

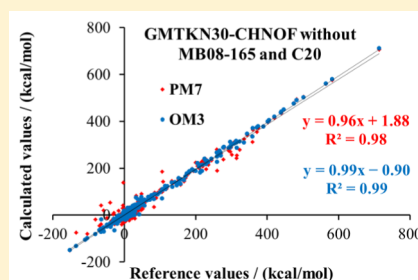
Semiempirical Quantum-Chemical Orthogonalization-Corrected Methods: Benchmarks for Ground-State Properties

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S Supporting Information

ABSTRACT: The semiempirical orthogonalization-corrected OM x methods (OM1, OM2, and OM3) go beyond the standard MNDO model by including additional interactions in the electronic structure calculation. When augmented with empirical dispersion corrections, the resulting OM x -D n approaches offer a fast and robust treatment of noncovalent interactions. Here we evaluate the performance of the OM x and OM x -D n methods for a variety of ground-state properties using a large and diverse collection of benchmark sets from the literature, with a total of 13035 original and derived reference data. Extensive comparisons are made with the results from established semiempirical methods (MNDO, AM1, PM3, PM6, and PM7) that also use the NDDO (neglect of diatomic differential overlap) integral approximation. Statistical evaluations show that the OM x and OM x -D n methods outperform the other methods for most of the benchmark sets.



1. INTRODUCTION

Fast quantum-chemical methods are indispensable for computationally demanding calculations of electronic properties of large molecules. In the 1970s and 1980s, semiempirical quantum-chemical (SQC) methods were the workhorse in computational studies of ground-state properties. Since the 1990s, they have largely been replaced in such studies by *ab initio* and density functional theory (DFT) approaches, which are typically slower by at least 3 orders of magnitude but also generally more accurate and robust.

However, even nowadays, SQC methods often remain the only practical choice when treating huge molecules or very large numbers of molecules or when performing extensive molecular dynamics (MD) simulations, *e.g.*, in the context of quantum mechanics/molecular mechanics (QM/MM) studies on large biomolecular systems.^{1,2} Examples of recent SQC applications include the calculation of electronic properties used in 3D-QSAR models (3D-quantitative structure–activity relationship),³ QM-based computer-aided drug design,^{4–7} the study of band gaps, UV/vis spectra, and charge-transfer processes in systems relevant for molecular nanoelectronics and organic photovoltaics,^{8,9} the investigation of local properties used to understand electron and hole transport mechanisms in transistors,^{10,11} gas-phase MD simulations of electron impact mass spectra,^{12–15} ground-state QM/MM MD simulations of enzymes,^{2,16} excited-state nonadiabatic dynamics simulations of organic chromophores,¹ and studies of organic and enzymatic reactions in solution.^{17–20}

Most of the widely used SQC methods are variants of the MNDO model^{21,22} which is based on the NDDO (neglect of diatomic differential overlap) integral approximation.¹ These MNDO-type methods include AM1,²³ PM3,^{24,25} MNDO/d,^{26–28} AM1*,²⁹ RM1,³⁰ PDDG/MNDO and PDDG/

PM3,^{31,32} PM6,³³ and PM7³⁴ (see the cited references for details and the meaning of the acronyms). A common feature of these approaches is that they attempt to improve the accuracy within the confines of the given electronic structure model, mainly by adding modifications to the core repulsion functions and by performing a more thorough and extensive parametrization. Prime examples of this strategy are the PM x methods (PM3, PM6, and PM7).

An alternative strategy is to improve the underlying model. All MNDO-based methods solve the Hartree–Fock secular equations as if the basis set were orthogonal, without explicitly accounting for the terms arising in the *ab initio* treatment when transforming the Fock matrix from the original nonorthogonal to an orthogonal basis.¹ This neglect of orthogonalization terms gives rise to several qualitative deficiencies of standard SQC methods that cannot always be eliminated simply by parametrization.³⁵ It has been shown that reintroduction of the overlap matrix into the secular equations can indeed significantly improve the accuracy of the MNDO method.³⁶ In the orthogonalization models (OM x) developed in our group, orthogonalization corrections are included into the Fock matrix to different extent (along with other interactions of similar size), which leads to the following general-purpose SQC methods: OM1,^{37,38} OM2,^{39,40} and OM3.⁴¹ The theoretical formalism, the optimized parameters, and the initial validation of the OM x methods are described in detail in a companion Article.⁴²

Both the MNDO-type and OM x methods formally neglect dispersion which causes their poor performance in systems where dispersion interactions play an important role.⁴³ In

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recent years, a number of empirical dispersion corrections have been developed and successfully applied for DFT methods, e.g., the D2 and D3 corrections proposed by Grimme.^{44–46} The same types of dispersion corrections can also be combined with the OMx methods, with no change in the OMx parameters and only minor adjustment of the D2 and D3 parameters.^{42,47,48} The resulting OMx-Dn methods provide a much improved treatment of noncovalent interactions.^{42,47–49} Their formalism, parameters, and initial validation are described in detail in ref 42. Among the MNDO-type methods, the latest variant (PM7) incorporates explicit dispersion corrections in its definition, and unlike in the case of the OMx-Dn methods, its parameters were optimized with these corrections included.³⁴

Given the severe approximations in the formalism of SQC methods and the presence of empirically determined parameters, it is essential to validate these methods carefully against reliable experimental data and/or accurate high-level theoretical results. Some validation studies are available for OMx methods, which cover both ground-state and excited-state properties.^{42,48,50–52} They indicate that the OMx methods outperform other SQC methods in most cases.^{42,50–52} Some of this validation work also offers comparisons between SQC methods and standard DFT approaches showing that the former may approach or sometimes even exceed the accuracy of DFT results for ground-state properties of organic molecules.^{1,8,31,48,52,53}

Considering the extensive recent benchmark exercises for *ab initio* and DFT methods, it is obvious that a more comprehensive validation of the OMx and OMx-Dn methods is required to establish their reliability and to allow for a more detailed assessment of their accuracy compared with other SQC methods. The objective of this Article is to provide such validation for ground-state properties. We cover standard MNDO-type SQC methods (MNDO, AM1, PM3, PM6, and PM7), OMx methods (OM1, OM2, and OM3), and dispersion-corrected OMx-Dn methods (OM2 and OM3 with D2 and D3 corrections as well as D3T corrections with additional three-body terms). The OMx and OMx-Dn methods are fully specified in ref 42.

In addition to our own validation sets, we use benchmark sets mostly taken from the available *ab initio* and DFT literature. We include from these sets only those reference molecules that contain the elements H, C, N, O and/or F, for the simple reason that the OMx methods have up to now only been parametrized for these elements. We address the following ground-state properties: heats of formation, bond lengths, bond angles, dihedral angles, relative energies, reaction energies, dissociation energies, atomization energies, proton affinities, activation barriers, vertical and adiabatic ionization potentials (IPs), adiabatic electron affinities (EAs), dipole moments, noncovalent interaction energies, and geometries of noncovalent complexes. Overall, the benchmarks contain 13035 original or derived reference data. The results from the benchmarking will help to establish the accuracy of different SQC methods in different areas and can also serve as a guide for choosing the most appropriate SQC method in specific application projects.

2. METHODS AND COMPUTATIONAL DETAILS

All MNDO, AM1, PM3, OMx, and OMx-Dn calculations were carried out with our locally modified MNDO2005 program.⁵⁴ The PM6, PM7, and RM1 calculations were done with the

MOPAC2012 program.^{55,56} Molecules were visualized with Chemcraft 1.7.⁵⁷

Standard conventions were used in all calculations.⁴² For the sake of documentation, we specify some of these standard options here. The convergence criterion for the SCF energy was set to 10^{-9} eV; in addition, the diagonal elements of the density matrix were required to be converged to 10^{-9} in MNDO2005. Doublet and triplet states were treated with the restricted open-shell half-electron approach,⁵⁸ and higher spin states were described using unrestricted Hartree–Fock (UHF) calculations. We did not use molecular mechanics corrections for peptides in PM6 or PM7, and we did not apply any cutoffs for the three-center orthogonalization corrections in the OMx and OMx-Dn methods.

Geometry optimizations were considered converged when the gradient norm became smaller than 0.01 kcal/(mol·Å). In MNDO2005 the BFGS optimization algorithm was used by default; in difficult cases, we also applied eigenvector following, with the Hessian being computed numerically by one-sided finite differences of the gradient (at the first step and every 10 following steps) and with a minimum trust radius of 0.00001. In MOPAC the eigenvector following algorithm was used throughout; in most cases the full Hessian matrix was constructed and recalculated every 10 steps using numerical single-sided derivatives of the gradient. Frequently MOPAC stopped when the heat of formation remained essentially constant in subsequent cycles; in these cases the gradient norm was usually smaller than 0.1 kcal/(mol·Å).

It is well-known that SQC methods generally predict the heat of formation of the proton with very large errors.⁵² Therefore, in line with common semiempirical practice,⁵⁹ we used the experimental value of 367.171 kcal/mol⁶⁰ for the heat of formation of the proton at 298 K to calculate the proton affinities included in the GMTKN30-CHNOF and CE345-CHNOF databases (see later text).

The reference molecules in the various benchmark sets are generally still quite small by semiempirical standards. Therefore, they were computed using single-CPU serial versions of the MNDO2005 and MOPAC programs. For large-scale applications, parallel versions of MNDO2005 are available using shared-memory and distributed-memory message-passing parallelization,^{61,62} as well as a hybrid version using graphics processing units (GPUs).⁶³ Similarly, there are shared-memory and GPU-parallelized versions of MOPAC.^{55,56} To illustrate the scope of SQC calculations, we note that the hybrid GPU version of MNDO2005 has been used to compute water clusters of up to 5400 atoms and to optimize the geometries of a large series of representative proteins.^{63,64}

Calculations with D3 and D3T dispersion corrections were done using our interface of the MNDO2005 program to the DFT–D3 stand-alone program by Grimme (versions 3.0 Rev 2 and 3.1 Rev 0).⁶⁵ Default cutoffs (95 au for two-body terms and 40 au for coordination numbers) were used with version 3.0 and increased cutoffs (95 au for two-body terms, coordination numbers, and three-body terms) with version 3.1.

3. DATA SETS

In this section we define the benchmark sets used presently to evaluate different SQC methods. We divide these sets into two groups: those designed to benchmark ground-state properties in general (OVS7-CHNOF, G2G3-CHNOF, W4-11-CHNOF, GMTKN30-CHNOF, CE345-CHNOF, PDDG, PM7-CHNOF, and C7H10O2) and those specifically designed to

Table 1. Data Sets Used for Benchmarking General Ground-State Properties^a

data set	N	description	ref values	ref
OV57-CHNOF	1131	our own compilation of 7 validation sets	expt and theor	
radicals71	71	heats of formation, relative energies and ionization potentials of radicals	expt and theor	66
anions24	24	heats of formation of nonradical organic and inorganic anions	expt	37
cations41	41	heats of formation and relative energies of organic and inorganic cations	expt and theor	37
BIGMOL20	20	heats of formation of relatively large organic molecules	expt	37, 67
conformers30	30	heats of formation and barriers of different organic conformers	expt and theor	39
isomers44	44	heats of formation and relative energies of isomers of organic compounds	expt	39
fluorine91	91	properties of 91 fluorine-containing compounds	theor	68
	455	heats of formation	G3	
	355	bond lengths	MP2/6-31G(d)	
		bond angles	MP2/6-31G(d)	
G2G3-CHNOF	173			
G2	93	heats of formation of small molecules from the G2 set	expt	69
G3	52	heats of formation of midsize molecules from the G3 set	expt	70
alkanes28	28	heats of formation and relative energies of alkanes C1–C16	expt	41, 71
W4-11-CHNOF	593	high-confidence benchmark data set for computational thermochemistry	W4 or higher	72
TAE140	88	atomization energies	W4	72
TAE_nonMR124	43	TAE140 without multireference cases	W4	72
BDE99	79	bond dissociation reaction energies	W4	72
HAT707	394	heavy-atom transfer energies	W4	72
ISOMER20	19	isomerization energies	W4	72
SN13	13	"nucleophilic substitution" energies	W4	72
GMTKN30-CHNOF	480	general main group thermochemistry, kinetics, and noncovalent interactions	back-corr expt and theor ^b	73
MB08-165	25	decomposition energies of artificial molecules	est CCSD(T)/CBS	74
W4-08	50	atomization energies of small molecules	W4	75
W4-08woMR	43	W4-08 without multireference cases	W4	75
G21IP	15	adiabatic ionization potentials	expt	76
G21EA	12	adiabatic electron affinities	expt	76
PA	8	adiabatic proton affinities	est CCSD(T)/CBS and W1	77, 78
SIE11	5	self-interaction error related problems	est CCSD(T)/CBS	79
BHPERI	22	barrier heights of pericyclic reactions	W1 and CBS-QB3	75, 80–83
BH76	54	barrier heights of hydrogen and heavy-atom transfers, nucleophilic substitution, unimolecular, and association reactions	W1 and theor est	84, 85
BH76RC	22	reaction energies of the BH76 set	W1 and theor est	84, 85
RSE43	34	radical stabilization energies	est CCSD(T)/CBS	86
O3ADD6	6	reaction and association energies and barrier heights for addition of O ₃ to C ₂ H ₄ and C ₂ H ₂	est CCSD(T)/CBS	87
G2RC	15	reaction energies of selected G2/97 systems	expt	69
ISO34	34	isomerization energies of small and medium-sized organic molecules	expt	88
ISOL22	18	isomerization energies of large organic molecules	SCS-MP3/CBS	89
DC9	7	nine difficult cases for DFT	expt and theor	79, 82, 90–95
DARC	14	reaction energies of Diels–Alder reactions	est CCSDT/CBS	96
BSR36	36	bond separation reactions of saturated hydrocarbons	est CCSD(T)/CBS	97
IDISP	6	intramolecular dispersion interactions	expt and theor	88, 98, 99

