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1. ABSTRACT

In this work, we have developed a general AMBER force field (GAFF) for rational drug design. GAFF is compatible with the AMBER force field and it has parameters for almost all the organic molecules made of C, N, O, H, S, P, F, Cl, Br and I. As a complete force field, GAFF is suitable for study of a great number of molecules (such as database searching) in an

automatic fashion.

2. INTRODUCTION

Molecular mechanics are the key component in the armamentarium used by computational chemists for rational drug design and many other tasks. Force fields are the cornerstone of molecular mechanics. A successful force field in drug design should work well both for the biological molecules and the organic molecules. AMBER force fields have a good reputation for the study of proteins and nucleic acids. However, the fact that AMBER only has limited parameters for organic molecules prevents it from being widely used in drug design. Therefore, it is necessary to develop a general AMBER force field that works for most pharmaceutical molecules. It should also be as compatible as possible with the traditional AMBER force fields. Our objective is to develop a general, complete, and compatible force field for rational drug design.

3. FUNCTION FORM

Similar to the other AMBER force fields, the GAFF also applies the following simple harmonic functional form:

$$E_{\text{pair}} = \sum_{\text{bonds}} K_r (r - r_{\text{eq}})^2 + \sum_{\text{angles}} K_\theta (\theta - \theta_{\text{eq}})^2 + \sum_{\text{dihedrals}} \frac{V_n}{2} [1 + \cos(n\phi - \gamma)] + \sum_{i < j} \left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^6} + \frac{q_i q_j}{\epsilon R_{ij}} \right]$$

Here, r_{eq} and θ_{eq} are equilibrium structural parameters; K_r , K_θ , V_n are force constants; n is multiplicity and γ is phase angle for torsional angle parameters. Details will be given below on how these parameters were derived.

4. ATOM TYPE DEFINATION

Compared to traditional AMBER force field, atom types in GAFF are more general and cover most of the organic chemical space. Table I lists the basic (a) and special (b) atom

types in GAFF.

Table I (a). Basic Atom Types in GAFF

Atom type	Description	Atom type	Description
c c1 c2 c3 ca	sp ² C in C=O, C=S sp ¹ C sp ² C, aliphatic sp ³ C sp ² C, aromatic	o oh os	sp ² O in C=O, COO- sp ³ O in hydroxyl group sp ³ O in ether and ester
n n1 n2 n3 n4 na nh no	sp ² N in amide sp ¹ N sp ² N with 2 subst. readl double bond sp ³ N with 3 subst. sp ³ N with 4 subst. sp ² N with 3 subst amine N connected to the aromatic rings N in nitro group	s2 sh ss s4 s6 hc ha hn ho hs hp	sp ² S (p=S, C=S etc) sp ³ S in thiol group sp ³ S in -SR and SS hypervalent S, 3 subst. hypervalent S, 4 subst. H on aliphatic C H on aromatic C H on N H on O H on S H on P
f cl br i	any F any Cl any Br any I	p2 p3 p4 p5	sp ² P (C=P etc) sp ³ P, 3 subst. hypervalent P, 3 subst. hypervalent P, 4 subst.

Table I (b). Special Atom Types in GAFF

Atom type	Description	Atom type	Description
h1 h2 h3	H on aliphatic C with 1 EW group; H on aliphatic C	cc(cd) ce(cf) cp(cq)	inner sp ² C in conj. ring systems inner sp ² C in conj.

h4 h5	with 2 EW group; H on aliphatic C with 3 EW group; H on aromatic C with 4 EW group; H on aromatic C with 5 EW group;	cu cv cx cy	chain systems bridge aromatic C sp ² C in three- membered rings sp ² C in four- membered rings sp ³ C in three- membered rings sp ³ C in four- membered rings
n nb nc(nd) sx sy	aromatic nitrogen inner sp ² N in conj. ring systems inner sp ² N in conj. chain systems conj. S, 3 subst. conj. S, 4 subst.	pb pc(pd) pe(pf) px py	aromatic phosphorus inner sp ² P in conj. ring systems inner sp ² P in conj. chain systems conj. P, 3 subst. conj. P, 4 subst.

