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Ab initio and molecular mechanics (MM3) calculations on alkyl- and arylboronic acids

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ABSTRACT: The boronic acid functional group has been incorporated into various biologically important compounds. In order to study this class of compounds better with molecular mechanics, five alkyl- and arylboronic acids were calculated using *ab initio* methods (Spartan) at the RHF/6–31G* level. MM3 force field parameters were developed based on the theoretically calculated geometries, vibrational spectra, and torsional profiles. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: alkylboronic acids; arylboronic acids; *ab initio;* MM3; molecular mechanics; force field parameters

INTRODUCTION

A wide variety of boronic acid derivatives of divergent biologically important compounds have been synthesized as anti-metabolites for a possible two-pronged attack on cancer.[1–3] In addition to inhibition of tumor growth, the use of boron-10 neutron capture therapy[4] would be possible owing to the preferential localization of boron compounds in tumor tissue. Boronic acid analogs have been synthesized as transition state analogs for acyl transfer reactions[5] and inhibitors of dihydoorotase.[6] The boronic acid moiety has also been incorporated into amino acids and nucleosides as anti-tumor, anti-viral agents.[7] In order to study these biologically important type of molecules by molecular mechanics methods (MM3), the necessary parameters had to be developed.

Molecular mechanics is a standard tool used to study molecular structures and their conformational energies. The MM3 force field[8–10] has significantly advanced the accuracy of these calculations. MM3 can accurately handle many different functional groups, including alcohols and ethers,[11] amines,[12] aldehydes and ketones,[13] carboxylic acids and esters,[14] sulfides[15] and sulfones[16] phosphines.[17] Force field parameters for alkylboronic acids have been developed for a generic force field[18] in which reproducing the geometry was the main goal. In this work, however, highly accurate force field parameters for both alkyl-and arylboronic acids were derived by fitting the geometries, vibrational frequencies, and torsional profiles of five model molecules calculated using the RHF/6– 31G* basis set.

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COMPUTATIONAL METHODS

Owing to the lack of high-quality experimental data for boronic acid compounds in our training set, the force field parameterization was based almost entirely on *ab initio* calculations. Methyl-, ethyl-, propyl-, isopropyl-, and phenylboronic acids were calculated at the RHF/6–31G* level using Spartan 4.0 (Wavefunction, Irvine, CA, USA) (Fig. 1).

The *ab initio* structures were then fully optimized by MM3 with an initial parameter set using a full-matrix scheme to obtain both vibrational frequencies and low-energy structures. The MM3 and RHF/6–31G* frequencies were compared, as also were other structural data including bond lengths and angles. The root mean square deviations (RMSDs) of vibrational frequencies, bond lengths, angles, etc., between all MM3 and RHF/6–31G* values were tabulated. Each parameter was then modified systematically in cycles to obtain the best correlation between the molecular mechanics and *ab initio* values by the Parameter Analysis Refinement Toolkit System (PARTS) program.[19] The optimizations of bonded parameters and torsion curves by PARTS were repeated in turn in cycles until the change in RMSD between MM3 and *ab initio* values was smaller than a specifically defined threshold value.

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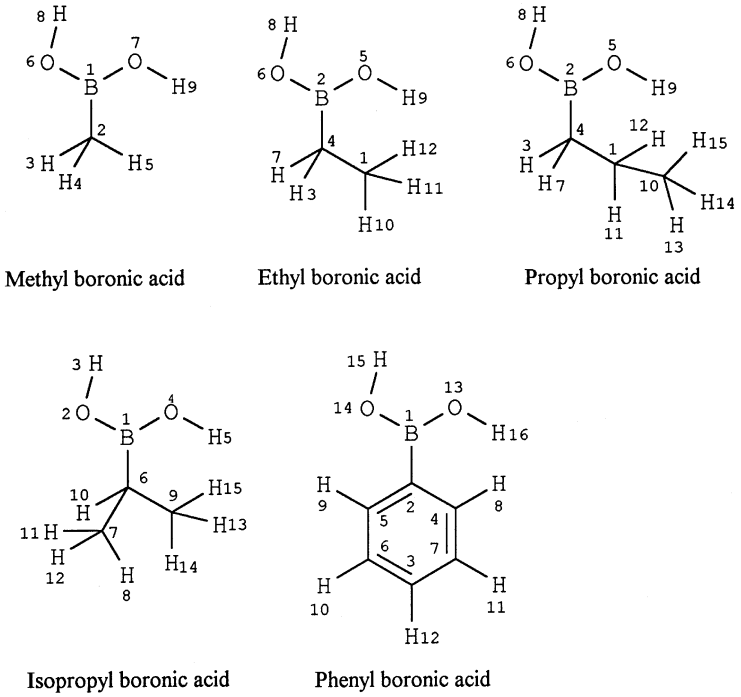