Table 1. continued

data set	N	description	ref values	ref
WATER27	27	binding energies of water, $H^+(H_2O)_n$ and $OH^-(H_2O)_n$ clusters	est CCSD(T)/CBS; MP2/CBS	100
S22	22	binding energies of noncovalently bound dimers	est CCSD(T)/CBS	101, 102
ADIM6	6	interaction energies of <i>n</i> -alkane dimers	est CCSD(T)/CBS	97, 103
PCONF	10	relative energies of phenylalanyl-glycyl-glycine tripeptide conformers	est CCSD(T)/CBS	104
ACONF	15	relative energies of alkane conformers	W1h-val	105
SCONF	17	relative energies of sugar conformers	est CCSD(T)/CBS	79, 106
CE345-CHNOF	187	chemistry energetic database with 345 data	back-corr expt and theor ^b	107, 108
MGAEl09/11	74	main group atomization energies	expt, W4, W4.2, W4.3, W4.4	109, 110
IsoL6/11	6	isomerization energies of large molecules	CCSD(T)-F12a/aug-cc-pVDZ	111
IP21	4	adiabatic ionization potentials	expt	109, 112–116
EAl3/03	4	adiabatic electron affinities	expt	109, 112–114
PA8/06	4	proton affinities	expt	78
ABDE12	12	alkyl bond dissociation energies	expt	109, 117–119
HC7/11	7	hydrocarbon chemistry	expt and theor	119
π TC13	13	thermochemistry of π systems	expt, CCSD(T)/cc-pVTZ, est CCSD(T)/CBS	78, 112, 117
HTBH38/08	26	hydrogen transfer barrier heights	expt and theor	85, 109, 120, 121
NHTBH38/08	23	non-hydrogen transfer barrier heights	Wn ($n = 1, 4$) ^c	85, 109, 120, 121
NCCF31/05	14	noncovalent complexation energies	W1, est CCSD(T)/CBS	113, 122
PDDG	979	set used for training and validating PDDG/MINDO and PDDG/PM3	expt	31
	622	heats of formation		
	153	bond lengths		
	54	bond angles		
	6	dihedral angles		
	97	ionization potentials		
	47	dipole moments		
PM7-CHNOF	1595	set used for training and validating PM7	expt and theor	34
	1168	heats of formation		
	175	bond lengths		
	90	bond angles		
	104	ionization potentials		
	58	dipole moments		
C7H10O2	6095	atomization enthalpies at 298 K of 6095 isomeric $C_7H_{10}O_2$ molecules	G4MP2	123

^aSubsets are indented. Descriptions are taken from the cited literature. ^bData in these databases were normally corrected to represent total energies without any zero-point vibrational energies and thermal corrections; this is also true for the “expt” and “theor” values given for the subsets; “theor” usually means “best theoretical estimate”. ^cMost of the data in this subset.

Table 2. Data Sets Used for Benchmarking Noncovalent Interactions^a

data set	N	description	ref values	ref
A24-CHNOF	21	very accurate interaction energies of small noncovalent complexes	est CCSDT(Q)/CBS + relativistic corrections	124
	23	selected interatomic distances ^b	est CCSD(T)/CBS	
	40	selected angles ^b	est CCSD(T)/CBS	
S66	66	interaction energies of 66 noncovalent complexes	CCSD(T)/CBS	125, 126
	172	selected interatomic distances ^b	MP2/cc-pVTZ + est CCSD(T)/CBS ^c	
	141	selected angles ^b	MP2/cc-pVTZ + est CCSD(T)/CBS ^c	
S66a8	528	sampling angular degrees of freedom in the S66 complexes	est CCSD(T)/CBS	126
JSCH-2005-CHNOF	134	interaction energies of base and amino acids pairs	CCSD(T) or MP2 with est CBS	101
S7L	7	energies of σ - σ and π - π interactions of 7 large complexes	est CCSD(T)/CBS	127
	28	selected interatomic distances ^b	B3LYP + CCSD(T)/ha-cc-pVDZ ^d	
S30L-CHNOF	24	interaction energies of very large complexes	back-corr expt	49
AF6	6	folding energies of alkanes	CCSD(T)/CBS, CCSD+FNO(T)/cc-pVTZ	128
	6	folding enthalpies at 298 K	CCSD+FNO(T)/cc-pVTZ+ZPE(MP2/cc-pVTZ)+temp.dep.shifts	
	27	selected interatomic distances ^b	MP2/cc-pVTZ	
	74	selected angles ^b	MP2/cc-pVTZ	

^aDescriptions are taken from the cited literature. ^bThis work; based on geometries from the cited references. ^cIntermolecular distances were obtained from MP2/cc-pVTZ geometries by interpolating estimated CCSD(T)/CBS energies along dissociation curves.¹²⁵ ^dReference geometries were obtained by optimizing intermolecular distances at the CCSD(T)/ha-cc-pVDZ level using monomer geometries optimized at the B3LYP level with large basis sets.¹²⁷

benchmark noncovalent interactions (A24-CHNOF, S66, S66a8, JSCH-2005-CHNOF, S7L, S30L-CHNOF, and AF6). We note that this division is somewhat arbitrary as some reference molecules and complexes from the first group also feature noncovalent interactions and may thus appear again in the second group.

All data sets and subsets from the first and second groups are listed in Tables 1 and 2, respectively. Most of them are taken from the literature and described in the same terms as in the published work. Included are all molecules from the original data sets that contain only the elements C, H, N, O, and/or F, for which OM x parameters are available;⁴² all other molecules are ignored.

Detailed numerical results on all individual reference molecules from all benchmark sets are compiled in the Supporting Information (SI) which also cites the origin of the published reference data. In the following two sections, we will focus on statistical evaluations of these results for all sets and subsets (with more than two molecules).

Following semiempirical tradition, all SQC methods tested presently were parametrized with regard to heats of formation. Their performance can thus be evaluated in a straightforward manner when reliable reference data for heats of formation are available either from experiment or from high-level *ab initio* calculations. This is the case for the CHNO and FLUOR data sets used during the parametrization of the OM x methods⁴² and for the OVS7-CHNOF, G2G3-CHNOF, PDDG, and PM7-CHNOF sets used in the present benchmarking. The corresponding reference data are mostly taken from experiment. Performance evaluation of atomization enthalpies at 298 K is also straightforward for the C7H10O2 set as reference values can be easily obtained from the reference *ab initio* enthalpies at 298 K.

Most of the entries in the other databases of Tables 1 and 2 represent relative energies, for example isomerization energies, interaction energies, binding energies, reaction energies, barrier heights, proton affinities, ionization potentials, and electron

affinities. The corresponding *ab initio* reference data are generally obtained from energy differences, whereas the respective semiempirical values are differences of heats of formation (i.e., enthalpies at 298 K) that implicitly include zero-point vibrational energies (ZPVEs) and thermal enthalpic corrections (from 0 to 298 K). These corrections are normally quite similar for related molecules since they tend to be bond-specific and transferable,¹²⁹ and hence they will cancel to a large extent when comparing related systems. As in many semiempirical studies over the past decades, we will thus mostly ignore the distinction between relative energies and heats of formation in the following, and consider the semiempirical values to be directly comparable with *ab initio* relative energies.

This line of reasoning obviously breaks down when it comes to atomization energies, because there is no longer any cancellation. For a realistic comparison between *ab initio* and semiempirical atomization energies, the ZPVEs and thermal enthalpic corrections have to be taken into account explicitly. This is computationally demanding at an accurate *ab initio* level,¹³⁰ and therefore we computed both these corrections at the SQC level using the harmonic-oscillator and rigid-rotor approximations. To illustrate the necessity of including these corrections, we compare the OM2 results for propane with experimental and *ab initio* W4 reference data:⁷⁵ the experimental heat of formation at 298 K (−25.0 kcal/mol) is well-reproduced by a straight OM2 calculation (−24.4 kcal/mol at the *ab initio* reference geometry), whereas the W4 atomization energy (1007.9 kcal/mol) is well-reproduced by OM2 (1005.6 kcal/mol) only after applying the corrections described previously, which are far from negligible (51.8 kcal/mol). The distinction between relative energies and heats of formation is also relevant for the reaction energies in other fragmentations, e.g., bond dissociation reactions: while the corresponding ZPVE and thermal enthalpic corrections are much smaller than for atomization energies, they are still non-negligible.

Table 3. Mean Absolute Errors in Calculated Heats of Formation (kcal/mol), Relative Energies (kcal/mol), Ionization Potentials (eV), Barriers (kcal/mol), Bond Lengths (Å), and Bond Angles (deg) for the OVS7-CHNOF Benchmark Set: MNDO, AM1, PM x , and OM x

subset	N	method							
		MNDO	AM1	PM3	PM6	PM7	OM1	OM2	OM3
Heats of Formation									
radicals71	42	11.86	10.60	10.94	11.13	10.04	7.28	4.98	5.57
anions24	24	14.41	11.29	9.59	11.43	10.65	11.55	8.37	9.56
cations41	36	11.52	9.96	11.45	11.12	12.07	9.32	6.93	6.89
BIGMOL20	20	9.20	12.11	8.25	9.43	8.57	10.45	4.85	5.05
conformers30	11	3.14	6.48	2.72	3.40	2.40	1.83	2.95	3.05
isomers44	27	6.41	4.40	2.92	2.92	2.05	3.32	1.05	1.81
fluorine91	91	11.13	11.05	7.76	9.04	8.17	7.17	7.15	7.34
Relative Energies									
radicals71	4	13.00	10.09	9.94	11.78	10.61	8.74	3.95	5.46
cations41	5	13.20	9.30	9.02	20.97	10.96	5.65	3.68	3.53
isomers44	17	8.04	5.59	3.22	1.81	1.70	5.67	0.80	2.07
Ionization Potentials									
radicals71	25	0.88	0.73	0.84	0.79	0.80	0.38	0.37	0.53
Barriers									
conformers30	19	2.38	2.00	2.17	2.65	2.46	1.50	1.26	1.34
Bond Lengths									
fluorine91	455	0.027	0.022	0.015	0.017	0.021	0.015	0.016	0.022
Bond Angles									
fluorine91	355	3.41	3.28	2.94	3.68	3.17	1.97	2.04	1.78

Table 4. Mean Absolute Errors in Calculated Heats of Formation (kcal/mol) and Relative Energies (kcal/mol) for the G2G3-CHNOF Benchmark Set: MNDO, AM1, PM x , and OM x

subset	N	method							
		MNDO	AM1	PM3	PM6	PM7	OM1	OM2	OM3
Heats of Formation									
G2	93	7.71	7.44	6.86	5.69	5.14	4.64	3.37	3.83
G3	52	7.51	6.73	5.01	3.86	3.40	4.25	3.18	3.71
alkanes28	22	3.26	8.81	2.03	4.20	1.76	2.16	1.91	0.72
Relative Energies									
alkanes28	6	6.16	4.35	1.76	1.05	1.51	4.68	0.61	1.48

In the next section, we will apply these SQC corrections to all benchmarks for atomization energies (especially W4-11-CHNOF). We will also investigate their effect on the reaction energies covered by the four subsets of the W4-11-CHNOF set and by those subsets of the GMTKN30-CHNOF and CE345-CHNOF sets that address fragmentation reactions. The SQC corrections are combined with single-point SQC results obtained at the *ab initio* reference geometries. The conversion of semiempirical heats of formation at 298 K to ZPVE-exclusive relative energies at 0 K is described in detail in the [Supporting Information](#).

4. GENERAL BENCHMARK OF GROUND-STATE PROPERTIES

The OM x methods have been parametrized using the relatively small CHNO and FLUOR training sets (140 and 48 molecules, respectively).⁴² For these sets, the OM x results are generally found to be superior to the results from other SQC methods, as documented in detail in a companion Article.⁴² These data are not presented here again.

4.1. OVS7-CHNOF. Various OM x parametrization runs starting from different initial values were often found to produce different parameter sets that gave results of similar quality for the molecules in the training set; therefore we

performed further tests on several validation sets to help identify the most suitable parameters.⁴² The main validation sets are collected in the OVS7-CHNOF benchmark which consists of seven subsets. Detailed numerical results are given in the [SI](#) (Tables S9–S14), while statistical evaluations in terms of mean absolute errors (MAEs) are provided in [Table 3](#).