EW: electron-withdraw group

5. CHARGE APPROACH

The charge method used in GAFF is HF/6-31G* RESP charge. However, AM1-BCC, which was parameterized to reproduce the HF/6-31G* RESP charges can be applied in case of large amount of calculations, such as database searching. The van der Waals parameters of GAFF are as same as those used by the traditional AMBER force field.

6. BOND LENGTH PARAMETERIZATION

There are several resources to derive the reference bond length r_{eq} , including the statistic mean values of bond lengths from X-ray and neutron diffraction as well as high level ab initio calculations (MP2/6-31G*). Force constants were derived using the following empirical function forms:

$$K_r = K_{ij}^{ref} \left(\frac{r_{ij}^{ref}}{r_{ij}} \right)^6$$

$$K_r = K_{ij} \left(\frac{1}{r_{ij}} \right)^m$$

$$\log K_r = -m \log r_{ij} + \log K_{ij}$$

Here, m and K_{ij} were determined using bond length parameters in traditional AMBER force field. As a compromise, the parameter m in the above equation is set to 4.0. Fitting details are shown in Figure 1-3. The parameters are listed in Table II.

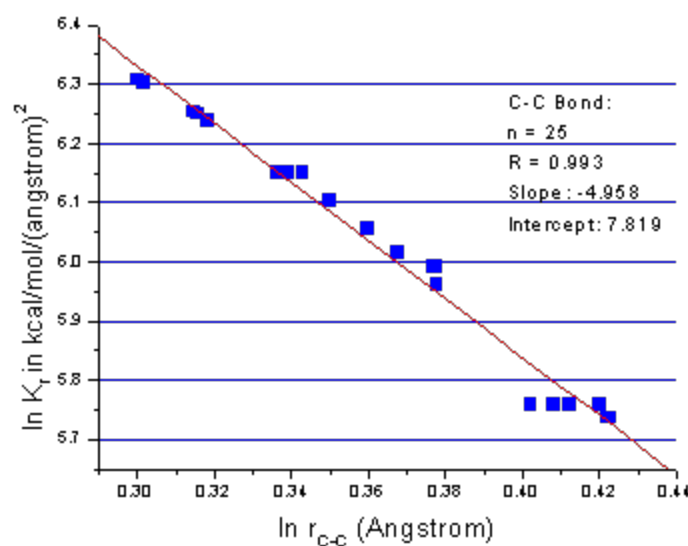


Figure 1

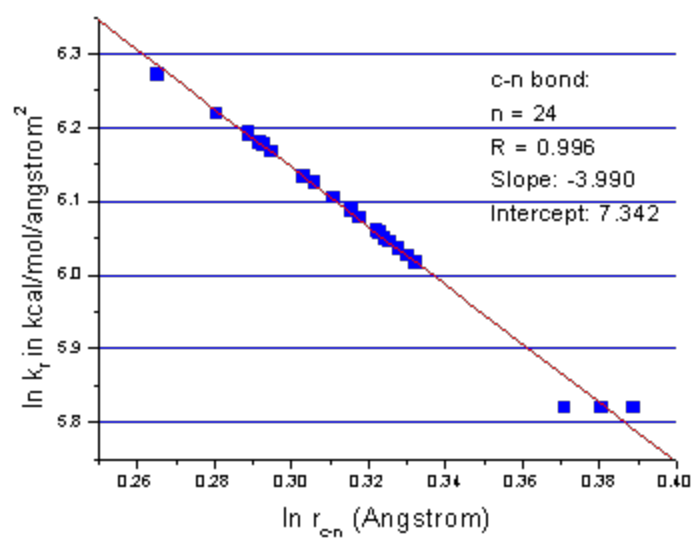


Figure 2

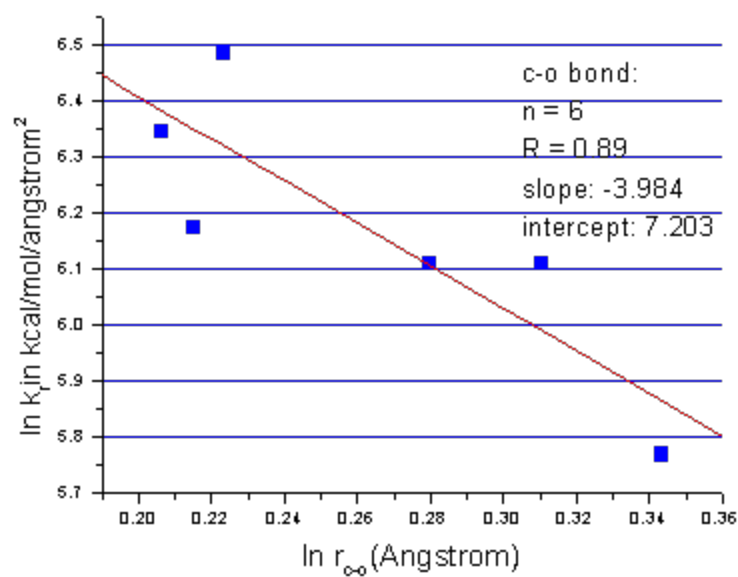


Figure 3

Table II. Bond length parameterization

<i>i</i>	<i>j</i>	<i>r_{ij}</i>	<i>K_{ij}</i>	<i>i</i>	<i>j</i>	<i>r_{ij}</i>	<i>K_{ij}</i>
H	H	0.738	4.661	H	C	1.090	6.217
H	N	1.010	6.057	H	O	0.96	5.794
H	F	0.920	5.600	H	Cl	1.280	6.937
H	Br	1.410	7.301	H	I	1.600	7.802
H	P	1.410	7.257	H	S	1.340	7.018