Figure 1. Structures of alkyl-and arylboronic acids used in the training set

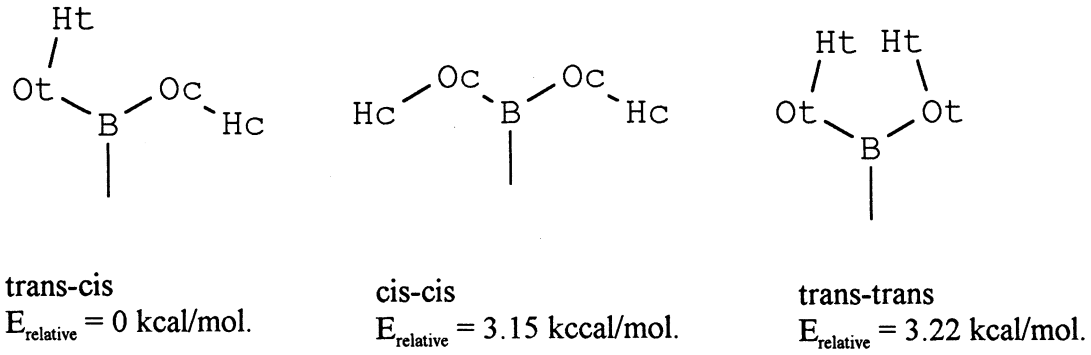

Figure 2. Relative conformations of the boronic acid hydroxyl groups and their energies

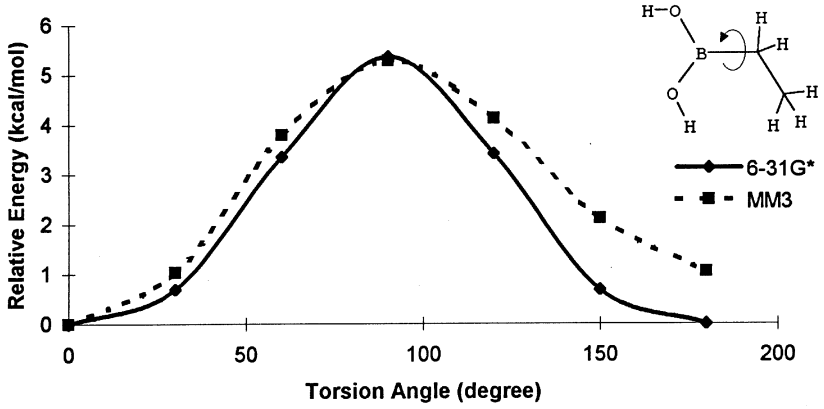

Figure 3. Torsion profile of C—C—B—O_t in ethylboronic acid

Table 1. MM3 parameter set for boronic acid[a]

Bond stretching parameters

Bond	K_s(mdyn Å^{-1})	l_r (Å)
1–26	3.9304	1.5612
6–26	3.9430	1.3638
2–26	2.3718	1.5038

Angle bending parameters

Angle	K (mdyn Å rad^{-2})	θ (°)
1–26–6	0.4808	122.6377
6–26–6	0.7187	120.8639
1–1–26	0.6085	109.2459
5–1–26	0.4948	109.9322
21–6–26	0.5120	109.5659
2–26–6	0.6786	127.0404
2–2–26	0.6854	121.1796

Out-of-plane bending parameters

Angle	K_{opb} (mdyn Å rad^{-2})
0–2–26	0.1082
0–26–6	0.1082
0–26–1	0.1082
0–26–2	0.1082

Torsion parameters

Type	V_1 (kcal mol^{-1})	V_2 (kcal mol^{-1})	V_3 (kcal mol^{-1})
1–1–26–6	0.0000	2.9168	0.0000
1–1–1–26	−1.2376	0.7815	0.2011
5–1–1–26	0.0000	0.0000	0.0503
5–1–26–6	0.0000	0.0000	0.3250
21–6–26–1	−1.4600	5.0964	−0.1052
21–6–26–6	−0.5197	4.5608	0.3140
2–2–2–26	0.0000	11.6000	0.0000
5–2–2–26	0.0000	11.6000	0.0000
21–6–26–2	−1.6710	4.1751	0.7787
2–2–26–6	0.0000	1.6702	0.0000

Dipole moment

Bond	Dipole moment (D)
1–26	−0.6000
2–26	−0.6000
6–26	−1.5000

[a] The atom type numbers have their usual meanings: 1 is saturated carbon; 2 is phenyl carbon; 5 is alkane or alkene hydrogen; 6 is alcohol oxygen; 21 is alcohol hydrogen; 26 is boron.