With regard to heats of formation, OM2 and OM3 outperform all other SQC methods for six of the seven subsets, namely, radicals71,⁶⁶ anions24,³⁷ cations41,³⁷ BIGMOL20,^{37,67} isomers44,³⁹ and fluorine91;⁶⁸ the corresponding MAEs for OM2 and OM3 are 5.0–5.6, 8.4–9.6, ca. 6.9, ca. 5.0, 1.1–1.8, and 7.2–7.3 kcal/mol, respectively. In the conformers30³⁹ subset, OM1 gives the lowest MAE (1.8 kcal/mol) followed by PM7 (2.4 kcal/mol) and OM2 and OM3 (ca. 3.0 kcal/mol). Considering relative energies, OM2 and OM3 again outperform all other SQC methods in the case of the radicals71 and cations41 subsets, and they also give very good results for the isomers44 subset (MAEs of 0.8–2.1 kcal/mol).

Ionization potentials for the radicals71 subset (from Koopmans' theorem) are best predicted by the three OM x methods, with MAEs of 0.4–0.5 eV. This is also true for the barriers in the conformers30 subset, for which the MAEs for the OM x methods range between 1.3 and 1.5 kcal/mol. In the fluorine91 subset, bond lengths are well-described by OM1,

Table 5. Mean Absolute Errors in Calculated Atomization and Reaction Energies (kcal/mol) for the W4-11-CHNOF Benchmark Set: MNDO, AM1, PM x , and OM x ^a

subset	N	method							
		MNDO	AM1	PM3	PM6	PM7	OM1	OM2	OM3
TAE140 (corr)	88	11.90	9.09	8.00	7.73	6.51	7.02	4.81	6.47
TAE_nonMR124 (corr)	80	9.45	8.26	7.28	7.73	6.75	6.25	4.84	6.05
BDE99	79	17.24	12.75	13.77	12.19	10.01	10.54	8.15	9.65
BDE99 (corr)	79	14.91	10.86	12.22	10.56	8.26	8.28	6.25	7.51
HAT707	394	20.85	16.50	12.72	13.96	11.64	10.55	8.92	9.44
HAT707 (corr)	394	21.08	16.70	12.74	13.89	11.52	10.83	9.17	9.73
ISOMER20	19	8.65	7.65	7.68	9.37	8.48	8.67	8.54	8.32
ISOMER20 (corr)	19	8.90	7.77	8.09	9.23	8.33	8.47	8.34	8.13
SN13	13	8.23	7.70	4.98	5.43	3.14	4.02	5.55	4.31
SN13 (corr)	13	7.30	6.01	4.05	4.39	3.59	5.14	5.36	4.98

^a(corr) means that energies are obtained by removing ZPVE and thermal corrections from the SQC results (see text).

OM2, PM3, and PM6, while bond angles are best reproduced by the OM x methods.

Finally, we note that the inclusion of dispersion corrections must deteriorate the accuracy of the OM x methods for heats of formation, because the OM x parameters were optimized without such corrections. Since dispersion effects are always attractive, their subsequent introduction will systematically lower the computed heats of formation and thus increase their errors compared with experiment. On the other hand, dispersion corrections have no or very little effect on ionization potentials and barriers; they improve the relative energies for the isomers44 subset while leaving those for the radicals71 and cations41 subsets almost unaffected (for further details see the SI Table S1).

4.2. G2G3-CHNOF. The G2⁶⁹ and G3⁷⁰ sets provide well-established accurate reference data that have often been used to validate the performance of *ab initio* and DFT methods. They have been published after the development of OM1 and OM2. In previous work⁵⁰ we have reported an evaluation of the OM x methods for the G2 and G3 sets, and we can thus be brief. The statistical results are summarized in Table 4 (for detailed numerical results, see SI Tables S16–S18). Overall, OM2 and OM3 perform best closely followed by PM7. OM2 yields the lowest MAEs for the heats of formations in G2 and G3 (3.2–3.4 kcal/mol) and for the relative energies in the alkanes28 subset^{41,71} of the G3 set (0.6 kcal/mol), while OM3 gives the lowest MAE for the heats of formations in alkanes28 (0.7 kcal/mol).

As pointed out before,⁵⁰ the performance of OM2 and OM3 for the G2 and G3 sets is respectable, even when compared with standard DFT approaches, and there is no systematic error for alkane chains of increasing length that plagues some standard DFT functionals (including B3LYP).

Again, as in the OVS7-CHNOF set and for the same reasons, dispersion corrections deteriorate the accuracy of the OM x methods for heats of formation in the G2G3-CHNOF set, while improving relative energies (SI Table S2).

4.3. W4-11-CHNOF. The W4-11 benchmark set⁷² includes the W4-08 subset of the GMTKN30 set (see later discussion) and, in addition, contains numerous further atomization energies (collected in the extended subset TAE140) as well as four other subsets with reaction energies (BDE99, HAT707, ISOMER20, and SN13; see Table 1). We reduced the W4-11 to the W4-11-CHNOF data set in the usual manner, by eliminating entries for species containing elements other than H, C, N, O, and F. The SQC results from single-point

calculations at the reference geometries are compared with the reference data obtained from *ab initio* total energies without zero-point vibrational corrections. For reasons discussed above, we converted the semiempirical heats of formation to atomization energies at 0 K by applying ZPVE and thermal enthalpic corrections. We also compared the results for the reaction energies in the subsets calculated with and without such corrections (see Table 5 for the statistical evaluation).

The atomization energies in the TAE140 subset are computed with errors somewhat larger than typical errors for heats of formation. These errors are of similar magnitude in the OM x and PM7 methods (MAEs of 4.81–7.02 kcal/mol, OM2 lowest). The MAEs remain roughly of similar size when multireference cases are excluded (TAE_nonMR124, MAEs of 4.84–6.75 kcal/mol, OM2 lowest).

Errors in the corrected and uncorrected reaction energies for heavy-atom transfer (HAT707 subset), for isomerization (ISOMER20 subset), and for transformations in the SN13 subset are very close to each other, without any systematic improvement due to the corrections. This provides further justification for the usual practice of directly comparing the semiempirical SCF energies with *ab initio* relative energies in such cases. Thus, we will discuss for these sets and similar benchmark sets of this kind only the noncorrected reaction energies calculated from the semiempirical SCF energies.

On the other hand, removing the ZPVE and thermal corrections from the semiempirical SCF energies systematically improves the computed bond dissociation energies (BDE99 subset, MAE lowered by ca. 2 kcal/mol). This indicates that these corrections are generally relevant for fragmentation reactions, and hence we will discuss them for such transformations in the following.

The reference energies for bond dissociation and heavy-atom transfer are best reproduced by OM2 (MAEs of 6.25 and 8.92 kcal/mol) followed by OM3 (MAEs of 7.51 and 9.44 kcal/mol). Isomerization energies are computed reasonably well by all SQC methods considered (MAEs of 7.65–9.37 kcal/mol, AM1 lowest). The reaction energies in the SN13 subset are also well-reproduced, particularly by PM7, OM1, and OM3 (MAEs of 3.14, 4.02, and 4.31 kcal/mol, respectively).

The largest outliers in the computed atomization energies are found for C₂ (OM1), isocyanic acid HNCO (OM2), HNNN (OM3), and H₂ and N₂ (PM7), with errors ranging from 21 to 35 kcal/mol.

Dispersion corrections have only very little effect on any of the statistical results reported presently (see SI Table S19).

Table 6. Mean Absolute Errors (kcal/mol) for the GMTKN30-CHNOF Benchmark Set: MNDO, AM1, PM_x, and OM_x^a

no.	subset	N	method							
			MNDO	AM1	PM3	PM6	PM7	OM1	OM2	OM3
	overall	480	27.48	16.45	14.44	16.29	16.49	11.93	7.94	7.17
	overall ^{*b}	454	27.34	14.65	11.26	10.17	9.60	11.29	6.95	6.30
1	MB08-165	25	25.53	43.66	68.73	124.39	138.35	19.47	22.47	19.46
1	MB08-165 (corr) ^c	25	26.52	31.84	52.27	119.53	134.55	11.04	12.20	15.03
2	W4-08 (corr)	50	14.11	10.24	9.33	7.95	6.53	7.58	4.19	6.20
2a	W4-08woMR ^d (corr)	43	10.32	8.90	7.66	8.00	6.51	6.00	4.12	5.37
3	G21IP	15	24.75	28.12	20.41	35.74	32.29	22.45	12.00	11.45
4	G21EA	12	27.44	25.84	14.23	20.08	18.94	24.81	11.39	9.31
5	PA	8	12.48	12.87	16.12	18.45	21.46	4.96	14.82	11.99
6	SIE11	5	21.22	9.49	12.00	4.03	4.82	4.39	7.78	4.31
7	BHPERI	22	25.15	9.97	14.05	9.73	6.13	10.67	8.21	8.25
8	BH76	54	23.84	13.06	13.36	13.39	13.68	10.39	9.72	10.66
9	BH76RC	22	11.88	13.49	11.57	15.72	16.28	5.28	4.29	5.37
10	RSE43	34	5.00	3.55	4.02	6.10	5.83	3.74	4.31	5.24
11	O3ADD6 ^e	6	14.90	10.57	9.87	2.03	26.84	4.01	12.24	10.97
12	G2RC	15	9.23	13.42	21.68	29.47	33.48	9.07	8.23	4.16
13	ISO34	34	7.44	6.45	4.04	3.46	2.92	4.45	4.44	4.37
14	ISOL22	18	16.76	10.25	8.27	7.41	6.55	7.99	5.31	6.05
15	DC9	7	41.46	35.75	25.99	17.39	21.94	26.38	25.02	24.69
15a	DC9woC20 ^f	6	24.66	15.68	13.30	5.18	8.64	11.40	13.59	13.20
15b	C20 ^g	1	142.25	156.16	102.09	90.66	101.72	116.24	93.63	93.61
16	DARC	14	13.10	4.65	5.32	3.91	4.26	4.10	7.24	4.91
17	BSR36	36	52.36	39.56	16.66	7.38	9.63	30.29	10.77	3.46
17	BSR36 (corr) ^h	36	56.86	44.24	18.53	14.33	17.40	35.01	7.08	1.90
18	IDISP	6	34.58	13.52	8.58	13.78	16.82	13.69	7.34	6.19
19	WATER27	27	165.05	48.62	31.61	17.81	5.78	36.09	12.28	9.19
19	WATER27 (upd) ⁱ	27	164.26	47.83	30.82	17.02	6.51	35.30	11.49	8.40
20	S22	22	16.74	6.78	5.91	3.37	0.76	5.10	3.05	3.54
21	ADIM6	6	11.37	3.14	0.48	2.78	0.22	4.30	3.13	4.09
22	PCONF	10	10.08	5.35	3.68	2.27	2.97	3.60	1.28	1.33
23	ACONF	15	1.97	0.44	0.44	0.56	0.56	0.52	0.64	0.86
24	SCONF	17	17.52	2.39	3.05	2.61	2.38	5.87	1.67	1.32

^a(corr) means that energies are obtained by removing ZPVE and thermal corrections from the SQC results (see text). ^bWithout MB08-165 and C20. ^cUpon geometry optimization, some of the artificial molecules adopted structures very different from the reference geometries so that the computed corrections may be less accurate in these cases (see text). ^dSubset W4-08 without multireference cases. ^eThe adduct O₃ + C₂H₂ is better described as an open-shell singlet at OM_x-D_n. ^fSubset DC9 without C₂₀ bowl/cage isomerization energy. ^gC₂₀ bowl/cage isomerization energy. ^hFor some SQC methods the corrections suffer from large accumulation errors (see text). ⁱReference dissociation energies of four (H₂O)₂₀ clusters were updated with more accurate values from ref 132 (see text).

4.4. GMTKN30-CHNOF. The Grimme group published comprehensive collections of validation sets for general main group thermochemistry, kinetics, and noncovalent interactions,^{73,79,131} to allow for a thorough assessment of the performance of various DFT methods. In previous work,⁵² we extracted from the initial GMTKN24 database⁷⁹ all species containing only the elements H, C, N, and O. For the resulting GMTKN24-hcno database, we performed calculations using the AM1, PM6, OM1, OM2, OM3, SCC-DFTB, B3LYP, and PBE methods and their dispersion-corrected counterparts to compare their accuracy in a comprehensive manner.⁵²

Here we update our previous evaluation of SQC methods by starting from the more recent GMTKN30 database^{73,131} and extracting all species containing only the elements H, C, N, O, and F. The resulting GMTKN30-CHNOF database differs from the previous GMTKN24-hcno variant in the following aspects. (a) It incorporates fluorine-containing compounds. (b) It includes three new subsets ISOL22, BSR36, and ADIM6 from GMTKN30; the other three new subsets in GMTKN30 contain elements other than H, C, N, O, and F and are

therefore disregarded. (c) It also includes the full W4-08 subset⁷⁵ with multireference (MR) cases, in addition to the previously used W4-08woMR subset⁷⁵ without MR cases. (d) It utilizes updated, more accurate reference data from the GMTKN30 database whenever available (in subsets IDISP, S22, BHPERI, and PA). Specifically, the GMTKN30 reference data for the BHPERI subset^{75,80–83} are now based on W1 rather than CBS-QB3 calculations;⁷⁵ the latter had been employed in GMTKN24-hcno for some reaction barriers. The GMTKN30 reference values for the proton affinities of small molecules in the PA set are now taken from vibrationally back-corrected W1 data⁷⁷ rather than from “best estimates” from vibrationally back-corrected experimental values⁷⁸ in GMTKN24-hcno.

