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Looking at Self-Consistent-Charge Density Functional Tight Binding from a Semiempirical Perspective†

Nikolaj Otte, Mirjam Scholten, and Walter Thiel*

Max-Planck-Institut für Kohlenforschung, D-45470 Mülheim an der Ruhr, Germany

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The self-consistent-charge density functional tight binding (SCC-DFTB) method is compared with other semiempirical methods (MNDO, AM1, PM3, OM1, OM2, OM3). Despite the differences in the underlying philosophy and derivation, these methods share many common features. Systematic evaluations of their performance are reported for standard test sets that are in common use. The overall accuracy of SCC-DFTB and the other methods is in the same range, with the overall tendency AM1 < SCC-DFTB < OM2, but any such ranking depends on the properties and compound classes considered. SCC-DFTB is excellent for geometries and performs well for biological systems. It seems less suitable for the energetics of radicals and electronically excited states, and suffers from occasional outliers (e.g., for compounds with NO bonds). In an overall assessment, SCC-DFTB is a viable semiempirical method with specific strengths and weaknesses which may be an attractive choice especially for biomolecular applications.

1. Introduction

Over the past decades, the semiempirical molecular orbital (MO) methods of quantum chemistry have been used widely in computational studies, and there are several reviews that describe this field.[1−6] The most popular of these methods are based on the neglect of diatomic differential overlap (NDDO) and are known under the labels MNDO,[7] AM1,[8] and PM3.[9] Different variants of the basic MNDO model[7] have been introduced over the years, with general-purpose and system-specific parametrizations. Successful recent examples include the PDDG/ MNDO and PDDG/PM3 treatments.[10]

Density functional theory (DFT) has by now become the method of choice for computational studies of medium-sized molecules because of its generally good and robust performance at reasonable cost. DFT calculations are, however, significantly more expensive than semiempirical MNDO-type calculations, typically by 2 to 3 orders of magnitude, and hence there is a need for simplified DFT-based approaches that attempt to retain DFT-type accuracy at reduced computational effort. To achieve this goal, tight-binding (TB) approximations have been introduced, for example in the framework of the DFTB method.[11,12] The non-iterative DFTB implementation encounters problems in polar systems, which are better treated by an iterative procedure such as SCC-DFTB (self-consistent-charge DFTB).[13] This method has found widespread attention in recent years, particularly in the context of combined quantum mechanical/ molecular mechanical (QM/MM) studies of large biomolecules.[14,15] Recent reviews of SCC-DFTB and its application to biological systems are available.[16,17]

The MNDO-type semiempirical methods and SCC-DFTB are both designed for approximate and efficient calculations on large molecules. The accuracy and the shortcomings of MNDO-type methods have been thoroughly documented in the literature, much more so than for the more recent SCC-DFTB approach which has been validated less extensively.[18−20] Motivated by the need for a thorough assessment of general-purpose computational methods, we present in this article an evaluation of the performance of SCC-DFTB for some standard test sets that are in common use.[7,21−23] This evaluation covers compounds containing hydrogen, carbon, nitrogen, and oxygen. It includes comparisons of SCC-DFTB with MNDO, AM1, and PM3 as well as NDDO-based methods with orthogonalization corrections,[3−5] i. e., OM1,[24,25] OM2,[26,27] and OM3.[28]

2. Theoretical Background

The DFTB approach employs a minimal valence basis of atomic orbitals (AOs). The MOs ψ_i are obtained by solving the secular equations with explicit consideration of overlap. In usual matrix notation:

$$\mathbf{H^0C} = \mathbf{SCE} \qquad (1)$$

where $\mathbf{H^0}$ denotes the Hamiltonian matrix, $\mathbf{S}$ is the overlap matrix, $\mathbf{C}$ is the matrix of MO eigenvectors, and $\mathbf{E}$ is the diagonal matrix of orbital energies. The Hamiltonian matrix elements are calculated using the kinetic energy operator $\hat{T}$ and an effective Kohn−Sham potential which is approximated as the sum of the Kohn−Sham potentials V_0 of the associate neutral atoms (A, B).

$$H^0_{\mu\nu} = \langle \phi^A_\mu | \hat{T} + V^A_0 + V^B_0 | \phi^B_\nu \rangle \qquad (2)$$