RESULTS AND DISCUSSION

Vibrational Spectra

The compounds included in this study were methyl-, ethyl-, propyl-, isopropyl- and phenylboronic acids. All the newly developed MM3 parameters are listed in Table 1. Owing to the lack of experimental data for alkyl- and arylboronic acid vibrational spectra, the vibrational spectra were obtained by *ab initio* molecular orbital calculation using Spartan 4.0. Since the Hartree–Fock method usually overestimates the experimental frequencies by about 10%,[20] the MM3 vibrational frequencies were compared with scaled *ab initio* values (90%). The RMS error for the vibrational spectra of all five training molecules ranges from 15 to 50 cm^{-1} (Table 2–6). For methylboronic acid, the frequency for methyl rotation is an imaginary frequency in MM3 calculation, owing to the pseudo-'sixfold'; symmetry of the methyl group rotation. This methyl group can be considered as a free rotor only controlled by non-bonded interactions between methyl hydrogen and hydroxyl hydrogen. The rotation barrier is

Table 2. Structural data and vibrational modes of methylboronic acid

Bond length	***Ab initio***	**MM3 (r_g)**	**Deviation**	**MM3 (r_e)**	**Deviation**
B(1)—C(2)	1.585	1.582	−0.003	1.572	−0.013
B(1)—O(6)	1.354	1.357	0.003	1.348	−0.006
B(1)—O(7)	1.366	1.358	−0.008	1.350	−0.016
O(6)—H(8)	0.950	0.954	0.004	0.935	−0.015
O(7)—H(9)	0.950	0.953	0.003	0.935	−0.015
C—H	1.089	1.112	0.023	1.089	0.000
			RMSD = 0.016		RMSD = 0.012

Bond angle	***Ab initio***	**MM3**	**Deviation**
C(2)—B(1)—O(6)	120.1	120.6	0.5
C(2)—B(1)—O(7)	122.8	121.4	−1.4
O(6)—B(1)—O(7)	117.2	118.1	0.9
B(1)—O(6)—H(8)	112.1	111.3	−0.8
B(1)—O(7)—H(9)	114.2	113.1	−1.1
H(4)—C(2)—H(5)	106.6	108.1	1.5
B—C—H	111.4	111.6	−0.5
			RMSD = 0.8

Vibrational mode	***Ab initio***	**MM3**	**Deviation**
O_c—H str.	3732	3706	−26
O_t—H str.	3697	3702	4
asym C—H str.	2955	2979	24
asym C—H str.	2905	2979	74
sym C—H	2865	2883	18
H—C—H bend	1463	1426	−37
H—C—H bend	1458	1421	−36
C—B str.	1378	1399	21
asym B—O str.	1351	1316	−35
C—B str.	1271	1245	−26
H—O_t—B bend, B—O_c str.	1009	1045	35
H—O_c—B bend, B—O_t str.	982	992	11
B—O—O—C out-of-plane	906	906	0
CH_3 rock	850	872	22
C—B str.	723	696	−26
H—O_c out-of-plane	488	608	121
H—O_t out-of-plane	594	558	−36
O—B—O bend	422	437	15
C—B—O bend	316	348	31
B—O—O—C out-of-plane	427	319	−108
CH_3 torsion	37	− 62	−99
			RMSD = 50

less than 0.2 kcal mol^{-1}. (1 kcal = 4.184 kJ). Since the parameters for van der Waals interaction between the alkyl hydrogen and the hydroxyl hydrogen were adjusted previously to fit alcohol compounds best, we did not alter these parameters. Also, it is not worthwhile to introduce a new atom type to fit the methyl group (free rotor) rotation profile. Another main source of difference between the *ab initio* and MM3 frequencies is the mode of C—B—O_c—H_c torsion. The deviation between *ab initio* and MM3 frequency is *ca* 110 cm^{-1} for methyl-, ethyl-, propyl-, and isoprophylboronic acids. The higher frequency values calculated by MM3 can be attributed to the overestimated van der Walls interaction between hydroxyl and alkyl hydrogen by MM3.