Overall, the GMTKN30-CHNOF database consists of 24 subsets with 480 reference data that are determined from 806 single-point calculations at the reference geometries.^{73,131} Six subsets from the full GMTKN30 database are missing (AL2X, NBPRC, ALK6, RG6, HEAVY28, and CYCONF), because they

Table 7. Mean Absolute Errors (kcal/mol) for the GMTKN30-CHNOF Benchmark Set: OM x -D n Results^a

no.	subset	N	method					
			OM2			OM3		
			D2	D3	D3T	D2	D3	D3T
	overall	480	7.91	7.76	7.76	7.21	7.26	7.24
	overall ^{*b}	454	6.94	6.77	6.77	6.36	6.37	6.35
1	MB08-165	25	22.31	22.35	22.36	19.51	20.11	20.11
1	MB08-165 (corr) ^c	25	11.53	11.50	11.51	15.44	15.72	15.72
2	W4-08 (corr)	50	4.40	4.41	4.41	6.17	6.26	6.26
2a	W4-08woMR ^d (corr)	43	4.39	4.41	4.41	5.34	5.51	5.51
3	G21IP	15	12.00	12.00	12.00	11.46	11.45	11.45
4	G21EA	12	11.40	11.39	11.39	9.33	9.31	9.31
5	PA	8	14.90	14.88	14.88	11.77	11.69	11.69
6	SIE11	5	8.20	8.07	8.07	4.52	4.70	4.70
7	BHPERI	22	6.42	6.68	6.69	6.98	6.76	6.78
8	BH76	54	9.69	9.71	9.71	10.83	10.93	10.93
9	BH76RC	22	4.22	4.22	4.22	5.43	5.48	5.48
10	RSE43	34	4.16	4.24	4.24	5.03	5.12	5.12
11	O3ADD6 ^e	6	12.70	12.61	12.61	11.12	11.39	11.38
12	G2RC	15	7.71	7.75	7.75	3.73	3.62	3.62
13	ISO34	34	4.59	4.55	4.55	4.47	4.49	4.48
14	ISOL22	18	5.04	4.96	4.95	6.28	6.23	6.17
15	DC9	7	25.25	24.98	24.93	22.64	23.27	23.30
15a	DC9woC20 ^f	6	14.97	14.00	13.94	11.87	12.32	12.36
15b	C20 ^g	1	86.93	90.92	90.89	87.27	88.96	88.94
16	DARC	14	10.34	9.42	9.38	7.88	9.08	9.03
17	BSR36	36	15.37	14.08	13.99	7.86	7.14	7.05
17	BSR36 (corr) ^h	36	11.71	10.37	10.28	4.35	3.48	3.40
18	IDISP	6	10.85	9.97	9.86	7.63	8.11	8.00
19	WATER27	27	7.36	6.99	7.13	6.65	6.84	6.81
19	WATER27 (upd) ⁱ	27	6.57	6.20	6.34	6.42	7.52	7.38
20	S22	22	1.14	0.91	0.94	1.21	0.97	0.95
21	ADIM6	6	0.45	0.11	0.09	0.69	0.26	0.39
22	PCONF	10	0.94	1.11	1.02	1.25	1.54	1.39
23	ACONF	15	0.19	0.20	0.22	0.29	0.30	0.31
24	SCONF	17	1.57	1.63	1.62	1.35	1.35	1.34

^a(corr) means that energies are obtained by removing ZPVE and thermal corrections from the SQC results (see text). ^bWithout MB08-165 and C20. ^cUpon geometry optimization, some of the artificial molecules adopted structures very different from the reference geometries so that the computed corrections may be less accurate in these cases (see text). ^dSubset W4-08 without multireference cases. ^eThe adduct O₃ + C₂H₂ is better described as an open-shell singlet at OM x -D n . ^fSubset DC9 without C₂₀ bowl/cage isomerization energy. ^gC₂₀ bowl/cage isomerization energy. ^hFor some SQC methods the corrections suffer from large accumulation errors (see text). ⁱReference dissociation energies of four (H₂O)₂₀ clusters were updated with more accurate values from ref 132 (see text).

consist of species containing elements not yet parametrized for the OM x methods.

Detailed numerical results for the GMTKN30-CHNOF database are documented in the [Supporting Information](#). The corresponding statistical evaluations are given in [Tables 6 and 7](#). Generally speaking, our present results support and generalize the conclusions on the performance of SQC methods obtained previously for the GMTKN24-hcno set.⁵²

Overall, the OM x and OM x -D n methods provide the most accurate results. The MAEs for the entire GMTKN30-CHNOF set are lowest for OM3 (7.17 kcal/mol) followed by OM2 (7.94 kcal/mol), but are substantially higher for the PM x methods (14.44–16.49 kcal/mol) and AM1 (16.45 kcal/mol). Inclusion of dispersion corrections for OM2 and OM3 changes the overall MAEs only very slightly (OM3-D n , 7.21–7.26 kcal/mol; OM2-D n , 7.76–7.91 kcal/mol).

Compared to the previously reported uncorrected values in ref 52 (W4-08woMR subset), the semiempirical SCF atomization enthalpies at 298 K become much more accurate by

correcting to ZPVE-exclusive atomization energies at 0 K (errors reduced by *ca.* 50%). The OM x methods remain the most accurate SQC methods in the W4-08woMR subset (MAEs of 4.12–6.00 kcal/mol). For the full W4-08 subset, the MAEs of the corrected atomization energies are somewhat higher at the OM x level (4.19–7.58 kcal/mol) and still slightly larger for PM6 and PM7 (6.53–7.95 kcal/mol). Dispersion corrections have only little effect on these atomization energies.

In the case of the MB08-165 subset,⁷⁴ the ZPVE and thermal corrections reduce the errors for all of the methods except for MNDO. This subset is generally most challenging as it was especially designed to test the robustness of computational approaches. It consists of the dissociation energies of randomly generated species with unusual bonding situations to diatomics and hydrides. For some of the artificial molecules in this subset, the geometry optimization (needed to evaluate the ZPVE and thermal corrections) led to structures very different from the reference geometries (especially with MNDO), and hence to corrections that may be less accurate; the corrected values were

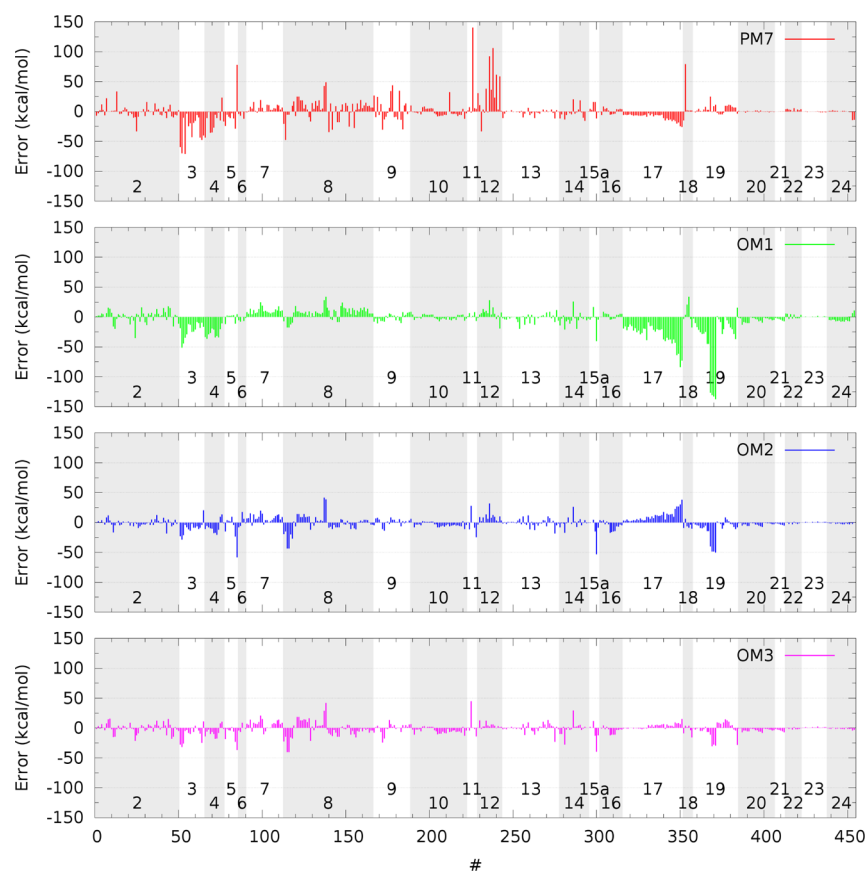


Figure 1. Error distribution of ground-state properties calculated at the OM x and PM7 levels for the GMTKN30-CHNOF benchmark set (excluding the MB08-165 subset and the isomerization energy of C₂₀). The subsets are marked with alternating gray and white backgrounds, and their numbers correspond to those in Table 6.

included in the statistics also in these cases. The OM x methods have the smallest MAEs for both the uncorrected (19.46–22.47 kcal/mol, OM1 and OM3 lowest) and the corrected (11.04–15.03 kcal/mol, OM1 lowest) dissociation energies of the MB08-165 subset, while the MAEs for PM6 and PM7 exceed 100 kcal/mol.

In the case of the BSR36 subset, going from the SCF bond separation enthalpies at 298 K to the corresponding ZPVE-exclusive energies at 0 K reduces the errors only for the OM2, OM3, and OM x -D n methods. The reason for the increased error with the other methods is the way in which this benchmark is constructed: bond separation energies refer to reactions of hydrocarbons with methane to produce ethane molecules; thus large numbers of CH₄ and C₂H₆ molecules are involved (up to 22 and 18, respectively), and any errors in the computed ZPVE and thermal corrections for these two molecules will accumulate. This happens, for instance, in the case of PM7 where the MAE for the BSR36 subset drops from 17.40 to 9.08 kcal/mol (similar to the value of 9.63 kcal/mol without corrections) when using the ZPVE energies of methane and ethane calculated at the W4 level⁷² instead of the PM7 values. Such problems are not encountered with the OM2, OM3, and OM x -D n methods which give realistic ZPVE and thermal corrections for methane and ethane. OM3 is most accurate for the BSR36 subset, both for the uncorrected (MAE of 3.46 kcal/mol) and the corrected (MAE of 1.90 kcal/mol) bond separation energies.

As noted previously,⁵² the cage/bowl isomerization of C₂₀ fullerene is also a very challenging problem for SQC methods:

the absolute error in the isomerization energy exceeds 85 kcal/mol for all SQC methods tested here. C₂₀ is part of the DC9 subset with only seven members; to avoid misleading impressions because of the C₂₀ outlier, we provide MAEs not only for the complete DC9 subset but also for DC9woC20 (DC9 without C20), as well as the errors for C20.

If we remove the most challenging test cases (MB08-165 and C20) from the overall statistics, the MAEs remain lowest for OM3 (6.30 kcal/mol) and OM2 (6.95 kcal/mol), whereas those for the PM x methods drop considerably (9.60–11.26 kcal/mol); AM1 benefits less (14.65 kcal/mol). Inclusion of dispersion corrections for OM2 and OM3 again affects their MAEs only slightly.

According to the statistical evaluations, the OM x and OM x -D n methods are most accurate for barrier heights of hydrogen transfers, heavy-atom transfers, nucleophilic substitutions, unimolecular reactions, and association reactions (BH76^{84,85}) and for the corresponding reaction energies (BH76RC^{84,85}); and for selected reaction energies in the G2 set (G2RC⁶⁹). The OM2, OM3, and OM x -D n methods also perform best for adiabatic ionization potentials (G21IP⁷⁶) and electron affinities (G21EA⁷⁶); for isomerization energies of large organic molecules (ISOL22⁸⁹); and for relative energies of phenylalanyl-glycyl-glycine tripeptide conformers (PCONF¹⁰⁴) and of sugar conformers (SCONF^{79,106}).

The lowest MAEs are provided for proton affinities (subset PA) by OM1 followed by OM3 and OM3-D n ; for systems with intramolecular dispersion interactions (IDISP^{88,98,99}) by OM2, OM3, and OM3-D n ; for interaction energies between n -alkane

Table 8. Mean Absolute Errors (kcal/mol) for the CE345-CHNOF Benchmark Set: MNDO, AM1, PM x , and OM x ^a

no.	subset	N	method							
			MNDO	AM1	PM3	PM6	PM7	OM1	OM2	OM3
	overall ^b	186	15.33	10.08	9.85	10.94	10.85	7.91	6.40	6.89
1	MGAE109/11 (corr)	74	7.89	6.94	6.73	7.42	6.28	4.98	4.26	4.73
2	IsoL6/11	6	9.25	4.63	3.74	2.41	2.05	7.68	1.99	3.22
3	IP21	4	25.29	21.39	19.48	61.38	55.91	31.85	13.24	11.91
4	EA13/03	4	28.56	21.36	11.75	16.67	18.20	31.16	9.80	9.18
5	PA8/06	4	11.68	16.27	19.52	25.28	29.98	4.83	25.04	17.89
6	ABDE12 (corr)	12	28.94	17.92	21.64	18.39	19.92	8.19	8.98	10.52
7	HC7/11	7	17.97	16.24	6.26	4.57	9.18	12.81	8.66	6.75
8	π TC13	13	12.25	6.16	12.00	9.22	10.58	2.82	2.54	5.17
9	HTBH38/08	26	25.36	10.79	9.52	10.50	11.77	11.29	4.96	5.99
10	NHTBH38/08	23	22.16	15.16	15.66	16.44	15.53	9.60	13.64	14.18
11	NCCE31/05 ^b	13	11.46	4.52	3.19	2.70	1.58	3.48	2.15	2.61

^a(corr) means that energies are obtained by removing ZPVE and thermal corrections from the SQC results (see text). ^bSCF calculations of the NH₃...F₂ complex in the NCCE31 subset could not be converged with OM2 and OM3; thus we excluded this complex from the statistics.

