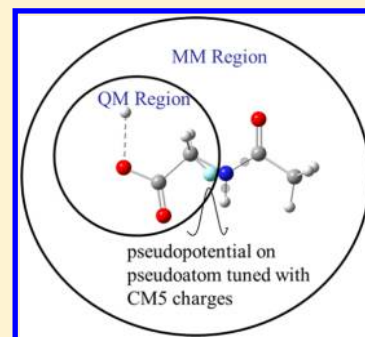# Tuned and Balanced Redistributed Charge Scheme for Combined Quantum Mechanical and Molecular Mechanical (QM/MM) Methods and Fragment Methods: Tuning Based on the CM5 Charge Model

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ABSTRACT: Tuned and balanced redistributed charge schemes have been developed for modeling the electrostatic fields of bonds that are cut by a quantum mechanical–molecular mechanical boundary in combined quantum mechanical and molecular mechanical (QM/MM) methods. First, the charge is balanced by adjusting the charge on the MM boundary atom to conserve the total charge of the entire QM/MM system. In the balanced smeared redistributed charge (BSRC) scheme, the adjusted MM boundary charge is smeared with a smearing width of 1.0 Å and is distributed in equal portions to the midpoints of the bonds between the MM boundary atom and the MM atoms bonded to it; in the balanced redistributed charge-2 (BRC2) scheme, the adjusted MM boundary charge is distributed as point charges in equal portions to the MM atoms that are bonded to the MM boundary atom. The QM subsystem is capped by a fluorine atom that is tuned to reproduce the sum of partial atomic charges of the uncapped portion of the QM subsystem. The new aspect of the present study is a new way to carry out the tuning process; in particular, the CM5 charge model, rather than the Mulliken population analysis applied in previous studies, is used for tuning the capping atom that terminates the dangling bond of the QM region. The mean unsigned error (MUE) of the QM/MM deprotonation energy for a 15-system test suite of deprotonation reactions is 2.3 kcal/mol for the tuned BSRC scheme (TBSRC) and 2.4 kcal/mol for the tuned BRC2 scheme (TBRC2). As was the case for the original tuning method based on Mulliken charges, the new tuning method performs much better than using conventional hydrogen link atoms, which have an MUE on this test set of about 7 kcal/mol. However, the new scheme eliminates the need to use small basis sets, which can be problematic, and it allows one to be more consistent by tuning the parameters with whatever basis set is appropriate for applications. (Alternatively, since the tuning parameters and partial charges obtained by the new method do not depend strongly on basis set, one can continue to use available CM5-tuned parameters even when one changes the basis set.) Furthermore, we found that, as compared to Mulliken charges, the CM5 charges describe the charge distributions in test molecules better, and they reproduce the dipole moments of full quantum mechanical calculations better; therefore the new tuning procedure is more physical and should be more reliable and robust.

1. INTRODUCTION

The combined quantum mechanical and molecular mechanical (QM/MM) method is one of the most powerful methods available for simulations of large and complex systems.[1–5] One of the critical issues is the treatment of QM−MM boundaries that cut covalent bonds. Various methods have been developed to terminate the dangling bonds in the QM region, including link atoms,[6–8] orbitals,[9–11] and other kinds of capping atoms,[12–18] sometimes called pseudoatoms.

We have recently developed tuned and balanced redistributed charge schemes to better treat the QM/MM boundary.[19,20] Mulliken charges were used to tune fluorine-like link atoms in order to obtain the correct total charge on the uncapped portion of the QM region. However, since Mulliken charges can be problematic when large basis sets are used in calculations, only small basis sets, including 6-31G* and STO-3G basis sets, were used for this tuning, and it would be problematic to extend the tuning process based on Mulliken charges to larger basis sets.

