262	-0.4757
H3	0.1080	0.1220	0.1305	0.1246	0.1129	0.1452	0.1594
H4	0.1200	0.1254	0.1295	0.1179	0.0985	0.1187	0.1315
C5	-0.1088	-0.0740	-0.0332	-0.0674	-0.1151	-0.0610	-0.0247
H6	0.0828	0.0774	0.0674	0.0759	0.0808	0.0757	0.0613
H7	0.0828	0.0773	0.0677	0.0770	0.0814	0.0754	0.0660
C8	0.4019	0.3807	0.3771	0.3788	0.4027	0.3674	0.3666
O9	-0.3544	-0.3475	-0.3462	-0.3484	-0.3554	-0.3456	-0.3439
N10	-0.8101	-0.7952	-0.8017	-0.7970	-0.8077	-0.7841	-0.7948
H11	0.3676	0.3639	0.3659	0.3654	0.3667	0.3623	0.3650
H12	0.3587	0.3538	0.3553	0.3532	0.3585	0.3486	0.3534

Table-3: continued

Atom/ϕ	210°	240°	270°	300°	330°	Average
H1	0.1155	0.1049	0.1174	0.1270	0.1219	0.1266
C2	-0.4075	-0.3367	-0.4097	-0.4493	-0.4150	-0.4128
H3	0.1396	0.1194	0.1210	0.1275	0.1175	0.1273
H4	0.1206	0.1193	0.1401	0.1524	0.1400	0.1345
C5	-0.0810	-0.0926	-0.0814	-0.0659	-0.0683	-0.0719
H6	0.0777	0.0792	0.0765	0.0742	0.0745	0.0750
H7	0.0775	0.0781	0.0767	0.0745	0.0756	0.0758
C8	0.3891	0.3965	0.3905	0.3928	0.3823	0.3939
O9	-0.3504	-0.3545	-0.3509	-0.3489	0.3491	-0.3469
N10	-0.8037	-0.8094	-0.8007	-0.8072	-0.7982	-0.8008
H11	0.3661	0.3681	0.3649	0.3671	0.3653	0.3657
H12	0.3564	0.3576	0.3557	0.3558	0.3535	0.3554

usual molecular mechanics calculation, the atomic charges from one conformation are applied to the calculation of all conformations of the same compound. In Table-4 the energies of the 12 conformations calculated by molecular mechanics method are given, where in the uncorrected case the atomic charges of all the conformations take the atomic charges of the first conformation (traditional molecular mechanics method) and in the corrected case, the atomic charges of one conformation take its values corresponding to the associated conformation.

From Table-4 we can find that the atomic charges have a strong influence on the conformational energies which can be seen more obviously from Figure 2. We can see that correction to the energies of the sable conformation (conformer, corresponding to the minimum of the curve in Figure 2) is more apparent. The energy of the conformer from ϕ =120° is higher than the energy of the conformer from ϕ =0° when it is not corrected. But the energy of the conformer from ϕ =120° is lower than the energy of the conformer from ϕ =0° when it is corrected. Therefore we can conclude that the ESP charges depend greatly on its conformation and has strong influence on the conformational energies and in order to accurately calculate the conformational energy and accurately compare the conformational

Table-4: Conformational energies (Kcal/mol) of compound I*

Method\ϕ	0°	30°	60°	90°	120°	150°
MM	-5.6815	-3.3177	-0.7519	-3.4147	-5.3466	-3.1431
	(0.0)	(2.3638)	(4.9296)	(2.2668)	(0.3349)	(2.5384)
MM	-5.6815	-3.1498	-3.2590	-3.2590	-5.7843	-2.9667
(Corrected)	(0.0)	(2.5317)	(5.3396)	(2.4225)	(-0.1028)	(2.7148)

Table-4: Continued

Method\ϕ	180°	210°	240°	270°	300°	330°
MM	-0.5593	-3.2926	-5.3525	-3.2725	-0.7489	-3.4624
	(5.1222)	(2.3885)	(0.3290)	(2.4090)	(4.9326)	(2.2191)
MM	-0.3378	-3.4379	-5.5480	-3.3070	-0.6891	-3.2712
(Corrected)	(5.3437)	(2.2436)	(0.1335)	(2.3758)	(4.9924)	(2.9103)

*The values in the parentheses are the energies relative to the first conformation.