Table 9. Mean Absolute Errors (kcal/mol) for the CE345-CHNOF Benchmark Set: OM x -D n ^a

no.	subset	N	method					
			OM2			OM3		
			D2	D3	D3T	D2	D3	D3T
	overall ^b	186	6.17	6.18	6.18	6.51	6.52	6.52
1	MGAE109/11 (corr)	74	4.19	4.20	4.19	4.38	4.53	4.53
2	IsoL6/11	6	2.26	2.19	2.16	3.15	3.28	3.28
3	IP21	4	13.23	13.24	13.24	11.91	11.91	11.91
4	EA13/03	4	9.80	9.80	9.80	9.18	9.18	9.18
5	PA8/06	4	24.98	24.97	24.97	17.83	17.77	17.77
6	ABDE12 (corr)	12	7.32	7.77	7.78	8.97	8.90	8.91
7	HC7/11	7	7.31	7.15	7.16	4.35	3.20	3.21
8	π TC13	13	2.74	2.73	2.73	4.90	4.77	4.77
9	HTBH38/08	26	4.95	4.96	4.96	6.44	6.61	6.61
10	NHTBH38/08	23	13.55	13.58	13.58	14.05	14.07	14.07
11	NCCE31/05 ^b	13	1.26	1.08	1.11	1.51	1.23	1.26

^a(corr) means that energies are obtained by removing ZPVE and thermal corrections from the SQC results (see text). ^bSCF calculations of the NH₃...F₂ complex in the NCCE31 subset could not be converged with OM2 and OM3; thus we excluded this complex from the statistics.

dimers (ADIM6^{97,103}) by OM x -D3, OM x -D3T, and PM7; and for relative energies of alkane conformers (ACONF¹⁰⁵) by OM x -D n .

PM6 is statistically most accurate for systems with problems related to the DFT self-interaction error (SIE11⁷⁹); for other molecules that are difficult cases for DFT (DC9^{79,82,90–95} and DC9woC20); for reaction energies and barriers of ozone addition to C₂H₄ and C₂H₂ (O3ADD6⁸⁷); and for energies of Diels–Alder reactions (DARC⁹⁶).

PM7 appears best suited for calculating barrier heights of pericyclic reactions (BHPERI); isomerization energies of small- and medium-sized organic molecules (ISO34⁸⁸); and binding energies of noncovalently bound dimers (S22).^{101,102} In the latter case, the OM x -D n methods are of similar accuracy (see section 5).

Benchmark energies for four (H₂O)₂₀ clusters used in the WATER27 subset (binding energies of water, H⁺(H₂O) _{n} and OH⁻(H₂O) _{n} clusters)¹⁰⁰ were taken from MP2/CBS calculations.¹³³ Recently more accurate reference energies were obtained at the CCSD(T)/CBS(45) level of theory for those four complexes.¹³² When including these updated reference data, the PM7, OM2-D n , and OM3-D2 methods perform similarly well (MAEs of 6.20–6.57 kcal/mol, OM2-D3 lowest).

Interestingly, radical stabilization energies (RSE43⁸⁶) are best predicted by the venerable AM1 method closely followed by OM1. This demonstrates that the most recent SCQ models and parametrizations may not always be the best for a problem at hand. Hence, if possible, SQC methods should generally be calibrated against available experimental or high-level theoretical data for related systems before using them in actual applications.

As already discussed earlier the largest outliers (SI Figure S1 and Table S20) are often found for species in the MB08-165 subset; this is the case for PM x , OM2, and OM2-D n , with especially large errors of more than 100 kcal/mol seen frequently with PM x . In the case of the OM3 and OM3-D n methods, the largest errors are encountered for the isomerization energy of C₂₀, followed by species in the MB08-165 subset. Other notable outliers (Figure 1) occur for OM1 in the WATER27 subset (four errors larger than 100 kcal/mol); for OM2 in the PA subset (error of -58 kcal/mol in the proton affinity of molecular hydrogen); and for OM3 in the O3ADD6 subset (error of 45 kcal/mol in the energy of adduct formation between O₃ and C₂H₂).

According to the statistical evaluations, the OM x -D n methods have essentially the same overall accuracy as the

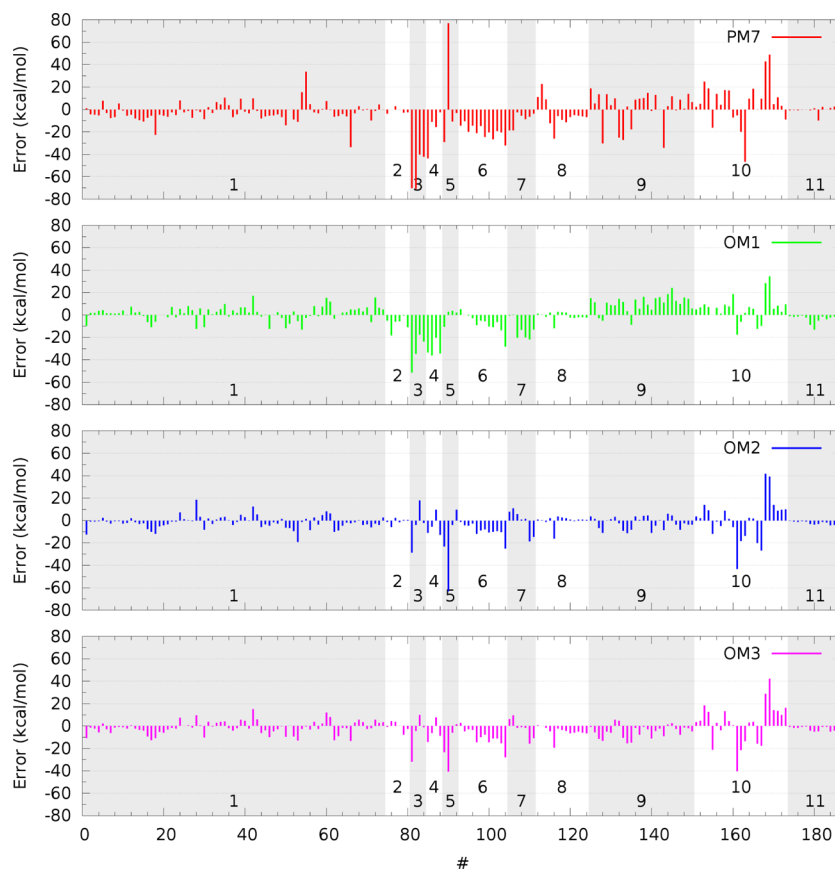


Figure 2. Error distribution of ground-state properties calculated at the OM x and PM7 levels for the CE345-CHNOF set. The subsets are marked with alternating gray and white backgrounds, and their numbers correspond to those in Table 8.

standard OM x methods. As expected, the dispersion corrections significantly improve the accuracy for systems, in which noncovalent interactions play a significant role. This is especially true for the WATER27, S22, and ADIM6 subsets. The barriers of pericyclic reactions (BHPERI subset) are also slightly improved when using the OM x -D n methods, on average by more than 1 kcal/mol.

On the other hand, as already noted, inclusion of dispersion corrections (without any change in the standard OM x parameters) will lower the total energies systematically and thus tend to increase the errors in the calculated heats of formation. Interestingly, the dispersion corrections even deteriorate the results for the IDISP subset designed to capture the effects of intramolecular dispersion. Apparently, intramolecular noncovalent interactions of this kind are already largely taken into account (on average) by the general parametrization of OM x methods such that adding further dispersion interactions is detrimental.

Overall, the positive and negative effects of including empirical dispersion corrections (while retaining the standard OM x parameters) seem to cancel out in the case of the GMTKN30-CHNOF benchmark set so that the overall MAEs are similar for the OM x and OM x -D n methods.

4.5. CE345-CHNOF. The chemistry energetic database with 345 entries (CE345)^{107,108} is a collection of accurate reference data used for the evaluation and parametrization of DFT functionals.¹⁰⁸ We note that some of the reference data in the CE345 database are also present in the GMTKN30 database, although the actual reference values may differ slightly because of the use of different methodology for obtaining them.⁷³

We reduced the CE345 database to the CE345-CHNOF set by accepting only species containing exclusively the elements H, C, N, O and/or F. Therefore, the SRMBE13 subset had to be excluded. The MRBE10 and DC9 subsets were also excluded from the error analysis because there are only two surviving species in each subset. Finally, we also disregarded the AE17 subset with atomic energies. The final CE345-CHNOF set consists of 11 subsets with a total of 187 entries.

The results from the statistical evaluations are summarized in Tables 8 and 9. Overall, the lowest MAEs for the CE345-CHNOF set are obtained from the OM x and OM x -D n methods (6.17–7.91 kcal/mol). As expected, the inclusion of dispersion corrections improves the results for the NCCE31/05 subset targeting noncovalent complexation energies; this is also true for the subsets ABDE12, HC7/11, and π TC13 that contain systems in which dispersion plays a prominent role.

Looking at the statistical evaluation for the individual subsets, atomization energies (after correcting SCF atomization enthalpies at 298 K to ZPVE-exclusive energies at 0 K, MGAE109/11^{109,110}) are found to be best reproduced by OM x and OM x -D n methods (MAEs of 4.19–4.98 kcal/mol, OM2 and OM2-D n lowest).

Isomerization energies (IsoL6/11¹¹¹) are best reproduced by OM2 and PM7 (MAE of *ca.* 2.0 kcal/mol). We note that this subset contains the six smallest pairs of isomers from the ISOL22 subset of GMTKN30; their isomerization energies were calculated at a more accurate level of theory than those in ISOL22.

The subsets for adiabatic ionization potentials (IP21^{109,112–116}) and electron affinities (EA13/03^{109,112–114})

Table 10. Mean Absolute Errors in Calculated Heats of Formation (kcal/mol), Bond Lengths (Å), Bond Angles (deg), Dihedral Angles (deg), Ionization Potentials (eV), and Dipole Moments (D) for the PDDG Benchmark Set and Its Subsets: MNDO, AM1, PM x , and OM x

subset	N	method							
		MNDO	AM1	PM3	PM6	PM7	OM1	OM2	OM3
Heats of Formation									
overall	622	8.04	6.72	4.24	4.05	3.34	5.51	3.55	3.68
CH	254	7.92	5.63	3.40	3.70	3.19	4.92	2.30	2.38
CHN	89	6.01	7.30	4.61	4.54	4.63	6.77	5.01	4.86
CHO	238	8.03	7.15	4.55	4.12	3.01	4.97	3.86	4.58
CHNO	41	13.25	9.70	6.93	4.76	3.41	9.53	6.24	3.96
Bond Lengths									
overall	153	0.013	0.016	0.011	0.012	0.011	0.012	0.014	0.018
CH	81	0.011	0.013	0.012	0.009	0.010	0.013	0.011	0.010
CHN	34	0.012	0.015	0.011	0.012	0.010	0.009	0.015	0.025
CHO	35	0.019	0.020	0.009	0.016	0.013	0.013	0.020	0.026
CHNO	3	0.024	0.038	0.009	0.026	0.018	0.010	0.027	0.044
C–H	38	0.008	0.011	0.008	0.010	0.012	0.009	0.010	0.013
C–C	52	0.012	0.015	0.012	0.011	0.010	0.013	0.010	0.010
C=C	15	0.012	0.011	0.010	0.008	0.007	0.013	0.009	0.009
C≡C	5	0.009	0.010	0.015	0.002	0.005	0.004	0.019	0.025
N–C	7	0.016	0.020	0.021	0.029	0.017	0.016	0.018	0.018
N–H	4	0.005	0.012	0.019	0.006	0.002	0.003	0.007	0.044
N≡C	5	0.009	0.007	0.006	0.002	0.004	0.005	0.017	0.046
O–H	6	0.012	0.013	0.010	0.032	0.025	0.011	0.037	0.058
O–C	7	0.018	0.015	0.015	0.024	0.011	0.015	0.018	0.022
O=C	9	0.014	0.021	0.006	0.006	0.007	0.011	0.015	0.019
Bond Angles									
overall	54	2.97	1.98	2.09	2.15	2.12	2.04	2.17	1.90
CH	20	1.57	0.73	0.89	0.88	1.12	1.14	1.37	0.94
CHN	12	1.94	1.42	1.88	1.74	1.80	1.90	1.30	1.33
CHO	21	4.46	3.21	3.12	3.33	3.04	2.66	3.08	2.76
∠CCH	16	1.32	1.03	1.14	1.62	1.64	1.23	1.02	1.00
∠CCC	13	2.11	0.96	1.17	0.78	1.06	1.27	1.78	1.19
∠OCH	3	1.61	3.26	3.46	4.04	3.75	2.27	3.03	3.02
∠COH	3	7.71	2.38	2.91	5.41	6.16	2.43	2.75	3.23
∠OCC	5	2.18	2.06	2.38	2.13	2.01	1.62	2.59	1.81
Dihedral Angles									
overall	6	26.42	19.94	28.90	28.88	28.87	8.02	8.53	5.74
CH (∠CCCC)	3	3.40	5.16	5.83	5.39	5.83	5.20	6.00	5.43
Ionization Potentials									
overall	97	0.70	0.53	0.60	0.52	0.52	0.48	0.37	0.60
CH	41	0.74	0.49	0.61	0.48	0.54	0.50	0.35	0.57
CHN	21	0.61	0.46	0.51	0.52	0.55	0.40	0.28	0.44
CHO	31	0.67	0.60	0.60	0.53	0.45	0.46	0.42	0.75
CHNO	4	1.00	0.83	1.01	0.83	0.74	0.85	0.66	0.66
Dipole Moments									
overall	47	0.32	0.24	0.27	0.37	0.38	0.26	0.27	0.25
CH	10	0.24	0.15	0.15	0.26	0.26	0.10	0.11	0.11
CHN	14	0.52	0.46	0.38	0.52	0.55	0.43	0.25	0.30
CHO	20	0.20	0.12	0.22	0.34	0.34	0.23	0.34	0.27
CHNO	3	0.56	0.25	0.53	0.31	0.33	0.24	0.44	0.41

overlap with the corresponding GMTKN30-CHNOF subsets (G21IP and G21EA). In all cases, the OM2 and OM3 methods perform best (MAEs of 0.52–0.57 eV for IP21 and 0.40–0.42 eV for EA13/03), with substantially larger errors for the other SQC methods. As expected, dispersion corrections have essentially no effect on the OM2 and OM3 results for these properties.