In the present study, we applied the CM5 charge model[21] to derive the tuning parameters to be used in the QM/MM simulations; this tuning process can be applied with any basis set because CM5 charges are well behaved even for extended basis sets. CM5 charges are also used as the molecular mechanical (MM) charges in the present improved method. This provides a more consistent way to do tuned and balanced redistributed charge schemes in the QM/MM calculations.

Although the tuned capping atoms will be tested in the present article only in the context of QM/MM methods, we note that the same challenge of physically capping dangling bonds on a truncated subsystem formed by cutting one or more bonds also occurs in a wide variety of fragment methods,[22] and the tuned capping atoms tested here should be equally useful for such fragment-method applications.
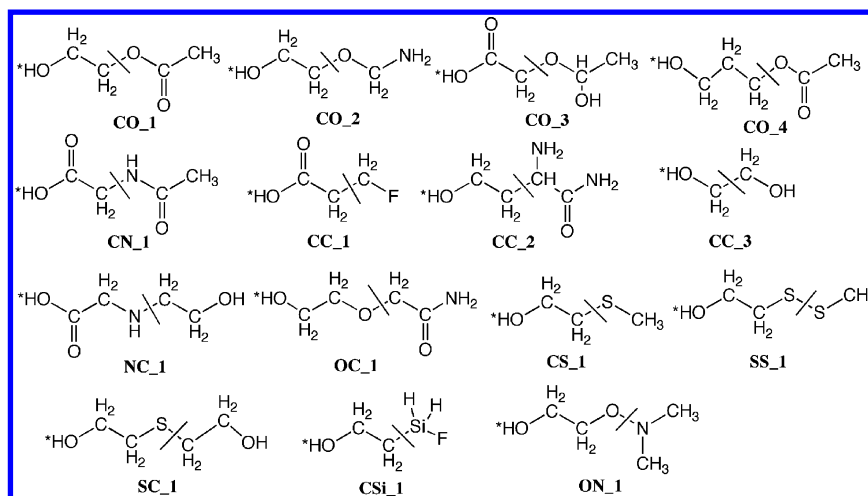
Figure 1. Test Suite. The asterisk (∗) denotes the deprotonation site. The QM region is on the left of the cut bond, and the MM region is on its right. The test suite is the same as that in ref 20.

2. METHODS

2.1. Tuned and Smeared Balanced Redistributed Charge Schemes. The treatments of the boundary charges and tuned link atoms are described in previous studies,[19,20] and we only summarize the key points here. First, we define M1 atoms as MM atoms directly bonded to a QM atom (through a bond that is cut by the partition) and M2 atoms as MM atoms directly bonded to M1 atoms. The balancing consists in adjusting the MM point charges on M1 atoms to conserve the total charge of the entire QM/MM system. The balanced M1 charge q_0 is then redistributed in various possible ways to avoid unphysical interactions due to MM charges being too close to the QM subsystem; in particular, we here employ two schemes that were recommended previously[20] for this redistribution.

The first redistribution scheme is the balanced RC2 (BRC2) scheme,[19] in which we move equal portions of the adjusted charge to all M2 atoms.

The second redistribution scheme is the balanced and smeared redistributed charge scheme (BSRC), based on an earlier method called the RC method,[23] in which we moved equal portions of the M1 charge to the midpoints of all M1−M2 bonds. In the BRC2 and RC schemes, the MM charges under consideration are point charges. In the RC scheme, the redistributed point charges at the midpoints of M1−M2 bonds are sometimes (especially when tuned F link atoms are used to cap the QM region) so close to the QM region that one encounters problems in the geometry optimizations. To alleviate this difficulty, the second charge redistribution scheme that we have recommended[20] redistributes the adjusted point charges to smeared charge distributions $\rho(r) = q_i A \exp(-2r/r_0)$, where q_i is the redistributed charge, A is the normalization factor for the charge density,[20] r is the distance to the redistributed charge center, and r_0 is the smearing width of the charge density. This is equivalent to writing the redistributed charge as[20]