Torsional profiles

The two hydroxyls of boronic acid can be all-*trans*, all-*cis* and mixed *trans–cis* relative to the B—C bond (Fig. 2). According to the *ab initio* results, the *cis–trans* conformation is the most stable. Both hydrogens are in the O—B—O plane. Most probably, the oxygen lone pairs have a resonance interaction with the empty p orbital of boron, which forces the hydrogen to be in the O—B—O plane. The energy for the *trans–trans* conformation is 3.22 kcal mol^{-1} higher owing to the unfavorable steric interaction between the two hydroxyl hydrogens, while the energy for the *cis–cis* conformation is 3.15 kcal mol^{-1} higher than that for the *trans–cis*

Table 3. Structural data and vibrational modes of ethylboronic acid

Bond length	***Ab initio***	**MM3 (r_g)**	**Deviation**	**MM3 (r_e)**	**Deviation**
C(1)—C(4)	1.533	1.529	−0.004	1.519	−0.014
B(2)—C(4)	1.585	1.583	−0.002	1.574	−0.011
B(2)—O(5)	1.363	1.359	−0.004	1.351	−0.013
B(2)—O(6)	1.356	1.359	0.003	1.350	−0.006
O(5)—H(9)	0.945	0.952	0.007	0.934	−0.012
O(6)—H(8)	0.948	0.954	0.006	0.935	−0.013
C—H (CH_3)	1.087	1.114	0.027	1.090	0.003
C—H (CH_2)	1.089	1.115	0.026	1.092	0.003
			RMSD = 0.018		RMSD = 0.010

Bond angle	***Ab initio***	**MM3**	**Deviation**
C(4)—B(2)—O(5)	124.3	124.0	−0.3
C(4)—B(2)—O(6)	118.4	118.9	0.5
O(5)—B(2)—O(6)	117.3	117.1	−0.2
C(1)—C(4)—B(2)	116.4	116.4	0.1
B(2)—O(5)—H(9)	114.4	114.5	0.0
B(2)—O(6)—H(8)	112.1	111.3	−0.8
C(1)—C(4)—H(3)	109.8	108.6	−1.2
C(1)—C(4)—H(7)	109.8	108.6	−1.2
H(3)—C(4)—H(7)	104.8	106.1	1.3
C—C—H	111.6	111.5	−0.1
			RMSD = 0.6

Vibrational mode	***Ab initio***	**MM3**	**Deviation**
O_c—H str.	3738	3728	−10
O_t—H str.	3699	3702	3
asym C—H str.	2915	2964	49
CH_2 asym C—H str.	2934	2960	25
CH_2 asym C—H str.	2889	2916	26
CH_2 CH_3 sym str.	2870	2874	4
CH_2 CH_3 sym str.	2867	2859	−8
H—C—C bend	1410	1486	76
H—C—H bend	1491	1462	−29
H—C—H bend	1488	1452	−36
H—C—H bend	1443	1425	−18
CH_3 umbrella	1410	1381	−29
B—O str.	1329	1325	−4
B—O str.	1235	1231	−3
CH_2 twist	1250	1215	−36
H—O_t—B bend	1005	1046	41
CH_3 twist	991	1011	21
H—O_c—B bend	983	1003	20
CH_3 rock	1026	998	−28
C—C str, H—O—B bend	938	950	13
CH_2 twist	752	787	35
B—O str. B—C str.	693	670	−24
H—O_c out-of-plane	492	592	101
H—O_t out-of-plane	581	558	−23
O—B—O bend	456	448	−9
O—B—C bend	378	355	−23
B—O—O—C out-of-plane	427	333	−94
B—C—C bend	199	244	45
CH_3 torsion	225	230	5
O—B—C—C torsion	35	92	56
			RMSD = 38

conformation owing to the loss of hydrogen bonding. In order to differentiate these two hydroxyls, the atoms of the hydroxyl that are *trans* to the B—C bond are called O_t, H_t, and the atoms of the hydroxyl that are *cis* are called O_c and H_c (Fig. 2). The torsion curve of C—C—B—O for both alkyl- and arylboronic acids show twofold symmetry with a corresponding barrier of 2.93 kcal mol^{-1} for ethyl- and 1.67 kcal mol^{-1} for