All entries in the subset for proton affinities (PA8/06⁷⁸) also appear in the PA subset of GMTKN30 (albeit with slightly

different reference values). As in the PA case, OM1 has the lowest statistical error (MAE of 4.8 kcal/mol). Alkyl bond dissociation energies (ABDE12^{109,117–119}) are best reproduced by the OM x -D n and OM x methods (MAEs after accounting for ZPVE and thermal corrections of 7.32–10.52 kcal/mol and above 17 kcal/mol for the MNDO-type methods), while hydrocarbon chemistry (HC7/11¹¹⁹) is best described by OM3-D n and PM6 (MAEs of 3.20–4.34 and 4.57 kcal/mol, respectively). The thermochemistry of π systems

(π TC13^{78,112,117}) is best treated by the OM2 and OM2-*Dn* methods (MAEs of 2.54 and 2.73–2.74 kcal/mol, respectively; the data set includes some proton affinities of polyenes that are part of the PA subset of GMTKN30).

The entries in the subsets for hydrogen and non-hydrogen transfer reactions (HTBH38/08 and NHTBH38/08)^{85,109,120,121} are also present in the BH76 subset of GMTKN30. OM2 and OM2-*Dn* perform best for the barrier heights to hydrogen transfer followed by OM3 and OM3-*Dn* (MAEs of 4.95–4.96 and 5.99–6.61 kcal/mol, respectively), while the barrier heights to non-hydrogen transfer are described less well (lowest MAE of OM1 9.60 kcal/mol).

As expected, noncovalent complexation energies (NCCE31/05)^{113,122} are best reproduced by the OM*x*-*Dn* methods (MAEs of 1.08–1.51 kcal/mol) followed by PM7 (MAEs of 1.58 kcal/mol).

The error distributions of the OM*x* and PM7 methods with regard to the CE345-CHNOF set are shown in Figure 2. They appear similar overall; however, there are more outliers for PM7 compared with the OM*x* methods and especially with OM2.

The largest outliers at the OM*x* and OM*x*-*Dn* levels have errors between 40 and 63 kcal/mol in the computed energies. These are the ionization energy of the carbon atom (OM1); the proton affinity of molecular hydrogen (OM2 and OM2-*Dn*); and the barrier of the HCN → HNC isomerization (OM3 and OM3-*Dn*); see the Supporting Information.

4.6. PDDG. The PDDG set was used in the development and validation of the PDDG/MNDO and PDDG/PM3 methods.³¹ It contains 979 experimental reference data for heats of formation, bond lengths, bond angles, dihedral angles, ionization potentials, and dipole moments of 622 closed-shell molecules (elements H, C, N, and O). The PDDG set is divided in the original work into CH, CHN, CHO, and CHNO subsets. We use the same conventions for these subsets as in the original work. In addition, we introduce subsets for bond lengths, bond angles, and dihedral angles according to the elements involved.

In our evaluations, full geometry optimizations were performed for each molecule. Ionization potentials were calculated using Koopmans' theorem. The resulting MAEs for the different properties are summarized in Table 10 for the MNDO, AM1, PM*x*, and OM*x* methods and in SI Table S3 for the OM*x*-*Dn* methods.

Considering heats of formation, the PDDG/PM3 method gives the lowest MAE for the PDDG set (3.2 kcal/mol), which is not too surprising since it was trained on this set.³¹ Slightly higher are the MAEs for PM7 (3.34 kcal/mol), OM2 (3.55 kcal/mol), and OM3 (3.68 kcal/mol), while those for the other SQC methods are above 4.0 kcal/mol. The OM2 and OM3 methods systematically overestimate the heats of formation in the PDDG set (mean signed errors (MSEs) of 0.92 and 1.08 kcal/mol, respectively), more so than PM7 (MSE of 0.49 kcal/mol). The error distribution is shown in Figure 3 for PM7 and the OM*x* methods. It is broadest for OM1 and rather similar for the other three methods. OM3 has the least number of outliers.

As noted previously, post-SCF dispersion corrections deteriorate the accuracy of heats of formation calculated by SQC methods parametrized at the SCF-MO level (compare Table 10 and SI Table S3). This shortcoming can be avoided by simultaneously fitting the parameters of the SQC method and of the dispersion corrections, as has been done in PM7;³⁴ this may contribute to its good performance for the PDDG set.

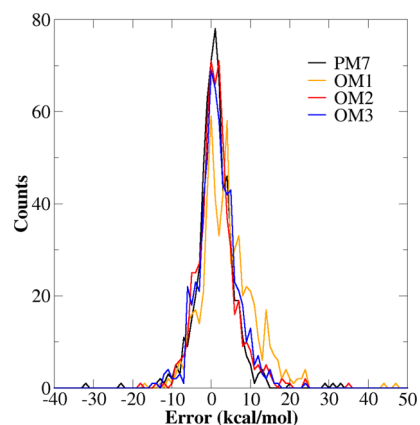


Figure 3. Error histogram of heats of formation calculated at the OM*x* and PM7 levels of theory for the PDDG benchmark set.

Considering geometries, all tested SQC methods perform reasonably well for bond lengths (overall MAEs of 0.011–0.018 Å, lowest for PM3 and PM7). Except for MNDO, this is also true for bond angles (overall MAEs of 1.90–2.15°, lowest for OM3). Dihedral angles are described best by the OM*x* methods (overall MAEs of 5.7–8.5°, lowest for OM3).

Ionization potentials are reproduced best by OM2 (MAE of 0.37 eV); the other SQC methods have somewhat larger errors (0.48–0.70 eV). The MAEs in the calculated dipole moments are in the range between 0.24 and 0.38 D; the AM1, PM3, and OM*x* methods provide the best estimates (MAEs of 0.24–0.27 D).

4.7. PM7-CHNOF. The PM7-CHNOF benchmark set was assembled from the online database¹³⁴ of reference data that have been used for the development and validation of the PM7 method.³⁴ It includes all species of the database that consist only of the elements H, C, N, O, and F. It contains 1595 experimental and high-level *ab initio* reference values for heats of formation, bond lengths, bond angles, ionization potentials, and dipole moments of 1177 neutral and charged, open-shell and closed-shell species. It is divided into the DA, CH, CHN, CHO, CHF, and CHNO subsets. The diatomic DA subset consists of the H₂, N₂, O₂ (triplet and singlet), and F₂ molecules.

In our evaluations, full geometry optimizations were performed for each species. Ionization potentials were determined using Koopmans' theorem. The resulting MAEs for the different properties are summarized in Table 11 for the MNDO, AM1, PM*x*, and OM*x* methods and in SI Table S4 for the OM*x*-*Dn* methods.

The PM7 method was trained and validated on this benchmark set, and it is thus not surprising that PM7 shows the best overall accuracy for the heats of formation (MAE of 3.78 kcal/mol, MSE of –0.18 kcal/mol); its error distribution is narrow and symmetric (Figure 4). The OM*x* methods tend to overestimate the heats of formation for this set, especially OM1 (Figure 4). OM2 and OM3 perform similarly (MAEs of 4.83–4.85 kcal/mol). They outperform PM7 in the DA and CHF subsets and have similar accuracy in the CH subset, while PM7 is superior in the CHN, CHO, and CHNO subsets. Again, for the same reasons as discussed before, post-SCF dispersion corrections deteriorate the accuracy of the heats of formation calculated by the OM*x* methods (compare Table 11 and SI Table S4).

Table 11. Mean Absolute Errors in Calculated Heats of Formation (kcal/mol), Bond Lengths (Å), Bond Angles (deg), Dihedral Angles (deg), Ionization Potentials (eV), and Dipole Moments (D) for the PM7-CHNOF Benchmark Set and Its Subsets: MNDO, AM1, PM x , and OM x

subset	N	method							
		MNDO	AM1	PM3	PM6	PM7	OM1	OM2	OM3
Heats of Formation									
overall	1168	11.26	9.30	5.51	4.43	3.78	8.25	4.85	4.83
DA	5	8.31	17.43	12.09	20.62	18.61	5.27	3.26	2.15
CH	310	13.67	9.85	5.23	4.72	4.18	9.23	4.16	3.63
CHN	214	7.63	7.19	5.32	3.73	3.42	7.90	5.43	5.69
CHO	373	9.26	8.03	5.42	4.33	3.40	6.43	4.22	5.18
CHF	32	6.73	8.15	6.25	3.77	4.54	2.42	3.50	2.44
CHNO	234	15.24	12.48	5.97	4.59	3.74	11.01	6.46	5.43
Bond Lengths									
overall	175	0.026	0.020	0.015	0.015	0.013	0.015	0.015	0.019
DA	4	0.079	0.056	0.039	0.043	0.033	0.023	0.036	0.053
CH	74	0.010	0.014	0.012	0.009	0.010	0.013	0.011	0.011
CHN	31	0.011	0.015	0.011	0.013	0.010	0.010	0.014	0.020
CHO	31	0.015	0.015	0.009	0.012	0.009	0.011	0.016	0.021
CHF	18	0.016	0.015	0.013	0.009	0.012	0.013	0.016	0.020
CHNO	17	0.146	0.061	0.037	0.043	0.032	0.043	0.028	0.040
Bond Angles									
overall	90	2.48	1.82	1.82	2.24	2.27	1.48	1.76	1.54
CH	32	1.61	1.01	0.76	2.14	2.33	0.64	0.90	0.49
CHN	20	1.62	1.19	1.53	0.96	1.08	1.39	1.44	1.35
CHO	20	3.47	2.08	2.33	2.31	2.12	1.79	2.33	1.98
CHF	11	2.59	2.38	1.43	2.35	2.18	1.45	1.47	1.11
CHNO	7	5.93	5.67	6.68	6.03	5.93	4.72	5.42	6.26
Ionization Potentials									
overall	104	0.59	0.49	0.50	0.42	0.42	0.40	0.33	0.53
CH	36	0.62	0.37	0.48	0.38	0.43	0.39	0.25	0.47
CHN	18	0.58	0.33	0.34	0.36	0.38	0.43	0.28	0.42
CHO	29	0.66	0.60	0.57	0.41	0.37	0.41	0.44	0.77
CHF	14	0.34	0.68	0.41	0.36	0.39	0.27	0.34	0.29
CHNO	5	0.70	0.67	0.78	0.64	0.59	0.59	0.47	0.55
Dipole Moments									
overall	58	0.34	0.25	0.27	0.35	0.33	0.26	0.24	0.22
CH	10	0.25	0.16	0.16	0.25	0.26	0.11	0.12	0.12
CHN	17	0.50	0.44	0.39	0.50	0.52	0.40	0.25	0.30
CHO	20	0.21	0.15	0.21	0.34	0.26	0.18	0.28	0.23
CHF	10	0.38	0.21	0.24	0.18	0.19	0.34	0.25	0.16

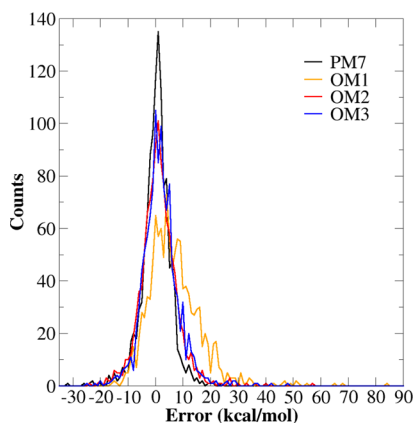


Figure 4. Error histogram for heats of formation calculated at the OM x and PM7 levels of theory for the PM7-CHNOF benchmark set.