$$q_i^* = q_i - q_i\left(1 + \frac{r}{r_0}\right)\exp(-2r/r_0) \tag{1}$$

The next consideration is adding a capping atom (sometimes called a link atom or a pseudoatom) on the dangling bonds of the cut QM system. In the tuned methods, this is done with a tuned F atom that has an adjustable pseudopotential centered at its nucleus. The adjustable pseudopotential is given by[19,20]

$$U(r) = C \exp[-(r/a_0)^2] \tag{2}$$

where a_0 is the Bohr radius and C is a tuning parameter adjusted to reproduce the sum of the partial charges of the uncapped portion of the QM subsystem. In previous studies,[19,20] the partial charges were computed using Mulliken analysis with a 6-31G* basis set when the M1 atom is from the second period (Li through F) and with an STO-3G basis set otherwise. In the present study, we computed the partial charges using a more physical model, namely the CM5 charge model, which is described below.

2.2. CM5 Charge Model. Our group has developed a new charge model, namely the CM5 charge model.[21] CM5 charges are obtained by mapping the charges from Hirshfeld population analysis[24] (HPA) through the following equations:

$$q_k^{CM5} = q_k^{HPA} + \sum_{k \neq k'} T_{kk'}B_{kk'} \tag{3}$$

$$B_{kk'} = \exp[-\alpha(r_{kk'} - R_{Z_k} - R_{Z_{k'}})] \tag{4}$$

where q_k^{CM5} and q_k^{HPA} are the CM5 charge and Hirshfeld charge of atom k, $r_{kk'}$ is the distance between atoms k and k', $T_{kk'}$ are parameters related to atoms k and k', and R_{Z_k} is the atomic radius of atom k, and it depends only on the atomic number Z_k of atom k.

CM5 charges predict more accurate dipole moments than Hirshfeld charges and Mulliken charges; and they are more stable than Mulliken and other population analysis methods with respect to changing basis sets. Furthermore, as compared to charges obtained by electrostatic fitting, they are more stable with respect to conformational changes, and the equations defining them are not ill-conditioned for the charges on buried atoms. Taking into consideration these favorable features of the CM5 charge model, we applied it in the present study to tune the parameters of the link atoms as well as to obtain the MM charges.

3. COMPUTATIONAL DETAILS

All computations were carried out by using the M06-2X density functional[25] for the QM subsystem. The MMFF94 force field[26]

was used for the valence terms and van der Waals terms in the force field.

Three basis sets have been tested, in particular 6-31G*,[27−29] def2-TZVP,[30] and MG3S.[31] The 6-31G* basis set is used for all calculations in sections 4.1, 4.2, 4.4, and 4.5, and the other basis sets are considered in section 4.3. For the MM charges, we used M06-2X/CM5[21] charges of the protonated molecules with the same basis set as used for the QM subsystem. M06-2X/6-31G*/CM4M[32] charges of the protonated molecules were also tested for comparison in section 4.5.

For the tuning process, we used CM5 charges, but results for link atoms tuned with Mulliken charges are shown for comparison. The tuning process is performed using the protonated molecules in sections 4.1, 4.2, 4.3, and 4.5, and using the deprotonated molecules in section 4.4.

The test suite, shown in Figure 1, contains 15 systems and is the same as that in the previous study.[20] All results in the present study are for single-point calculations without QM/MM optimizations of the structures. The geometries for the protonated molecules are the M06-2X/6-31G* optimized structures of the whole systems, and those of the deprotonated molecules are derived by deleting the protons of the protonated molecules without reoptimization.

All QM/MM calculations were carried out using our own QMMM program,[33] which is based on *Gaussian 09*,[34] and a modified TINKER program.[35] All QM calculations were carried out using *Gaussian 09*.[34] The CM5 charges were calculated by CM5PAC.[36] M06-2X/6-31G*/CM4M charges were derived from a locally modified module[37] of *Gaussian 09*.[34] (The CM5 charge model, which is parametrized for the entire periodic table, will be included in an upcoming revision of *Gaussian 09*.)