Table 4. Structural data and vibrational modes of propylboronic acid

Bond length	***Ab initio***	**MM3(R_g)**	**Deviation**	**MM3(R_e)**	**Deviation**
C(1)—C(4)	1.534	1.532	−0.002	1.522	−0.012
C(1)—C(10)	1.528	1.535	0.007	1.525	−0.003
B(2)—C(4)	1.585	1.583	−0.003	1.573	−0.012
B(2)—O(5)	1.364	1.359	−0.005	1.351	−0.013
B(2)—O(6)	1.356	1.359	0.003	1.350	−0.006
O(5)—H(9)	0.945	0.952	0.007	0.934	−0.012
O(6)—H(8)	0.948	0.954	0.006	0.935	−0.013
C—H (CH_2)	1.090	1.115	0.026	1.091	0.002
C—H (CH_3)	1.086	1.113	0.027	1.089	0.003
			RMSD = 0.019		RMSD = 0.009

Bond angle	***Ab initio***	**MM3**	**Deviation**
C(4)—C(1)—C(10)	113.3	112.4	−0.9
H(11)—C(1)—H(12)	106.3	107.1	0.7
C(4)—B(2)—O(5)	124.4	124.1	−0.2
C(4)—B(2)—O(6)	118.4	118.8	0.4
O(5)—B(2)—O(6)	117.2	117.1	−0.1
C(1)—C(4)—B(2)	116.7	116.6	−0.1
B(2)—O(5)—H(9)	114.4	114.5	0.1
B(2)—O(6)—H(8)	112.1	111.3	−0.7
C(1)—C(4)—H(3)	109.6	108.7	−1.0
C(1)—C(4)—H(7)	109.6	108.7	−1.0
H(3)—C(4)—H(7)	104.8	106.2	1.4
C—C—H (CH_2, CH_3)	108.7	109.0	0.3
B—C—H	107.7	108.1	0.4
			RMSD = 0.6

Vibrational mode	***Ab initio***	**MM3**	**Deviation**
O_c—H str.	3739	3730	−10
O_t—H str.	3699	3702	3
C—H str.	2936	2970	34
CH_3 asym C—H str.	2934	2968	34
CH_2 asym C—H str.	2890	2920	30
CH_2 asym C—H str.	2866	2916	50
sym CH_3, CH_2 str.	2879	2880	1
sym CH_3, CH_2 str.	2859	2867	7
sym CH_3, CH_2 str.	2859	2860	0
CH_2 rock	1410	1520	109
CH_3 twist	1480	1458	−21
H—C—H bend	1490	1453	−37
H—C—H bend	1476	1436	−40
H—C—H bend	1442	1425	−17
CH_3 umbrella, H—C—H bend	1410	1407	−4
CH_3 umbrella, CH_2 rock	1345	1353	8
B—O str.	1318	1325	7
CH_2 twist	1307	1236	−72
B—O str.	1213	1234	21
CH_2 twist	1307	1224	−83
C—C str.	1072	1053	−19
H—O_t—B bend	1008	1043	35
CH_3 wag	1021	1026	5
CH_3, CH_2 wag	1008	998	−10
H—O_c—B bend	977	973	−4
H—C—C bend	879	893	14
CH_2 wag	836	870	35
CH_2 wag	714	765	51
B—C str.	734	707	−27
H—O_c out-of-plane	491	592	101
H—O_t out-of-plane	582	558	−24
O—B—O bend	476	473	−3
O—B—C bend	371	357	−14
B—O—O—C out-of-plane	432	335	−97
B—C—C, C—C—C bend	307	310	3
CH_3 torsion	238	232	−6
B—C—C, C—C—C bend	146	179	32
B—C—C—C torsion	94	110	16
O—B—C—C torsion	46	87	41
			RMSD = 41

Table 5. Structural data and vibrational modes of isopropylboronic acid

Bond length	***Ab initio***	**MM3 (r_g)**	**Deviation**	**MM3 (r_e)**	**Deviation**
B(1)—O(2)	1.357	1.359	0.002	1.350	−0.007
B(1)—O(4)	1.363	1.360	−0.003	1.351	−0.012
B(1)—C(6)	1.585	1.588	0.003	1.578	−0.007
O(2)—H(3)	0.948	0.954	0.006	0.935	−0.013
O(4)—H(5)	0.945	0.952	0.007	0.934	−0.012
C(6)—C(7)	1.540	1.534	−0.005	1.525	−0.015
C(6)—C(9)	1.535	1.534	−0.001	1.524	−0.011
C(6)—H(10)	1.091	1.118	0.027	1.092	0.001
C—H(CH_3)	1.087	1.114	0.027	1.090	0.003
			RMSD = 0.012		RMSD = 0.009