Concerning the other properties, the conclusions for the PM7-CHNOF set are similar to those for the PDDG set (see

preceding discussion). Bond lengths and bond angles are generally reproduced reasonably well by all SQC methods, and there are no great differences in the overall accuracy of the computed ionization potentials and dipole moments. For bond lengths, PM7 has the lowest overall MAE (0.013 Å) followed by PM3, PM6, OM1, and OM2 (0.015 Å in each case). The OM x methods have a slight overall advantage over the other SQC methods for bond angles (MAEs of 1.48–1.76°, OM1 lowest), ionization potentials (0.33–0.53 eV, OM2 lowest), and dipole moments (0.22–0.26 D, OM3 lowest).

4.8. C₇H₁₀O₂. Accurate thermochemical calculations at the G4MP2¹³⁵ level of theory were recently performed for a set of 6095 constitutional isomers C₇H₁₀O₂.¹²³ They were drawn from the chemical universe database GDB-17 that contains 166.4 billion molecules with up to 17 non-hydrogen atoms.¹³⁶ Many of GDB-17 molecules belong to drug-like compounds.¹³⁶

We derived atomization enthalpies at 298 K for these 6095 C₇H₁₀O₂ isomers from the corresponding G4MP2 enthalpies reported in ref 123. The reported geometries were obtained at the B3LYP/6-31G(2df,p) level of theory,¹²³ which is not

Table 12. Mean Absolute Errors in Calculated Atomization Enthalpies at 298 K (kcal/mol) for the C7H10O2 Benchmark Set

subset	N	method							
		MNDO	AM1	PM3	PM6	PM7	OM1	OM2	OM3
overall	6095	9.27	13.43	7.92	7.26	6.44	8.92	6.30	7.67

Table 13. Mean Absolute Errors of the Interaction Energies (kcal/mol) for the A24-CHNOF, S66, S66a8, JSCH-2005-CHNOF, S7L, and S30L-CHNOF Sets and of the Folding Enthalpies and Energies (kcal/mol) for the AF6 Set, Calculated at the Reference Geometries Using PM7 and OM x -D n

subset	N	method							
		PM7	OM2			OM3			
			D2	D3	D3T	D2	D3	D3T	
A24-CHNOF									
overall	21	1.10	0.56	0.56	0.56	0.69	0.67	0.67	
overall* ^a	20	0.64	0.43	0.43	0.43	0.49	0.47	0.46	
H-bonded	5	2.66	1.39	1.40	1.40	1.36	1.32	1.32	
H-bonded* ^a	4	0.73	0.97	0.95	0.95	0.52	0.46	0.46	
mixed	10	0.49	0.19	0.17	0.17	0.41	0.34	0.34	
dispersion	6	0.84	0.47	0.52	0.52	0.61	0.67	0.67	
S66									
overall	66	0.79	1.02	0.82	0.85	1.05	0.82	0.81	
electrostatic	23	0.95	1.91	1.80	1.80	1.99	1.75	1.75	
mixed	20	0.71	0.39	0.26	0.27	0.64	0.37	0.39	
dispersion	23	0.70	0.68	0.32	0.39	0.45	0.27	0.23	
S66a8									
overall	528	0.78	0.77	0.60	0.61	0.80	0.62	0.60	
electrostatic	184	0.84	1.44	1.34	1.34	1.52	1.33	1.33	
mixed	160	0.60	0.32	0.22	0.22	0.48	0.26	0.26	
dispersion	184	0.86	0.50	0.20	0.21	0.36	0.22	0.18	
JSCH-2005-CHNOF									
overall	134	1.93	2.27	1.72	1.81	1.86	1.33	1.37	
overall* ^b	128	1.83	2.07	1.52	1.61	1.62	1.10	1.13	
H-bonded base pairs	31	2.62	3.50	3.11	3.05	3.12	2.53	2.47	
interstrand base pairs	32	2.46	0.99	0.72	0.72	0.90	0.70	0.70	
stacked base pairs	54	1.15	2.11	1.25	1.50	1.32	0.64	0.75	
amino acid pairs	17	2.19	2.95	2.51	2.55	3.08	2.56	2.62	
amino acid pairs* ^b	11	1.17	1.01	0.65	0.65	0.96	0.49	0.52	
S7L									
overall	7	4.91	3.19	2.25	2.38	1.97	0.66	0.79	
π - π	5	4.79	4.39	2.05	2.72	2.63	0.29	0.95	
S30L-CHNOF									
overall	24	15.44	6.69	5.32	5.01	4.90	4.36	3.59	
π - π stacking	7	18.54	6.13	3.58	3.04	4.20	5.08	3.17	
H-bonded ^c	8	13.17	6.93	6.95	6.49	5.84	4.49	4.62	
charged complexes ^c	8	21.76	9.55	9.46	8.41	5.71	6.38	4.56	
AF6									
folding enthalpies	6	1.18	0.20	0.45	0.34	0.79	0.76	1.00	
folding energies	6	1.05	0.18	0.44	0.34	0.96	0.93	1.17	

^aWithout the HF...HF complex, see text. ^bWithout the complexes of charged amino acids, see text. ^cTwo complexes correspond to both H-bonded and charged complexes subsets; see ref 49.

considered accurate enough to be used as reference in our present benchmarking.

We performed full geometry optimizations for all these molecules. The statistical evaluation of the results is given in Table 12. The OM x and PM x methods perform similarly, with MAEs ranging between 6.30 and 8.92 kcal/mol (OM2 lowest, closely followed by PM7). Dispersion corrections have essentially no effect on the atomization enthalpies for the molecules in the C7H10O2 set (SI Table S26).

4.9. RM1 Benchmark Results. Upon the request of a reviewer, we have carried out analogous RM1 calculations for

all benchmark sets considered in preceding discussion. The statistical evaluations of the RM1 results are given in the Supporting Information (Tables S34–S41) along with a brief assessment. Overall RM1 tends to be generally more accurate than AM1, about as accurate as the PM x methods, and somewhat less accurate than the OM x methods.

5. BENCHMARKS OF NONCOVALENT INTERACTIONS

Noncovalent interactions are difficult to describe for standard SQC methods which do not include dispersion in their

formalism and often also have well-documented problems with hydrogen bonding. In this section, we will focus on the PM7 and OM x -D n methods with explicit dispersion corrections, while presenting the results for the other (less accurate) SQC methods only in the [Supporting Information](#).

We selected seven data sets from the literature to benchmark the accuracy of SQC methods for noncovalent interactions. As usual, we excluded in these sets the species containing elements for which OM x parameters are not yet available. Thus, three of the data sets were reduced: A24¹²⁴ from 24 to 21 entries in A24-CHNOF, JSCH-2005¹⁰¹ from 143 to 134 entries in JSCH-2005-CHNOF, and S30L⁴⁹ from 30 to 24 entries in S30L-CHNOF. The remaining four sets were not changed (S66, S66a8, S7L, and AF6). The resulting sets are briefly specified in [Table 2](#).

In the following, we first report results from single-point calculations at the reference geometries for all seven data sets. Thereafter we present results from SQC geometry optimizations for the A24-CHNOF,¹²⁴ S66,¹²⁵ S7L,¹²⁷ and AF6¹²⁸ sets, for which high-level reference geometries are available. We note in this context that the S66a8 set is specifically designed for single-point calculations.^{125,126} The reference geometries in the JSCH-2005-CHNOF set are taken from different sources and include experimental, purely theoretical, and combined experimental/theoretical data,^{101,137} with purely theoretical geometries constituting only a minor part; many of these reference geometries are not minima in the gas phase, which would make it meaningless to compare them with optimized gas-phase SQC geometries.

In the validation studies with full geometry optimization, our focus is on the accuracy of the optimized SQC geometries. The reason is simple: if a method fails to predict the correct geometry for a noncovalent complex, the computed interaction energy will be meaningless. Hence, we primarily examine the most important intermolecular distances and angles for each complex (except for AF6 where we check the intramolecular geometry parameters in the folded conformation). The corresponding interaction energies are documented in the [Supporting Information](#).

5.1. Single-Point Calculations. The statistical evaluation of the interaction energies obtained from single-point SQC calculations is given in [Table 13](#) for the PM7 and OM x -D n methods and in [SI Table S5](#) for all other methods.

The OM x -D n methods perform best overall for the A24-CHNOF set (MAEs of 0.56–0.69 kcal/mol, OM2 lowest), while PM7 has somewhat larger errors (MAE of 1.10 kcal/mol). The most problematic case in A24-CHNOF is the HF...HF complex: at the nonoptimized reference geometry, the reference interaction energy is attractive (−4.57 kcal/mol); OM2 and OM2-D n give only a rather weak attraction (−1.47 to −1.15 kcal/mol), whereas MNDO, PM6, PM7, OM1, OM3, and OM3-D n yield a repulsive interaction energy (up to 5.81 kcal/mol in PM7); see the discussion in [section 5.2](#). When this complex is disregarded in the statistics, the errors drop further (MAEs of OM x -D n 0.43–0.49 kcal/mol and PM7 0.64 kcal/mol). Considering the subsets, the OM x -D n methods outperform PM7 for complexes with dispersion-dominated and mixed electrostatic/dispersion interactions, and the OM3-D n methods are best for H-bonded complexes.

In the S66 set, the PM7 and OM x -D3 methods are of similar accuracy (MAEs of 0.79 vs 0.82 kcal/mol), whereas the latter are superior in the S66a8 set (MAEs of 0.78 vs 0.60–0.62 kcal/mol); the OM x -D2 treatments are generally somewhat less

accurate. In all three sets, the OM x -D n methods outperform PM7 for the complexes with dispersion-dominated and mixed interactions.

In the JSCH-2005-CHNOF set (interaction energies of DNA base pairs and amino acid pairs), the OM x -D2 results are again slightly less accurate than the OM x -D3 results, and among the latter, OM3-D3 has generally the lowest or close-to-lowest errors. OM3-D3 also outperforms PM7 for the JSCH-2005-CHNOF set overall (MAEs of 1.33 vs 1.93 kcal/mol) as well as for two of the subsets (intrastrand and stacked base pairs), whereas the MAEs are similar in the case of H-bonded base pairs (MAEs of 2.53 vs 2.62 kcal/mol) and higher for OM3-D3 in the case of amino acid pairs (MAEs of 2.56 vs 2.19 kcal/mol). The largest outliers generally occur for pairs of oppositely charged amino acids: when these six complexes are excluded from the analysis, the errors drop substantially, as can be seen from the MAEs for OM3-D3 and PM7 for the neutral amino acid pairs (MAEs of 0.49 vs 1.17 kcal/mol) and for the overall set (MAEs of 1.10 vs 1.83 kcal/mol). Evidently, OM3-D3 performs best for the JSCH-2005-CHNOF set.

In a similar vein, OM3-D3 describes the σ - σ and π - π interactions for large complexes (S7L set) significantly better than any of the other SQC methods considered. The corresponding MAE value for OM3-D3 (0.66 kcal/mol) is small on an absolute scale and much lower than that for PM7 (4.91 kcal/mol).

The S30L set⁴⁹ is an expansion of the S12L set^{48,138} and consists of very large noncovalent complexes, which are deemed useful to check "against overfitting to too small molecular cases".⁴⁸ The OM x -D n methods perform fairly well (MAEs of 3.59–6.69 kcal/mol, OM3-D3T lowest). They outperform other SQC methods investigated here and in [ref 49](#), and especially PM7, which strongly overestimates most interaction energies (MAE of 15.44 kcal/mol). The OM x -D n methods generally describe π - π stacking interactions better than H-bonding interactions; however, even in the latter case, they are more accurate than PM7, which appears to suffer from an accumulation of errors in the very large noncovalent complexes of the S30L-CHNOF set. The largest outliers in the OM x -D n results are found for positively charged complexes, as previously reported for OM2-D3 and OM3-D3 in the case of the S12L set.⁴⁸

The AF6 set provides reference folding energies and enthalpies for a series of alkanes.¹²⁸ The PM7 values should be compared to the enthalpies, since PM7 was parametrized against heats of formation. In the case of the OM x -D n methods, one may argue that the computed values can be considered as enthalpies or as energies, since the parameters for the underlying OM x methods and for the dispersion corrections were calibrated against heats of formation and interaction energies, respectively. To be unbiased, we provide data for both types of comparisons, and the results differ only very slightly (see [Table 13](#)). The PM7 and OM x -D n methods have rather small errors both for the folding enthalpies (MAEs of 0.20–1.18 kcal/mol, OM2-D2 lowest, PM7 highest) and energies (MAEs of 0.18–1.05 kcal/mol, OM2-D2 lowest, PM7 highest). However, more important than these statistics is a qualitative finding: only OM2-D2, OM3-D2, and OM3-D3 correctly predict that the hairpin conformation of alkanes becomes more favorable than the linear conformation for 17 ± 1 carbon atoms, in agreement with experiment,¹³⁹ while the hairpin conformation is more favorable already for alkanes with less than 16 carbon atoms in the case of PM7 and OM2-D3.