4. RESULTS AND DISCUSSION

4.1. Overall Performance with 6-31G* Basis Set. Table 1 shows the mean signed error (MSE) and mean unsigned

Table 1. Mean Signed Error (MSE) and Mean Unsigned Error (MUE) of QM/MM Deprotonation Energies (kcal/mol) for the Test Suite Using H Link Atoms or Tuned F Link Atoms Tuned Either with Mulliken Charges or with CM5 Charges

			tuned F link atom				
	H link atom			Mulliken[b]		CM5	
scheme	MSE	MUE	scheme	MSE	MUE	MSE	MUE
BSRC[a]	7.6	7.6	TBSRC[a]	1.1	1.5	1.0	2.3
BRC2	7.1	7.2	TBRC2	0.7	1.5	0.5	2.4

[a]With a smearing width of 1.0 Å. M06-2X/6-31G* is used for all calculations in this table. [b]Schemes recommended in ref 20.

error (MUE) for QM/MM deprotonation energies compared with full QM calculations using the two recommended charge schemes,[20] the tuned BSRC scheme (TBSRC) with a smearing width of 1.0 Å and the tuned BRC2 scheme (TBRC2) without smearing. The results employing conventional hydrogen link atoms are shown for comparison.

For the tuned fluorine link atom, two different approaches were used for tuning. The first one is to use the Mulliken charge model proposed in previous studies,[19,20] and the other is to use the CM5 charge model proposed in the current study. Table 1 shows that both of the tuned methods perform much better than the conventional hydrogen link atom approach.

Though the schemes tuned with CM5 charges perform a little worse than the schemes tuned with Mulliken charges, a consistent 6-31G* basis set is used for tuning with CM5 charges while two different basis sets, 6-31G* and STO-3G, are used for tuning with Mulliken charges, and this consistency is expected to be both more robust and more convenient when one uses a greater variety of basis sets and considers a wider variety of systems in actual applications. Moreover, we found that, unlike some cases when using the Mulliken charge model, all tuning parameters from the CM5 model are equal to or greater than 0, meaning a repulsive potential is always added to the conventional F link atom, which is quite physical since F is the most electronegative atom in the periodic table. Therefore, we believe that tuning with CM5 charges is more realistic.

Tables 2 and 3 compare the dipole moments computed from the CM5 charge model and Mulliken charge model to those

Table 2. Dipole Moment (debye), Mean Unsigned Error in the Dipole Moment (debye), and Averaged Deviation in Direction (Unitless) of the Dipole of the Entire System Calculated from the Quantum Mechanical Electron Density and from the Mulliken, CM5, MK, NPA, and MMFF94 Charges[a]

molecule	QM	Mulliken	CM5	MK	NPA	MMFF94
CO_1	3.4	3.6	3.3	3.4	4.5	4.2
CO_2	1.1	1.6	1.1	1.1	2.1	1.7
CO_3	1.5	3.1	1.7	1.5	4.0	2.3
CO_4	1.1	0.9	1.0	1.1	1.3	0.8
CN_1	0.5	1.4	0.6	0.5	1.2	1.4
CC_1	3.1	2.6	3.0	3.1	3.3	4.0
CC_2	2.4	2.5	2.6	2.4	3.4	2.3
CC_3	0.0	0.0	0.0	0.0	0.0	0.0
NC_1	5.5	5.3	5.6	5.6	6.0	5.8
OC_1	3.0	3.8	3.1	3.0	5.0	4.2
CS_1	0.4	1.8	0.4	0.4	2.7	0.5
SS_1	2.0	1.8	1.8	2.0	2.5	2.4
SC_1	1.4	4.1	1.6	1.4	5.5	1.7
CSi_1	2.6	3.9	3.2	2.6	5.4	3.6
ON_1	1.3	1.6	1.4	1.3	2.0	2.0
MUE		0.7	0.1	0.0	1.3	0.6
ADD		0.28	0.01	0.01	0.33	0.04