Bond angle	***Ab initio***	**MM3**	**Deviation**
O(2)—B(1)—O(4)	117.0	116.7	−0.3
O(2)—B(1)—C(6)	118.4	120.1	1.7
O(4)—B(1)—C(6)	124.5	123.1	−1.4
B(1)—O(2)—H(3)	112.1	111.4	−0.8
B(1)—O(4)—H(5)	114.5	114.4	−0.1
B(1)—C(6)—C(7)	110.8	111.4	0.6
B(1)—C(6)—C(9)	114.2	113.7	−0.4
B(1)—C(6)—H(10)	105.8	106.1	0.3
C(7)—C(6)—C(9)	110.9	110.9	0.0
C(7)—C(6)—H(10)	107.0	107.1	0.1
C(9)—C(6)—H(10)	107.8	107.1	−0.6
C—C—H (CB, CH_3, H)	111.2	111.8	0.6
H—C—H	107.3	107.3	0.0
			RMSD = 0.6

Vibrational mode	***Ab initio***	**MM3**	**Deviation**
O_c—H str.	3741	3730	−11
O_t—H str.	3698	3703	4
CH_3 asym C—H str.	2906	2968	63
CH_3 asym C—H str.	2956	2964	8
CH_3 asym C—H str.	2927	2963	37
CH_3 asym C—H str.	2917	2962	45
CH C—H str.	2849	2900	51
CH_3 sym str.	2859	2873	14
CH_3 sym str.	2872	2870	−2
H—C—H bend	1494	1478	−17
H—C—H bend	1482	1467	−15
H—C—H bend	1494	1461	−33
H—C—H bend	1482	1453	−29
CH_3 twist	1476	1437	−39
CH_3 twist	1491	1431	−60
CH_3 umbrella, B—C str.	1415	1383	−32
CH rock	1309	1354	45
B—O str.	1309	1292	−17
CH wag	1234	1252	17
C—C str.	1074	1077	3
CH_3 rock	1164	1072	−92
H—O_t—B bend	1006	1042	36
CH_3 rock	1026	1027	1
H—O_c—B bend	976	975	−1
CH_3 twist	906	961	55
CH_3 wag	951	936	−15
C—C str.	863	857	−6
B—O str.	694	654	−40
H—O_c out-of-plane	494	597	103
H—O_t out-of-plane	549	556	6
O—B—O bend	494	471	−23
C—C—C bend	414	433	19
O—B—C bend	321	351	30
C—C—C bend	321	349	28
B—O—O—C out-of-plane	276	283	7
O—B—C bend	234	237	3
CH_3 torsion	208	199	−8
CH_3 torsion	234	193	−41
O—B—C—C torsion	31	63	32
			RMSD = 37

Table 6. Structural data and vibrational modes of phenylboronic acid

Bond length	***Ab initio***	**MM3 (r_g)**	**Deviation**	**MM3 (r_e)**	**Deviation**
B(1)—C(2)	1.576	1.577	0.000	1.565	−0.011
B(1)—O(13)	1.363	1.362	−0.001	1.353	−0.010
B(1)—O(14)	1.356	1.362	0.006	1.353	−0.003
C(2)—C(4)	1.394	1.402	0.008	1.394	0.000
C(2)—C(5)	1.396	1.401	0.005	1.393	−0.003
O(13)—H(16)	0.945	0.952	0.007	0.934	−0.011
O(14)—H(15)	0.948	0.954	0.006	0.935	−0.013
C—C	1.386	1.395	0.010	1.390	0.004
C—H	1.076	1.103	0.028	1.080	0.004
			RMSD = 0.017		RMSD = 0.008

Bond angle	*Ab initio*	**MM3**	**Deviation**
C(2)—B(1)—O(13)	124.2	124.2	0.1
C(2)—B(1)—O(14)	118.6	121.5	2.9
O(13)—B(1)—O(14)	117.2	114.3	−3.0
B(1)—C(2)—C(4)	122.7	122.0	−0.7
B(1)—C(2)—C(5)	119.7	119.2	−0.5
B(1)—O(13)—H(16)	115.5	113.7	−1.8
B(1)—O(14)—H(15)	112.1	111.4	−0.7
C(4)—C(2)—C(5)	117.6	118.8	1.2
C(2)—C(5)—C(6)	121.3	120.7	−0.5
C(2)—C(4)—C(7)	121.6	120.5	−1.1
C—C—C	119.9	119.7	−0.2
C—C—H	120.1	120.0	−0.6
			RMSD = 0.7