The basis orbitals φ_μ and potentials V_0 are taken from DFT calculations on atoms. The DFTB treatment is non-iterative. The total energy is given by the sum of the orbital energies ϵ_i and repulsive two-center correction terms U_{AB} determined by fitting the differences between reference DFT and tight-binding DFTB potential curves in suitable reference molecules:

$$E_0 = \sum_i^{occ} \epsilon_i + E_{rep} = \sum_i^{occ} \langle \psi_i | \hat{H}_0 | \psi_i \rangle + \sum_{A<B}\sum U_{AB} \qquad (3)$$

The basic DFTB approach may be improved by allowing for charge fluctuations. The derivation involves a second-order expansion of the DFT total energy with respect to the charge

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† Part of the “DFTB Special Section”.

* Corresponding author. E-mail: thiel@mpi-muelheim.mpg.de.

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density variation relative to a chosen reference density. The charge density variation is represented by atomic contributions Δq_A which are obtained as differences between actual and reference Mulliken charges: $\Delta q_A = q_A - q_A^0$. Their interaction is described by a damped Coulomb term γ_{AB} with the correct asymptotic behavior for large distances (→ $1/R_{AB}$) and for small distances (→ one-center-term γ_{AA}: chemical hardness computed from DFT using the PBE functional). The derivation yields the following working equations of the SCC-DFTB method:

$$\mathbf{HC} = \mathbf{SCE} \tag{4}$$

$$H_{\mu\nu} = H_{\mu\nu}^0 + \frac{1}{2}S_{\mu\nu}\sum_C \Delta q_C(\gamma_{AC} + \gamma_{BC}) \tag{5}$$

$$E = E_0 + \frac{1}{2}\sum_A\sum_B \Delta q_A \Delta q_B \gamma_{AB} \tag{6}$$

Due to the appearance of the Mulliken charges in the SCC-DFTB formalism, eqs 4−6 must be solved iteratively to obtain the self-consistent-field (SCF) MOs. As in the case of DFTB, the repulsive two-center correction terms in E_{rep} (which is part of E_0) must be parametrized against DFT reference data; see eqs 3 and 6.

Comparing SCC-DFTB with MNDO-type methods, the underlying philosophy and the derivation of the applied approximations seem quite different at first sight. If one focuses on the actual working equations and their implementation, there are, however, many similarities: All these methods are valence-electron SCF−MO treatments with a minimal valence AO basis set, only one-center and two-center terms are included, the two-center two-electron integrals are represented by damped Coulomb interactions with the correct limit at large and small distances, and there are repulsive atom-pair terms that correct for deficiencies in the formalism. The methods are semiempirical in the sense that they employ empirical parameters which are adjusted to reproduce selected reference data, i.e., DFT energies and potential curves in the case of SCC-DFTB, and experimental heats of formation and other experimental data in the case of the MNDO-type methods.

There are also some differences, of course: Overlap is explicitly included during the solution of the secular equations in SCC-DFTB, while it is neglected in MNDO-type methods in order to be consistent with the NDDO integral approximation. It should be noted that such overlap effects are at least partially taken into account in the OMx models with orthogonalization corrections[3−5,24−28] through additional parametric terms in the one-electron matrix elements. In this sense, the OMx models are formally intermediate between SCC-DFTB and MNDO-type approaches. Another distinction concerns the two-center one-electron integrals (“resonance integrals”) which are computed analytically in SCC-DFTB and represented by empirical functions in MNDO-type and OMx methods. Finally, the charge fluctuations in SCC-DFTB are formally treated at the simple CNDO (complete neglect of differential overlap) level while MNDO-type and OMx approaches make use of the more refined NDDO integral approximation.

In the parametrization, there is the conceptual difference that SCC-DFTB aims at reproducing the results from full DFT calculations whereas the MNDO-type and OMx methods attempt to reproduce experimental data. This should make little difference as long as the full DFT results are close to experiment, but the SCC-DFTB strategy may become problematic in areas where DFT faces problems, e.g., in the case of electronically excited states.[29] In practical terms, SCC-DFTB uses atom-pair parameters for the repulsive two-center correction terms (typically 10 per pair) which allows for fine-tuning, but makes it cumbersome to parametrize additional elements (since the effort increases quadratically with the number of elements). The MNDO-type and OMx methods employ atomic parameters so that the work per additional element is always similar.