C	C	1.526	7.643	C	N	1.470	7.504

C	O	1.440	7.347	C	F	1.370	7.227
C	Cl	1.800	8.241	C	Br	1.940	8.478
C	I	2.160	8.859	C	P	1.830	8.237
C	S	1.820	8.117	N	N	1.441	7.634
N	O	1.420	7.526	N	F	1.420	7.475
N	Cl	1.750	8.266	N	Br	1.930	8.593
N	I	2.120	8.963	N	P	1.720	8.212
N	S	1.690	8.073	O	O	1.460	7.561
O	F	1.410	7.375	O	Cl	1.700	8.097
O	Br	1.790	8.276	O	I	2.110	8.854
O	P	1.640	7.957	O	S	1.650	7.922
F	F	1.406	7.358	F	Cl	1.648	7.947
F	P	1.500	7.592	F	S	1.580	7.733
Cl	Cl	2.031	8.648	Cl	I	2.550	9.309
Cl	P	2.040	8.656	Cl	S	2.030	8.619
Br	Br	2.337	9.012	Br	I	2.671	9.380
Br	P	2.240	8.729	Br	S	2.210	8.728
I	I	2.836	9.511	I	P	2.490	9.058
I	S	2.560	9.161	P	P	2.324	8.805
P	S	2.120	8.465	S	S	2.038	8.316

7. BOND ANGLE PARAMETERIZATION

The following list the source of reference bond angles:

- Cambridge Structure Database (CSD)
- *ab initio* (MP2/6-31G*)
- empirical rules for q (A-B-C)

$$q(\text{A-B-C}) = 0.5 [q(\text{A-B-A}) + q(\text{C-B-C})]$$

The force constant K_q was also estimated using an empirical function as the following. The parameters are listed in Table III.

$$K_{ijk}^{\theta} = 143.9 \times Z_i C_j \times Z_k (r_{ij}^{eq} + r_{jk}^{eq})^{-1} \theta_{ijk}^{eq^{-2}} \exp(-2D)$$

$$D = (r_{ij}^{eq} - r_{jk}^{eq})^2 / (r_{ij}^{eq} + r_{jk}^{eq})^2$$

Table III. Parameters of bond angle force constant calculations

Element	C	Z
H	0.0	0.784
C	1.339	1.183
N	1.300	1.212
O	1.249	1.219
F	0.000	1.166
Cl	0.000	1.272
Br	0.000	1.378
I	0.000	1.398
P	0.906	1.620
S	1.448	1.280

8. TORSIONAL ANGLE PARAMETERIZATION

The following is the strategy to develop torsional angle parameters.