Vibrational mode	***Ab initio***	**MM3**	**Deviation**
O_c—H str.	3748	3730	−18
O_t—H str.	3705	3701	−4
asym C—H str.	2994	3066	71
asym C—H str.	3055	3057	2
asym C—H str.	3044	3051	8
asym C—H str.	3032	3045	13
asym C—H str.	3020	3040	21
aromatic C—C str.	1628	1663	35
aromatic C—C str.	1628	1659	31
aromatic C—C str.	1598	1618	20
sym aromatic C—C—H	1505	1509	4
asym aromatic C—C—	1444	1451	7
asym aromatic C—C—	1349	1368	19
B—O str.	1317	1300	−16
B—O str.	1325	1271	−54
asym aromatic C—C—	1199	1224	25
sym aromatic C—C—H	1181	1209	27
aromatic C—H out-of-plane	1021	1098	78
H—O_t—B bend	1093	1071	−22
asym aromatic C—C—	1065	1041	−24
H—O—B bend	999	1036	36
aromatic C—H out-of-plane	996	1028	33
aromatic C—C—C bend	1016	967	−49
H—O_c—B bend	950	938	−12
sym aromatic C—H out-of-plane	945	927	−18
sym aromatic C—C str	950	914	−35
aromatic C—H out-of-plane	867	771	−96
sym aromatic C—H out-of-plane	770	672	−99
aromatic C—C—C bend	700	663	−37
aromatic C—C—C bend	611	603	−8
H—O_t, C—H out-of-plane	540	589	49
H—O_t, aromatic C—H	540	577	37
O—B—O bend	512	533	20
H—O_c out-of-plane	450	483	33
H—O_c, aromatic C—H	450	449	−1
O—B—C bend	397	416	19
aromatic C—C—C—H out-of-plane	399	366	−33
B—O—O—C out-of-plane	416	339	−77
B—C str.	316	322	6
O—B—C bend	168	222	54
out-of-plane bend	134	149	15
O—B—C—C torsion	12	34	21
			RMSD = 39

phenylboronic acid. The torsion profile of C—C—B—O of ethylboronic acid showed some disagreement between MM3 and *ab initio* calculations when the *cis*-hydroxyl is rotated toward the methyl group (Fig. 3). This is caused by the overestimation of the van der Waals interaction between hydroxyl hydrogen and methyl hydrogen by MM3. Owing to the symmetrical nature of the phenyl group, this is not a problem for the C—C—B—O profile in phenylboronic acid. In the case of methylboronic acid, there is an imperfect sixfold symmetry (twofold in boron oxygen, threefold in methyl), so the torsion energy dose not depend on the V_1, V_2 or V_3 terms. The other torsional curves including C—C—C—B, H—C—C—B and H—O—B—C agree very well between *ab initio* and MM3 calculations.

Structural data

The *ab initio* and MM3 geometries for methyl-, ethyl-, propyl-, isopropyl- and phenylboronic acids given in Tables 2–6. The structures of five training molecules and their atom numbering are shown in Fig. 1. The agreement between MM3 and the RHF/6–31G* calculations is consistently good. For bond length calculations, MM3 calculates r_g values as default whereas the *ab initio* method calculates r_e values. Because of anharmonicity, in all normal cases r_e is shorter than r_g. The difference is very large in the case of hydrogen, which has a very small mass and lies high up in the potential well, so the r_g value will be larger than r_e by about 0.02–0.03 Å.[21] For atoms heavier than hydrogen, the differences are very small in most cases. Both MM3 r_g and MM3 r_e values are listed in Tables 2–6. The bond angles calculated by MM3 and the *ab initio* method are generally in good agreement. For methylboronic acid, the H—C—H bond angle next to the H_c hydroxyl is slightly larger (1.5°) in MM3 than in the corresponding *ab initio* structure (Table 2, Fig. 1). This may also be caused by the overestimation of the van der Waals interaction between the hydroxyl hydrogen and methyl hydrogen by MM3. For ethyl- and propyl boronic acids, the H—C—H bond angle for CH_2 that is next to boron is slightly larger (1.3°; Tables 3 and 4, Fig. 1) in MM3. At the same time, the MM3 C—C—H bond angle for the same CH_2 group is smaller (1°; Tables 3 and 4, Fig. 1). This may be traced to the equilibrium C—C—H and H—C—H bond angles which were parameterized previously for alkanes where the C—C—C bond angle that centered around the CH_2 group is about 110°. In alkylboronic acids, the C—C—B bond angle that centered around the CH_2 group is about 116°. Therefore, the increase in the C—C—B bond angle caused a decrease in two C—C—H bond angles and an increase in the H—C—H bond angle. For phenylboronic acid, the largest discrepancies between the *ab initio* and MM3 methods are the O—B—O and O_c—B—C bond angles. The O—B—O bond angle calculated by MM3 is about 3° smaller than that in the *ab initio* structure, and the O_c—B—C bond angle in the MM3 structure is about 3° larger than that in the *ab initio* structure (Table 6, Fig. 1). This disagreement may be attributed to a favorable interaction between the lone pair of O_c and the *ortho* aromatic hydrogen. Obviously this interaction is not reflected in the MM3 structure.