Table-5: The Structure parameters of the generated conformers*

D# / C+	ϕ1	ϕ2	ϕ3	ϕ4	ϕ5	ϕ6	ϕ7	ϕ8	ϕ9	ϕ10	ϕ11	ϕ12	ϕ13
I	189.6	306.2	73.3	168.3	351.4	56.5	172.8	292.5	193.0	310.3	75.2	49.1	231.3
II	297.0	52.6	181.1	325.3	41.7	42.3	158.4	277.9	183.8	300.7	65.6	53.4	236.9
III	300.4	56.2	184.8	187.7	9.5	37.3	153.6	272.7	182.2	299.0	63.7	86.6	264.1
IV	56.2	171.8	300.1	223.3	40.1	42.7	158.9	278.4	184.0	301.0	65.9	55.3	237.7
V	58.1	173.8	302.4	191.2	12.3	37.6	154.0	273.0	182.6	299.5	64.2	84.9	261.9
VI	176.3	293.5	56.8	117.5	299.8	178.5	295.2	58.1	174.2	291.6	55.8	46.5	230.3
VII	182.8	301.7	65.1	117.2	301.2	290.7	48.2	168.1	13.7	254.5	133.9	116.5	298.3
VIII	192.9	307.6	78.9	118.2	305.0	44.6	159.6	280.9	165.1	281.4	45.0	94.5	270.8
IX	184.4	301.8	67.7	176.0	358.7	60.7	177.5	297.9	304.0	64.2	183.7	345.3	166.0
X	178.2	295.2	61.2	192.2	13.4	64.1	181.0	301.0	312.9	72.9	193.8	132.9	314.8
XI	187.0	305.1	70.2	159.7	347.1	58.2	173.6	295.9	351.7	111.3	232.0	239.0	58.2
XII	184.3	298.9	68.1	237.3	52.7	86.0	201.2	325.7	54.9	171.8	288.6	299.4	115.4
XIII	183.2	297.7	67.4	232.5	46.6	81.3	196.7	321.5	54.9	172.3	292.2	103.5	293.6
XIV	185.6	300.8	70.3	235.8	51.8	46.6	162.1	281.4	182.4	299.4	61.5	253.3	65.3
XV	179.7	295.9	63.7	22.9	194.7	35.4	151.7	271.1	184.4	301.7	66.5	96.3	270.7
XVI	178.4	294.3	62.8	184.7	7.3	37.5	153.7	272.7	181.9	298.7	63.4	87.8	265.2

*ϕ1:H1-C2-C5-H-6, ϕ2:H1-C2-C5-C7, ϕ3:H1-C2-C5-C12, ϕ4:C2-C5-7-08, ϕ5: C2-C5-C7-N9, ϕ6: C2-C5-C12-H13, ϕ7: C2-C5-C12-H14, ϕ8: C2-C5-C-12-C15, ϕ9: C2-C12-C15-H16, ϕ10:C5-C12-C15-H17, ϕ11: C5-C12-C15-C18, ϕ12: C12-C15-C18-O19, ϕ13: C12-C15-C18-N20

C+:Conformer, D Dihedral angle

Table-6: Conformational energies (kcal/mol) of conformers

Conformer	I	II	III	IV	V	VI	VII	VIII
Energy	-14.457	-15.344	-15.465	-15.227	-15.315	-14.844	-17.298	-14.637
Table-6 (Continued)								
Conformer	IX	X	XI	XII	XIII	XIV	XV	XVI
Energy	-14.525	-16.181	-18.099	-14.326	-18.774	=19.086	-16.023	-15.515

energy it is necessary to use the ESP charges corresponding to that conformation.

Conformational search of compound II

The first step our work is to systematically increase the torsional angle X-C2-C5-Y,X-C5-C12-Y,X-12-C15-Y,X-C15-C18-Y, and X-C5-C7-Y of the compound II starting from the initial conformation given in Table-2 by 30° each time. Then the molecular mechanics method is employed to minimize the generated conformations. Comparing the energies and torsional angles of all the optimized conformations (conformer), we can get 16 different conformers that are listed in the Table-5 and 6, where only the torsional angles are given. We can see from Table 5 and 6 that XIV conformer is the most stable conformer.

Conclusion

It is shown that ESP charges depend greatly on conformations and to accurately calculate the energy of conformation using MM method it is

necessary to use the ESP charges of that conformation. Systematic search method is used to search the conformers of the model compound II of polyacrylamide, and 16 conformers are found from which the most stable conformers is also obtained.

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