[a]M06-2X/6-31G* is used for all calculations in this table except for the MMFF94 column.

calculated from the charge density for the full systems (Table 2) and the tuned capped primary systems (Table 3). Since the tuned capped primary systems are different when tuning with Mulliken charges and with CM5 charges, we have two columns of QM dipole moments for comparison in Table 3. The mean unsigned errors (MUEs) of the dipole moments from the two charge models are also listed in these two tables. In order to test whether the direction, as well as the magnitude, of the dipole moment is correctly predicted, for each model, we also calculated the average deviation of direction (ADD) of the dipole moment, as defined by

$$\mathrm{ADD} = \frac{1}{14} \sum_{i=1}^{14} \left| 1 - \frac{\boldsymbol{d}_{i,\mathrm{QM}} \cdot \boldsymbol{d}_{i,\mathrm{MM}}}{|\boldsymbol{d}_{i,\mathrm{QM}}||\boldsymbol{d}_{i,\mathrm{MM}}|} \right| \tag{5}$$

where $\boldsymbol{d}_{i,\mathrm{QM}}$ and $\boldsymbol{d}_{i,\mathrm{MM}}$ are the QM and MM dipole moment vectors of molecule i. Because of the symmetry of $\mathrm{HOCH_2CH_2OH(CC\_3)}$, all three components of its dipole

Table 3. Dipole Moment (debye) and Mean Unsigned Error in the Dipole Moment of the Tuned Capped Primary System from the Quantum Mechanical (QM) Electron Density and from the Mulliken and CM5 Charge Models[a]

molecule	tuned with Mulliken charges		tuned with CM5 charges	
	QM	Mulliken	QM	CM5
CO_1	2.1	2.0	1.8	1.8
CO_2	1.9	1.8	1.7	1.6
CO_3	0.7	1.4	0.6	0.6
CO_4	3.4	4.2	3.0	3.0
CN_1	5.0	5.8	4.9	4.9
CC_1	4.4	5.1	4.5	4.4
CC_2	1.7	1.9	1.7	1.5
CC_3	2.4	2.8	2.4	2.0
NC_1	5.0	5.5	4.5	4.9
OC_1	0.7	0.4	1.5	1.1
CS_1	1.6	1.7	1.6	1.5
SS_1	2.3	3.3	1.9	1.7
SC_1	1.4	2.4	1.4	1.0
CSi_1	1.6	1.8	1.5	1.4
ON_1	1.1	0.9	1.9	1.6
MUE		0.5		0.2

[a]M06-2X/6-31G* is used for all calculations in this table.

moment are zero. Therefore, $HOCH_2CH_2OH$ is excluded from the averaging in eq 5, which is why only 14 molecules are used to calculate ADD. Besides the Mulliken charge model and the CM5 charge model, we also list the results computed from the MK electrostatic fitting charge model,[38] the natural population analysis (NPA),[39] and the MMFF94 force field for comparison in Table 2.

We found that the MUE of the dipole moments for the CM5 charge model is much smaller than that for the Mulliken charge model, that is, 0.1 vs 0.7 in the full systems and 0.2 vs 0.5 in the tuned capped primary systems. The ADD values show that the directions of the dipole moments are also well reproduced in the CM5 charge model. This better reproduction of the fully quantum mechanical dipole moments indicates that the CM5 charge model is more physical than Mulliken analysis. As the partial atomic charges are used as an indicator of the charge distribution in the full systems and the tuned capped primary systems, CM5 charges should provide more reliable results than the previous Mulliken charges. In Table 2, we found that MK charges can also reproduce the QM dipole moment quite well. However, because the MK charges suffer from the buried atom problem and are not as stable as CM5 charges, we considered the CM5 charge model as the best choice.