CONCLUSION

A new set of MM3 force field parameters has been developed to model the structures and vibrational spectra of alkyl- and arylboronic acids. The close agreement between the MM3 and *ab initio* calculations will enable researchers to carry out quantitative molecular modeling studies of this biologically important class of compounds with high accuracy.

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REFERENCES

1. W. Tjarks, A. K. M. Anisuzzaman, L. Liu, S. H. Soloway, R. F. Barth, D. J. Perkins and D. M. Adams. *J. Med. Chem.* **35**, 16228–11633. (1992)
2. Y. Yamamoto. *Pure Appl. Chem.* **63**, 423–426 (1991).
3. F. Alam, A. H. Soloway, R. F. Barth, N. Mafune, D. M. Adam and W. H. Knoth. *J. Med. Chem.* **32**, 2326–2330 (1989).
4. A. H. Soloway and R. G. Fairchild. *Sci. Am.* **262**, 100–107 (1990).
5. D. A. Matthews, R. A. Alden, J. J. Birktoft, S. T. Freer and J. Kraut. *J. Biol. Chem.* **250**, 7120–7126 (1975).
6. D. H. Kinder, S. K. Frank and M. M. Ames. *J. Med. Chem.* **33**, 819–823 (1990).
7. R. F. Schinazi, B. H. Laster, R. G. Fairchild and W. H. Prusoff. *Antimicrob. Agents* **24**, 260–265 (1985).
8. N. L. Allinger, H. Y. Yuh and J. Lii. *J. Am. Chem. Soc.* **111**, 8511–8566 (1989).
9. N. L. Allinger, F. Li and L. Yan. *J. Comput. Chem.* **11**, 848–867 (1990).
10. N. L. Allinger, F. Li, L. Yan and J. C. Tai. *J. Comput. Chem.* **11**, 868–895 (1990).
11. N. L. Allinger, M. Rahman and J. Lii. *J. Am. Chem. Soc.* **112**, 8293–8307 (1990).
12. L. R. Schmitz and N. L. Allinger. *J. Am. Chem. Soc.* **112**, 8307–8315 (1990).
13. N. L. Allinger, K. Chen, M. Rahman and A. Pathiaseril. *J. Am. Chem. Soc.* **113**, 4505–4517 (1991).
14. N. L. Allinger, Z. Zhu and K. Chen. *J. Am. Chem. Soc.* **114**, 6120–6133 (1992).
15. N. L. Allinger, M. Quinn, M. Rahman and K. Chen. *J. Phys. Org. Chem.* **4**, 647–658 (1991).
16. N. L. Allinger and Y. Fan. *J. Comput. Chem.* **14**, 655–666 (1993).
17. P. Fox, J. P. Bowen and N. L. Allinger. *J. Am. Chem. Soc.* **114**, 8536–8544 (1992).
18. X. Chen, L. Bartolotti, K. Ishaq and A. Tropsha. *J. Comput. Chem.* **15**, 333–345 (1994).
19. G. Liang, P. C. Fox and J. P. Bowen. *J. Comput. Chem.* **17**, 940–953 (1996).
20. J. A. Pople, H. B. Schlegel, R. Krishnan, D. J. DeFrees, J. S. Binkley, M. J. Frisch, R. A. Whiteside, R. F. Hout and W. J. Hehre. *Int. J. Quantum Chem. Symp.* **15**, 269–278 (1981).
21. B. Ma, J. Lii, H. F. Schaefer and N. L. Allinger. *J. Phys. Chem.* **100**, 8763–8769 (1996).