Considering the computational effort, the most time-consuming steps in all these methods are matrix manipulations, especially matrix diagonalizations, which scale as N^3 for N basis functions (N being the same for a given molecule in all cases). The overall effort is thus of the same order (although somewhat higher in the case of SCC-DFTB due to the need for extra matrix operations involving the overlap matrix). Analytic gradients and Hessians are also available or can be implemented in all these methods.[30,31]

3. Results

All calculations were carried out using the MNDO99 program,[32] which was extended by adding the SCC-DFTB code obtained from Marcus Elstner. The evaluations employed standard semiempirical test suites that had been in use[7,23−28] long before the advent of SCC-DFTB, as well as the standard G2 and G3 tests[21−23] commonly applied in ab initio and DFT work. The evaluations are restricted to closed-shell singlets and to doublets since the implemented SCC-DFTB code handles only these multiplicities.

The performance of quantum-chemical methods with regard to energies is often judged by comparing with experimental heats of formation at 298 K under standard conditions, simply because experimental data are most readily available for these quantities. In MNDO-type and OMx methods, heats of formation are determined from the computed atomization energies and experimental heats of formations ΔH_f^A of the atoms:

$$\Delta E_t = E_{tot}^{mol} - \sum_A E_{el}^A + \sum_A \Delta H_f^A \tag{7}$$

where E_{tot}^{mol} is the total energy of the molecule and E_{el}^A is the total energy of atom A. This procedure is only justified if zero-point vibrational and thermal corrections are incorporated into E_{tot}^{mol} through the parametrization, which is true for MNDO-type and OMx methods, but not for SCC-DFTB.

A proper evaluation of heats of formation in SCC-DFTB thus requires the explicit inclusion of zero-point vibrational and thermal corrections, in analogy to ab initio and full DFT treatments.[21,22] We have implemented this option in the MNDO99 program and used it to run our standard CHNO test set with 140 mostly organic molecules. The resulting heats of formation showed strong overbinding in all cases except for H_2, with a mean absolute deviation of 54.5 kcal/mol from experiment. Errors (kcal/mol) for selected molecules are: H_2 + 28.0, methane −14.1, ethane −27.7, ethylene −18.8, acetylene −17.4, n-hexane −75.1, benzene −56.7, N_2 −32.4, ammonia −18.2, HCN −34.2, water −13.3, dimethylether −38.1, CO −31.8, CO_2 −37.5, formaldehyde −25.7, acetic acid −40.9, and nitric acid −130.8. It is obvious that the errors increase with molecular size and that they are particularly large for triple bonds (N_2, HCN, CO) and NO bonds. The typical overbinding per bond (kcal/ mol) amounts to the following: C−H 3−4, N−H and O−H 6−7, C−C and C=C 4−7, C≡C ca. 10, and C≡N ca. 25. Systematic errors of this size may thus be expected in SCC-DFTB predictions of the corresponding bond dissociation energies. Hence, calculations with explicit

TABLE 1: Optimized[20] and Directly Computed SCC-DFTB Electronic Energies (eV)

element	H	C	N	O
optimized	−7.7196445	−39.779913	−59.990944	−85.978530
computed	−6.4923169	−38.053012	−56.112025	−83.975273

TABLE 2: Mean Absolute Deviations for the Standard CHNO Test Set

property[a]	N^b	MNDO	AM1	PM3	OM1 OM1	OM2	OM3	DFTB
ΔH_f (kcal/mol)	140	6.3	5.5	4.2	3.5	3.1	2.9	7.7[c]
R (pm)	242	1.4	1.7	1.1	1.2	1.6	2.0	1.5
θ (deg)	101	2.6	1.9	2.1	1.8	2.2	1.8	1.3
IP (eV)	52	0.46	0.35	0.42	0.32	0.26	0.45	3.82
μ (D)	63	0.35	0.26	0.27	0.25	0.28	0.27	0.37
ν (cm^{-1})	112	241	172	151	189	155	120	90

[a] Heats of formation ΔH_f, bond lengths R, bond angles θ, vertical ionization potentials IP from Koopmans' theorem, dipole moments μ, harmonic vibrational wavenumbers ν. [b] N comparisons. [c] $N = 139$, triplet O_2 excluded.