4.2. Analysis of Individual Molecules. To better understand the trends, individual results for all 15 deprotonation reactions are shown in Table 4. We show results both for employing H link atoms and for employing F link atoms tuned with CM5 charges. The QM region is in bold characters in the table. The worst results are for the O−C and C−S bonds. However, even in these cases, the errors are smaller than the average error of using H link atoms.

To understand the trends for different QM regions and MM regions, we calculated three more molecules in which a C−O bond is cut. The protonated forms of the molecules and the signed errors of the QM/MM deprotonation energies are shown in Table 5. Molecules CO_1, CO_4, and CO_5 contain the same kind of QM/MM boundaries and the same MM regions, but they have different QM regions. The table shows

Table 4. QM/MM Signed Error (SE) and Mean Unsigned Error (MUE) of QM/MM Deprotonation Energy (kcal/mol) for the Test Suite Using the BSRC Scheme with H Link Atoms and the TBSRC Scheme with F Link Atoms Tuned with CM5 Charges[a]

	molecule	H link atom	tuned F link atom
CO_1	**HOCH₂CH₂**−OC(O)CH₃	12.3	3.2
CO_2	**HOCH₂CH₂**−OCH₂NH₂	10.6	2.6
CO_3	**HOOCCH₂**−OCHOHCH₃	7.2	1.0
CO_4	**HOCH₂CH₂CH₂**−OC(O)CH₃	7.8	1.8
CN_1	**HOOCCH₂**−NHCOCH₃	9.3	−0.7
CC_1	**HOOCCH₂**−CH₂F	4.2	−1.5
CC_2	**HOCH₂CH₂**−CHNH₂CONH₂	6.5	1.5
CC_3	**HOCH₂**−CH₂OH	14.3	2.7
NC_1	**HOOCCH₂NH**−CH₂CH₂OH	4.5	−1.2
OC_1	**HOCH₂CH₂O**−CH₂CONH₂	4.0	−5.8
CS_1	**HOCH₂CH₂**−SCH₃	14.0	6.9
SS_1	**HOCH₂CH₂S**−SCH₃	4.9	3.7
SC_1	**HOCH₂CH₂S**−CH₂CH₂OH	−0.1	0.7
CSi_1	**HOCH₂CH₂**−SiH₂F	5.4	0.6
ON_1	**HOCH₂CH₂O**−N(CH₃)₂	8.6	−0.8
MUE		**7.6**	**2.3**

[a]With a smearing width of 1.0 Å. M06-2X/6-31G* is used for all calculations in this table. The QM subsystem is bold. The QM region is in the bold characters in the table.

Table 5. QM/MM Signed Error (SE) of QM/MM Deprotonation Energy (kcal/mol) Using the BSRC Scheme with H Link Atoms and the TBSRC Scheme with F Link Atoms Tuned with CM5 Charges[a]

	molecule	H link atom	tuned F link atom
CO_5	**HOCH₂CH₂CH₂CH₂**−OC(O)CH₃	5.6	0.9
CO_6	**⁺H₂OCH₂CH₂**−OC(O)CH₃	9.8	0.6
CO_7	**HOCH₂CH₂**−OC(O)CH₂CH₃	12.2	3.0

[a]M06-2X/6-31G* is used for all calculations in this table. The QM region is in the bold characters in the table.

that when the QM/MM boundary is farther from the site of the reaction, the error decreases significantly for both kinds of scheme (using H link atoms and using tuned F link atoms). Molecules CO_1 and CO_6 differ by one proton in the QM region, but the results for these two cases are quite different. The tuned parameters (not shown in tables) for these two cases are 0.0 vs 0.15 hartrees. Nevertheless, the tuned F link atoms perform much better than the H link atoms in both cases. Molecules CO_1 and CO_7 contain the same QM regions and QM/MM boundaries but have different MM regions, and their signed errors are similar.