- Perform torsional angle scanning to get the rotational profile at MP4/6-311G(d,p)// MP2/6-31G* level
- Apply PARMSCAN to find the best torsional angle parameters to reproduce the rotational profile

Totally, 200 general torsional angle parameters were developed in GAFF, which gave an average unsigned error of 0.5 kcal/mol to MP4/6-311G(d,p) energies.

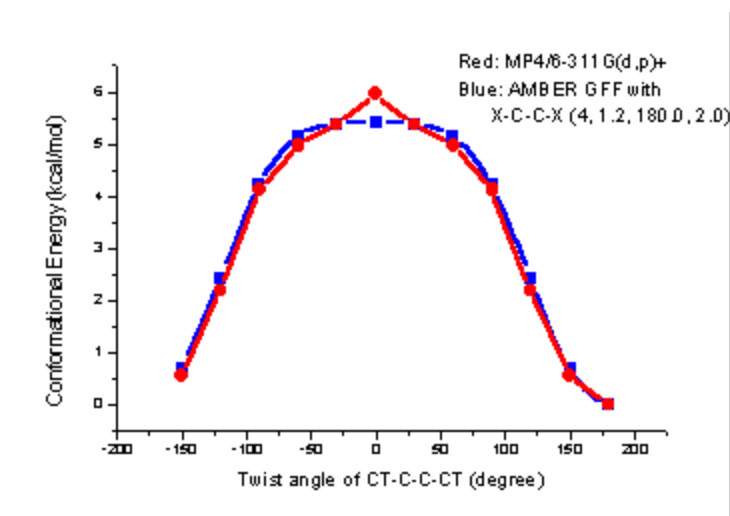


Figure 4. An example: rotation profiles of X-c-c-X

9. TEST CASES

- 9.a How well does GAFF predict the molecular structures?

Table IV Comparison of GAFF and other force fields in reproducing geometries of 75 crystallographic structures

	GAFF	MMFF94	DREIDING	TRIPOS 5.2	CHARMm
RMS of Atomic Displacement (Å)	0.34	0.47	0.24	0.25	0.44
RMS of Bond Length Deviation (Å)	0.027	0.021	0.035	0.025	~
RMS of Bond Angle Deviation (°)	2.2	2.0	3.22	2.5	~

- 9.b How well does GAFF predict the inter-molecular energies?

Table V How well does GAFF perform in calculating the inter-molecular energies

of 22 base pairs. All the comparison are made to the MP2/6-311G* energies.

	GAFF/BCC	GAFF/RESP	PARM99/ RESP
RMS of Atomic Displacements (Å)	0.56	0.49	0.19
RMS of ΔE Compared to <i>ab initio</i> (kcal/mol)	2.50	0.67	0.77

- 9.c How well does GAFF predict the intra-molecular energies?

Table VI Performances of widely used force field in reproducing the relative energies for 55 compounds. Comparison are made to the experiment.

	GAFF/ BCC	AMBER (parm99)	MMFF	MM3	CHARMm
Unsigned Average Error (kcal/mol)	0.51	0.28	0.43	0.52	0.57
RMS Deviation (kcal/mol)	0.69	0.40	0.54	0.75	0.76

10. SUMMARY

In this work, we have developed a general AMBER force field. We hope it is an ideal molecular mechanical tool in rational drug design. We have finished a total of 2000 MP2/6-31G* optimizations and 1260 MP4/6-311G(d,p) single

point calculations. From the three test cases, encouraging results were achieved. It is notable that in the third test case, GAFF has comparable performance to those of CHARMM and MM3, although GAFF applies very general force field parameters and crude charge approach.

Compared to other widely used fields, GAFF has the following distinguishing features. First of all, it is a complete force field, which means all the parameters are available, no parameter-missing happens to GAFF; secondly, this force field is very general and it covers almost all the organic chemical spaces; finally, GAFF is compatible to the AMBER force field. We believe that the combination of GAFF with traditional AMBER will offer a useful molecular mechanical tool for rational drug design, especially for things like binding free energy calculations.

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