TABLE 3: Mean Absolute Deviations for Heats of Formation (kcal/mol) (Own Test Sets)

	N^a	MNDO	AM1	OM2	DFTB[b]
neutral CHNO molecules	140	6.3	5.5	3.1	7.7
hydrocarbons	57	5.9	4.9	1.7	6.3
CHN compounds	32	6.2	4.6	3.9	6.1
CHO compounds	39	4.8	5.5	4.5	2.7
XNO compounds	8	16.3	11.4	2.9	43.9
anions	24	14.4	11.3	8.4	12.7
cations	33	11.5	9.8	7.2	14.5
radicals	42	11.9	10.6	5.0	17.0

[a] N comparisons. [b] $N = 139$, 31, and 39 in rows 1, 7, and 8, respectively, triplets excluded (see Supporting Information for details).

inclusion of zero-point vibrational and thermal corrections lead to inaccurate heats of formation in SCC-DFTB.

It has long been known that such systematic errors in heats of formation can be remedied, to a large extent, by adding empirical atomic increments when converting the computed total energies into heats of formations.[33,34] Equivalently, in semiempirical methods, one may treat $E_{\mathrm{el}}^{\mathrm{A}}$ as an adjustable parameter rather than computing it.

This idea has been applied by the Jorgensen group in their development of PDDG/PM3[10] and also in the case of SCC-DFTB.[20] The electronic energies $E_{\mathrm{el}}^{\mathrm{A}}$ of the atoms have been optimized by fitting against the experimental heats of formation of the PDDG/PM3 training set with 134 reference molecules. The results[20] are collected in Table 1.

It is obvious that the optimized and directly computed electronic energies of the atoms H, C, N, and O differ strongly in SCC-DFTB, by 1−4 eV. The use of the optimized values removes systematic errors from the SCC-DFTB atomization energies, without affecting reaction energies. All subsequent results for SCC-DFTB heats of formation are based on these fitted optimized values.[20]

Table 2 summarizes the statistical evaluations for the standard CHNO test set. Individual data are given in Supporting Information. It is obvious that the mean absolute deviations (MAD) for SCC-DFTB are generally in the same range as those for the other semiempirical methods. An exception are the ionization potentials which are obtained as the negative orbital energy of the highest occupied MO. This relation holds exactly in exact DFT, but it is well-known that the currently available approximate exchange-correlation potentials do not fulfill this relation, mainly because of their long-range asymptotic behavior, and that standard full DFT calculations therefore lead to large deviations (of several eV) − a fate that is shared by SCC-DFTB. Considering the other properties in Table 2, the MADs from SCC-DFTB are highest for heats of formation and dipole moments, and lowest for bond angles and harmonic vibrational wavenumbers (compared with the other methods). The excellent performance of SCC-DFTB for geometries and vibrational frequencies has been noted before.[18−20]

Table 3 presents more detailed statistics for heats of formation. Looking at the subgroups of the standard CHNO set, SCC-DFTB has huge errors for XNO compounds with NO bonds, as pointed out previously.[19,20] On the other hand, the SCC-DFTB errors for CHO compounds are appealingly low. Compared with the standard CHNO set, the MADs are generally higher for our test suites of anions, cations, and radicals. This is true for all methods considered, but particularly so for SCC-DFTB. The high MAD for radicals in SCC-DFTB reflects the inherent trend for overbinding that has been noted above: the radicals are mostly too unstable (on average by 13.7 kcal/mol), consistent with bond dissociation energies that are too large.

Table 4 lists the results for the G2 and G3 test sets[21−23] commonly used in ab initio and DFT work. The MADs of the heats of formation for the ab initio G3 method are of the order of 1 kcal/mol[22] while those for DFT (B3LYP) are around 2−3 kcal/mol for the small molecules of the G2 set[22] and increase for larger molecules, as emphasized previously for the alkane series.[23] The MADs of the semiempirical methods are comparable to those found with our standard CHNO test set (see Tables 2−4). The MADs of SCC-DFTB are relatively high for the G2 CHNO set which contains some molecules with unusual electronic structure, and relatively small for the G3 CHNO set which is mostly comprised of standard mid-size closed-shell molecules. The adiabatic ionization potentials (G2 IPs) and adiabatic electron affinities (G2 EAs) are obtained from differences in the heats of formation of the neutral molecule and the respective ion, and it is therefore not surprising that the corresponding MADs in Table 4 resemble those for cations and anions in Table 3. In the alkane series, SCC-DFTB shares the deficiency of the full DFT treatments that the errors systematically increase with molecular size (but much less so than in B3LYP).