4.3. Results with Other Basis Sets. To test the sensitivity of the tuning parameters and the deprotonation energies to the basis set, we performed calculations using two other basis sets, in particular MG3S and def2-TZVP.

Table 6 compares the tuning parameters obtained using 6-31G*, MG3S, and def2-TZVP basis sets. We found that the three sets of tuning parameters are very similar, with the typical difference being 0.05 or less. This confirms that the CM5 charge model is very stable with respect to the basis set, and we can use any basis set for tuning. This is quite different from the situation with the Mulliken charge model, in which only small balanced basis sets can be used for tuning, and one must be very careful in selecting basis sets for new elements of the

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Table 6. Tuning Parameters C (hartrees) of the Tuned F Link Atoms Using Various Basis Sets

	6-31G*	MG3S	def2-TZVP
CO_1	0.00	0.00	0.00
CO_2	0.20	0.20	0.20
CO_3	0.25	0.25	0.25
CO_4	0.00	0.00	0.00
CN_1	0.00	0.00	0.05
CC_1	0.70	0.70	0.70
CC_2	0.80	0.80	0.80
CC_3	0.75	0.75	0.75
NC_1	1.00	1.05	1.05
OC_1	0.80	0.90	0.85
CS_1	0.45	0.45	0.50
SS_1	0.65	0.60	0.60
SC_1	0.95	0.90	0.90
CSi_1	0.85	0.85	0.85
ON_1	0.55	0.60	0.60

periodic table. Calculations using the CM5 charge model can be reliable even if the model is tuned with a basis set different from that to be eventually used for applications. If desired, one can use a polarized double-ζ basis set to do the tuning, and use these tuned parameters for simulations with larger basis sets.

Table 7 shows the MSE and MUE of the QM/MM deprotonation energies using MG3S and def2-TZVP basis sets,

Table 7. QM/MM Mean Signed Error (MSE) and Mean Unsigned Error (MUE) of QM/MM Deprotonation Energies (kcal/mol)[a]

		H link atom		tuned F link atom	
basis set	scheme	MSE	MUE	MSE	MUE
MG3S	BSRC, TBSRC[b]	6.5	6.5	−1.6	2.6
	BRC2, TBRC2[c]	6.1	6.1	−1.9	2.5
def2-TZVP	BSRC, TBSRC[b]	6.8	6.8	−1.1	2.3
	BRC2, TBRC2[c]	6.4	6.4	−1.4	2.3

[a]The MG3S calculations were performed with the MG3S tuning parameters, and the def2-TZVP calculations were performed with the def2-TZVP tuning parameters. [b]With a smearing width of 1.0 Å and with CM5 used for the tuning. [c]With CM5 used for the tuning.

with the tuning parameters from Table 6. This table shows that for these basis sets, just as for the 6-31G* basis set employed in earlier sections, the schemes using tuned F link atoms perform better than those using H link atoms.

4.4. Tuning Schemes and Tuning Parameters. To see how sensitive the results are with respect to the tuning scheme and tuning parameter, we also performed the tuning process using the deprotonated molecules. The procedure is similar to that for the calculations described above except that we tune to the deprotonated molecules rather than the protonated ones. Only the results for the 6-31G* basis set are shown in Table 8, because the other two basis sets show similar trends. Compared with the first column in Table 6, the tuning parameters here are smaller than those derived from the protonated molecules by around 0.3. Next, we used the averaged parameters tuned from protonated forms and deprotonated forms for calculating the deprotonation energies, the results also shown in Table 8. We found that the overall results are similar to those where tuning was carried out on the protonated molecules. This indicates that it is not necessary to tune for both reactants and products