Considering the individual SCC-DFTB data that underly the statistics in Tables 2−4 (see Supporting Information), there are some notable trends, some of which have been pointed out before.[19,20] There are large errors in the computed heats of formation for several small molecules such as H_2 and CO. Three-membered rings are predicted to be too unstable, while compounds with CN triple bonds and particularly with NO bonds are calculated to be too stable (very much so in the latter case). Small carbocations, small anions, and radicals in general tend to be too unstable. While SCC-DFTB reproduces molecular geometries normally very well, there are occasional qualitative shortcomings, e.g., the prediction of planar geometries for cyclobutane (D_{4h}), cyclopentene (C_{2v}), and hydrogen peroxide (C_{2h} trans). The SCC-DFTB dipole moments are very reasonable for hydrocarbons, but usually too small for molecules containing heteroatoms, e.g., for amines and nitriles. For further individual comparisons, the reader is referred to Supporting Information and to the literature, e.g., with regard to reaction energies, isomerization energies, and conformational preferences.[19,20]

Many of the published applications of SCC-DFTB have addressed biological systems, and it is therefore of interest to check its performance in this area, for example with regard to peptide conformers and hydrogen bonding. Table 5 compares the results from AM1, OM2, and SCC-DFTB for our peptide

TABLE 4: Mean Absolute Deviations for Heats of Formation (kcal/mol) (G2 and G3 Sets)[a]

compounds	N^b	G3	B3LYP	MNDO	AM1	PM3	OM1	OM2	OM3	DFTB^c
G2 CHNO	81	0.69	2.35	7.72	7.37	6.77	4.39	3.36	3.82	9.19
G3 CHNO	47	0.94	7.12	7.13	6.27	4.43	4.36	3.15	3.62	4.50
G2 IPs	32	1.13	5.15	12.55	12.22	11.93	10.57	7.13	6.91	9.70
G2 EAs	29	0.97	3.57	15.44	11.80	9.22	13.70	8.60	8.39	12.30
alkanes C1−C16	16	0.49^d	15.44^e	1.81	10.94^e	2.24	1.54	2.03	0.44	5.99^e

[a] Reference data, G3 results, and B3LYP results from references 22 and 23. [b] *N* comparisons. [c] $N = 78$, 26, and 22 in rows 1, 3, and 4, respectively, triplets excluded (see Supporting Information for details). [d] G3 data only up to C_8H_{18}. [e] Error increases with molecular size, e.g., up to 30 kcal/mol for $C_{16}H_{34}$ in B3LYP.

TABLE 5: Mean Absolute Deviations for the Peptide Test Set[a]

	N	AM1	OM2	DFTB
relative energies (kcal/mol)	22	2.0	1.7	1.1
backbone H-bond lengths (Å)	67	0.22	0.34	0.26
backbone dihedral angles (deg)	190	17.0	12.0	9.0

[a] See text. Theoretical reference data, *N* comparisons.

test set.[35] Contrary to the validation sets used up to this point (Tables 2−4), the reference data are not taken from experiment, but from higher-level calculations: geometries generally come from RHF/6-31G* or RHF/6-31G**, relative energies mostly from MP2/6-31G*//RHF or LMP2/cc-pVTZ(-f)//RHF and sometimes from B3LYP/ 6-31G* (see ref 35 for details). The reference systems for geometries (total number in parentheses) comprise N-methylacetamide complexes (3), Ac−Ala−NHMe dipeptides (7), Ac−$(Gly)_2$−NHMe turns (4), Ac−$(Gly)_3$−NHMe turns (5), Ac−$(Ala)_3$−NHMe tetrapeptides (10), and Ac−$(Ala)_n$−NHMe ($n = 2-6$) helix and $C7_{eq}$ conformers (10). All except those in the first and last group also serve as reference systems for relative energies. Inspection of Table 5 shows that SCC-DFTB is superior to AM1 and OM2 with regard to the relative energies of the various conformers and the dihedral angles of the backbone, while the hydrogen bond lengths show rather large deviations for all three methods.

Concerning hydrogen bonding, we have recently assembled a new test set that contains all 57 CHNO complexes from the MMFF94 data base[36] with improved theoretical reference data.[37] Geometries are now taken from B3LYP/aug-cc-pVTZ optimizations. Binding energies come from single-point counterpoise-corrected MP2//B3LYP energies using the aug-cc-pVDZ and aug-cc-pVTZ basis sets and subsequent complete basis set extrapolation [ΔE(MP2/CBS)], with corrections for higher-order correlation effects estimated from single-point CCSD(T) and MP2 calculations with the aug-cc-pVDZ basis [ΔE_{corr}] such that the reference binding energy becomes $\Delta E_0 = \Delta E(\mathrm{MP2/CBS}) + \Delta E_{\mathrm{corr}}$. The MADs from these theoretical reference data for AM1, OM2, and SCC-DFTB amount to 2.8, 1.5, and 2.7 kcal/mol, respectively, for the binding energies of all 57 complexes considered: somewhat to our surprise, SCC-DFTB and AM1 show similar errors whereas OM2 is most accurate. SCC-DFTB performs best for the hydrogen-bond geometries: the MADs for the 148 hydrogen bond lengths are 0.25, 0.20, and 0.08 Å for AM1, OM2, and SCC-DFTB, respectively, while those for 74 hydrogen bond angles are 33.7°, 12.1°, and 6.2°. Moreover, the SCC-DFTB values scatter around the B3LYP reference geometries, while there are systematic errors for AM1 (bond lengths too long by 0.12 Å, angles too small by 32° on average) and also for OM2 (bond lengths too short by 0.14 Å, angles too small by 10° on average).

Our final comments concern electronically excited states. A careful investigation[29] of excited-state surfaces within TDDFT (time-dependent DFT) response theory has shown that standard TDDFT and TD-DFTB share similar limitations with regard to applicability and accuracy (for conjugated organic molecules), and it was concluded that both TDDFT and TD-DFTB should be applied to photochemical problems only with great care, critical issues being long-range charge transfer and polarization as well as the presence of multi-configurational ground states. Subsequently, different methods were compared[38] with regard to their ability to predict absorption shifts for retinal proteins, which led to the recommendation to use SCC-DFTB for ground-state optimizations and molecular dynamics, and the OM2-GUGACI or ab initio SORCI treatments for excitation energies. Recently this approach was used successfully to explain the color tuning in rhodopsins (i.e., the spectral shifts between different rhodopsins due to the enzyme environment).[39]

4. Conclusions

The results from the present evaluations are generally consistent with those obtained in other recent validation studies that have also focused on energetics and geometries.[19,20] In the present work, the performance of SCC-DFTB and NDDO-based semiempirical methods has been compared for commonly used test sets. The overall accuracy of these methods is in the same range, with an overall tendency AM1 < SCC-DFTB < OM2, but any such ranking depends on the properties and compound classes considered. In previous comparisons, the PDDG/PM3 approach was also found to perform well.[20] Like other semiempirical methods, SCC-DFTB has its strengths and weaknesses. It is excellent for geometries and provides reasonable energetics for many types of compounds, especially for biomolecular systems. It seems less suitable for radicals and excited states, and suffers from occasional outliers (e.g., for molecules with NO bonds).

In our opinion, SCC-DFTB is a viable semiempirical method that will be an attractive choice for many applications after proper validation, whereas other semiempirical methods may be more suitable in other cases. We advocate the simple and pragmatic approach of using the most appropriate treatment for a given problem which may involve the synergistic use of different methods: an example is provided by our recent work on electronically excited states of retinal proteins (see section 3), where SCC-DFTB and OM2 were applied for different aspects of the problem.[38,39] In our ongoing QM/MM work on enzymes, we have employed SCC-DFTB as QM component in mechanistic studies of reactions catalyzed by *Bacillus subtilis* lipase A[40] and by 4-oxalocrotonate tautomerase. The results from these studies will be reported elsewhere.[41,42]

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Supporting Information Available: Heats of formation, dipole moments, vibrational wavenumbers, ionization energies and electron affinities for the molecules in the test sets (11

Tables). This material is available free of charge via the Internet at http://pubs.acs.org.

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