Table 8. Parameters C (hartrees) Tuned with Deprotonated Molecules and the Signed Error (SE) and Mean Unsigned Error (MUE) for the QM/MM Deprotonation Energies (kcal/mol) Using the Averaged Tuning Parameters[a]

molecule	parameter	SE for deprotonation energy
CO_1	−0.20	2.6
CO_2	0.00	1.9
CO_3	0.05	0.7
CO_4	−0.15	1.5
CN_1	−0.30	−1.7
CC_1	0.55	−2.0
CC_2	0.45	0.3
CC_3	0.45	1.0
NC_1	0.85	−1.7
OC_1	0.75	−6.0
CS_1	0.00	5.4
SS_1	0.40	2.9
SC_1	0.80	0.3
CSi_1	0.55	−0.4
ON_1	0.45	−1.3
MUE		**2.0**

[a]M06-2X/6-31G* is used for all calculations in this table.

since the final results are not very sensitive to the parameters. We believe that tuning on either form catches the main feature to mimic various kinds of QM/MM boundaries.

4.5. Various MM Charges. We also carried out calculations with CM4M charges as the MM charges, shown in Table 9.

Table 9. QM/MM Mean Signed Error (MSE) and Mean Unsigned Error (MUE) of Deprotonation Energy (kcal/mol) for the Test Suite Using BSRC and BRC2 Schemes with H Link Atom or Tuned F Link Atom Tuned Either with Mulliken Charges or with CM5 Charges[a]

	H link atom			tuned F link atom			
				Mulliken		CM5	
scheme	MSE	MUE	scheme	MSE	MUE	MSE	MUE
BSRC[b]	6.7	6.8	TBSRC[b]	0.2	1.5	0.1	2.2
BRC2	6.3	6.5	TBRC2	−0.1	1.7	−0.3	2.5

[a]CM4M charges are used as MM charges. [b]With a smearing width of 1.0 Å. M06-2X/6-31G* is used for all calculations in this table.

Comparing with the results using the CM5 charges shown in Table 1, we found that CM4M charges give similar overall performance. This indicates that the quality of the results is not very sensitive to this kind of variation in the MM charges. But, unlike CM5 charges, CM4M charges cannot be derived for larger basis sets or for all electronic structure methods, so it is more convenient and consistent to use the CM5 charge model both to do the tuning process for the capping atoms and to derive MM charges.

5. CONCLUDING REMARKS

In the current study, we have improved the tuned and balanced redistributed charge schemes (TBSRC and TBRC2) proposed in previous studies[19,20] as refinements of an earlier[23] redistributed charge scheme (RC) for combined quantum mechanical and molecular mechanical (QM/MM) methods. The CM5 charge model, which is not restricted to small basis sets, is applied not only to derive the MM charges used on MM

atoms in the QM/MM methods but also to obtain the tuning parameters for the atoms that cap dangling bonds in the QM subsystem. This is more convenient, and it provides a more consistent way to parametrize tuned and balanced redistributed charge schemes in QM/MM calculations when using general, high-quality basis sets. We found that the CM5 charges better describe the charge distributions of molecules and hence are more physical. They are more stable with respect to basis set variations than are Mulliken charges so that they are also more reliable and so that it is not necessary to specify the basis set when deriving the tuning parameters for the capping atom. (This makes it possible in some cases to use tuning parameters developed in previous work.) Both the TBSRC scheme and the TBRC2 scheme perform well when tuned and used with CM5 charges; in particular, comparing the results from using tuned fluorine capping atoms to those from using conventional hydrogen link atoms, we find that the tuned fluorine capping atoms reduce the errors in a test suite of deprotonation reactions by about a factor of 3.

We note that tuned capping atoms may be used in other contexts as well as for QM/MM calculations. For example, they may be used for various fragment schemes,[22] such as adding electrostatic embedding to molecular tailoring or molecules-in-molecules methods, where one also faces the challenge of capping dangling bonds without perturbing the essential character of the electronic structure of the fragment atom. They may also be used to extend electrostatically embedded many-body methods[40] to cases where fragments are formed by cutting nondative covalent bonds.

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Notes
The authors declare no competing financial interest.

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