Table 14. Mean Absolute Errors in Selected Interatomic Distances (Å) and Angles (deg) for the A24-CHNOF, S66, S7L, and AF6 Benchmark Sets for Geometries Optimized with PM7 and OMx-Dn

subset	N	method						
		PM7	OM2			OM3		
			D2	D3	D3T	D2	D3	D3T
A24-CHNOF								
Selected Interatomic Distances								
overall	23	0.375	0.472	0.500	0.500	0.322	0.261	0.262
H-bonded	5	0.365	0.202	0.197	0.198	0.333	0.335	0.335
mixed	13	0.168	0.421	0.413	0.413	0.258	0.324	0.326
dispersion	5	0.926	0.876	1.027	1.027	0.477	0.023	0.023
Selected Angles								
overall	40	12.86	14.83	9.86	9.97	12.79	8.69	8.80
H-bonded	13	14.83	11.15	11.39	11.39	11.08	11.07	11.08
mixed	21	7.31	6.57	6.46	6.45	13.01	9.35	9.56
dispersion	6	28.00	51.74	18.46	19.18	15.73	1.19	1.20
S66								
Selected Interatomic Distances								
overall	172	0.407	0.381	0.348	0.348	0.290	0.320	0.317
electrostatic	28	0.083	0.181	0.173	0.173	0.308	0.333	0.283
mixed	63	0.449	0.433	0.415	0.415	0.303	0.344	0.361
dispersion	81	0.486	0.409	0.356	0.356	0.273	0.297	0.295
Selected Angles								
overall	141	15.83	11.68	12.27	12.32	11.32	13.15	12.99
electrostatic	28	6.29	14.41	13.37	13.30	11.83	12.37	9.97
mixed	52	25.14	14.28	14.50	14.54	15.74	18.95	19.73
dispersion	61	12.28	8.22	9.86	9.97	7.32	8.56	8.63
S7L								
Selected Interatomic Distances								
overall	28	0.325	0.510	0.428	0.420	0.390	0.389	0.393
C...C	20	0.310	0.547	0.433	0.421	0.408	0.467	0.468
H...H	8	0.361	0.419	0.415	0.416	0.345	0.193	0.207
AF6								
Selected Interatomic Distances								
overall	27	0.090	0.140	0.169	0.168	0.121	0.168	0.165
Selected Angles								
overall	74	6.58	5.17	6.48	6.42	6.42	7.05	7.03

Finally, we briefly compare the effect of the different dispersion corrections applied in the OMx-Dn calculations. In the large majority of cases, the D3 correction turns out to be superior to the D2 correction, albeit often only by a small margin. The role of three-body corrections is negligible in small complexes (A24-CHNOF, S66, and S66a8 sets) and still quite small but not entirely negligible in hydrogen-bonded and stacked base pairs (JSCH-2005-CHNOF) and in folded alkanes (AF6). As expected, three-body corrections become significant in stacked systems modeling π - π interactions between graphene layers (S7L) and in very large noncovalent complexes (S30L-CHNOF). Since OM2-D3 and OM3-D3 underestimate the attractive π - π dispersion interactions, the repulsive three-body corrections increase the corresponding errors (on average by 0.7 kcal/mol). On the other hand, OM2-D3 and OM3-D3 tend to overestimate the binding energies in most of the very large noncovalent complexes, and hence the repulsive three-body corrections decrease the error in this case by 0.31–0.77 kcal/mol for the S30L set, as already reported earlier for the S12L set⁴⁸ (OM2-D3 and OM3-D3) and for the S30L set⁴⁹ (OM2-D3).

5.2. Geometry Optimizations. Full geometry optimizations were carried out for the A24-CHNOF, S66, S7L, and AF6 sets using all SQC methods examined presently.

The *ab initio* reference geometries were taken from published work at the following levels: CCSD(T)/CBS extrapolation for A24-CHNOF;¹²⁴ counterpoise-corrected MP2/cc-pVTZ for S66 with intermolecular distances obtained by interpolating estimated CCSD(T)/CBS energies along dissociation curves;^{125,137} intermolecular distances optimized at the CCSD(T)/ha-cc-pVDZ level with monomer geometries optimized at the B3LYP level with large basis sets for S7L;¹²⁷ and MP2/cc-pVTZ for AF6.¹²⁸ In the original work on the A24 set, three π - π stacked complexes were not optimized but constrained artificially;¹²⁴ therefore they are not considered here.

The statistical evaluation of selected optimized interatomic distances and bond angles is presented in Table 14 for the PM7 and OMx-Dn methods and in SI Table S6 for the other SQC methods. The corresponding statistical data for the associated interaction energies are documented in the Supporting Information (Tables S7 and S8). We note that some of the noncovalent complexes are present in several data sets, with slightly different reference geometries.

We start with some general remarks before discussing individual data sets and complexes. The selected distances and angles mostly refer to intermolecular geometrical parameters, e.g., distances defining the separation between the monomers or the length of hydrogen bonds and angles characterizing the

Table 15. Methods with Lowest MAEs in Calculated Ground-State Properties^a

data set	N	properties	first best	MAE	second best	MAE
OVS7-CHNOF radicals71	42	heats of formation	OM2	4.98	OM3	5.57
	4	relative energies	OM2	3.95	OM3	5.46
	25	ionization potentials ^d	OM1, OM2	0.37–0.38	OM3	0.53
	24	heats of formation	OM2	4.98	OM3	5.57
	36	heats of formation	OM2	4.98	OM3	5.57
	5	relative energies	OM3	3.53	OM2	3.68
	20	heats of formation	OM2	4.85	OM3	5.05
	11	heats of formation	OM1	1.83	PM7	2.40
	19	barriers	OM2, OM3	1.26–1.34	OM1	1.50
	27	heats of formation	OM2	1.05	OM3	1.81
	17	relative energies	OM2-D3, OM2-D3T	0.69–0.70	OM2, OM2-D2	0.80–0.82
fluorine91	91	heats of formation	OM1, OM2	7.15–7.17	OM3	7.34
	455	bond lengths	OM1, OM2, PM3	0.015–0.016	PM6	0.017
	355	bond angles	OMx	1.78–2.04	MNDO, AM1, PMx	2.94–3.68
G2G3-CHNOF	93	heats of formation	OM2	3.37	OM3	3.83
G2-CHNOF	52	heats of formation	OM2	3.18	PM7	3.40
G3-CHNOF	22	heats of formation	OM3	0.72	PM7	1.76
alkanes28	6	relative energies	OM2-Dn	0.21–0.24	OM2	0.61
W4-11-CHNOF	88	atomization energies	OM2 ^b	4.81	OM3 ^b , PM7	6.47–6.51
TAE140	80	atomization energies	OM2 ^b	4.84	OM3 ^b	6.05
TAE_nomMR124	79	reaction energies	OM2 ^b	6.25	OM3 ^b	7.51
BDE99	394	reaction energies	OM2 ^b	8.92	OM3 ^b	9.44
HAT107	19	reaction energies	OM3 ^b	8.32	PM7, OM2 ^b	8.48–8.54
ISOMER20	13	reaction energies	PM7	3.14	OM1	4.02
SN13	480	energies	OM3 ^b	7.17	OM2 ^b	7.94
GMTKN30-CHNOF	25	reaction energies	OM3 ^b , OM1	19.46–19.47	OM2 ^b	22.47
MB08-165	50	atomization energies	OM2 ^b	4.19	OM3 ^b	6.20
W4-08	43	atomization energies	OM2 ^b	4.12	OM3 ^b	5.37
W4-08womMR	15	adiabatic ionization potentials	OM3 ^b	11.45	OM2 ^b	12.00
G2IIP	12	adiabatic electron affinities	OM3 ^b	9.31	OM2 ^b	11.39
G2IEA	8	adiabatic proton affinities	OM1	4.96	OM3 ^b	11.99
PA	5	reaction energies	PM6	4.03	OM3 ^b , OM1	4.31–4.39
SIE11	22	barriers	PM7	6.13	OM2-D2	6.42
BHPERI	54	barriers	OM2 ^b	9.72	OM1	10.39
BH76	22	reaction energies	OM2 ^b	4.29	OM1, OM3 ^b	5.28–5.37
BH76RC	34	reaction energies	AMI	3.55	OM1	3.74
RSE43	6	reaction energies and barriers	PM6	2.03	OM1	4.01
O3ADD6	15	reaction energies	OM3 ^b	4.16	OM2 ^b	8.23
G2RC	34	relative energies	PM7	2.92	PM6	3.46
ISO34	18	relative energies	OM2 ^b	5.31	OM3 ^b	6.05

Table 15. continued

data set	N	properties	first best	MAE	second best	MAE
DC9woC20 ^c	6	relative and reaction energies	PM6	5.18	PM7	8.64
DARC	14	reaction energies	PM6	3.91	OM1	4.10
BSR36	36	reaction energies	OM3	3.46	PM6	7.38
IDISP	6	interaction and reaction energies	OM3	6.19	OM2	7.34
WATER27	27	interaction energies	PM7	5.78	OM3-D2	6.65
S22	22	interaction energies	PM7	0.76	OMx-D3, OMx-D3T	0.91–0.97
ADIM6	6	interaction energies	OM2-D3, OM2-D3T	0.09–0.11	PM7, OM3-D3	0.22–0.26
PCONF	10	relative energies	OM2 ^b , OM3 ^b	1.28–1.33	PM6	3.27
ACONF	15	relative energies	OMx-Dn	0.19–0.31	AM1, PM3, OM1	0.44–0.52
SCONF	17	relative energies	OM3 ^b	1.32	OM2 ^b	1.67
CE345-CHNOF	187	relative energies	OM2 ^b	6.40	OM3 ^b	6.89
MGAE109/11	74	atomization energies	OM2 ^b	4.26	OM3 ^b	4.73
IsoL6/11	6	relative energies	OM2 ^b , PM7	1.99–2.05	PM6	2.41
IP21	4	adiabatic ionization potentials	OM3 ^b	11.91	OM2 ^b	13.24
EA13/03	4	adiabatic electron affinities	OM3 ^b	9.18	OM2 ^b	9.80
PA8/06	4	proton affinities	OM1	4.83	MNDO	11.68
ABDE12	12	dissociation energies	OM2-D2	7.32	OM2-D3, OM3-D3T	7.77–7.78
HC7/11	7	reaction energies	OM3-D3, OM3-D3T	3.20–3.21	OM3-D2	4.35
π TC13	13	relative energies and proton affinities	OM2 ^b	2.54	OM1	2.82
HTBH38/08	26	barriers	OM2 ^b	4.96	OM3 ^b	5.99
NHTBH38/08	23	barriers	OM1	9.60	OM2 ^b	13.64
NCCE31/05	14	interaction energies	OM2-D3, OM2-D3T	1.08–1.11	OM3-D3, OM3-D3T, OM2-D2	1.23–1.26
PDDG	622	heats of formation at 298 K	PM7	3.34	OM2	3.55
	153	bond lengths	all			0.011–0.018
	54	bond angles	all			1.90–2.97
	6	dihedral angles	OM3 ^b	5.74	OM1, OM2 ^b	8.02–8.53
	97	ionization potentials ^d	OM2 ^b	0.37	OM1	0.48
	47	dipole moments	all			0.24–0.32
PM7-CHNOF	1168	heats of formation at 298 K	PM7	3.78	PM6	4.43
	175	bond lengths	all			0.013–0.026
	90	bond angles	all			1.48–2.48
	104	ionization potentials ^d	OM2 ^b	0.33	OM1	0.40
	58	dipole moments	all			0.22–0.34
C7H10O2	6095	atomization enthalpies at 298 K	OM2	6.30	PM7	6.44

^aSubsets are indented. MAEs for energies in kcal/mol, for bond lengths in Å, for angles in degrees; for ionization potentials in eV, and for dipole moments in D. If MAEs differ by less than ca. 0.1 kcal/mol for energies or 0.01 Å for bond lengths, the corresponding methods are listed together. ^bMAE of dispersion-corrected counterpart (OM2-Dn or OM3-Dn) is very close (within 1.0 kcal/mol for energies and within 1.0° for angles) and may actually be slightly lower. ^cWithout the isomerization energy of C_{20j}; see text. ^dCalculated using Koopmans' theorem.

Table 16. Dispersion-Corrected Methods Predicting the Best Interaction Energies (kcal/mol) and Geometries (Distances, Å; Angles, deg) of Noncovalent Complexes^a

data set	N	property	first best	MAE	second best	MAE
A24-CHNOF	21	interaction energies ^{bc}	OMx-Dn	0.43–0.49	PM7	0.64
	23	selected interatomic distances ^d	OM3-D3, OM3-D3T	0.261–0.262	OM3-D2	0.322
	40	selected angles ^d	OM3-D3, OM3-D3T	8.69–8.80	OM2-D3, OM2-D3T	9.86–9.97
S66	66	interaction energies ^c	PM7, OMx-D3, OMx-D3T	0.79–0.85	OMx-D2	1.02–1.05
	172	selected interatomic distances ^d	OM3-D2	0.290	OM3-D3, OM3-D3T	0.317–0.320
	141	selected angles ^d	OM3-D2, OM2-Dn	11.32–12.32	OM3-D3, OM3-D3T	12.99–13.15
S66a8	528	interaction energies ^c	OMx-D3, OMx-D3T	0.60–0.62	all other	0.77–0.80
JSCH-2005-CHNOF	134	interaction energies ^c	OM3-D3, OM3-D3T	1.33–1.37	OM2-D3, OM2-D3T	1.72–1.81
S7L	7	interaction energies ^c	OM3-D3	0.66	OM3-D3T	0.79
	28	selected interatomic distances ^d	PM7	0.325	OM3-Dn	0.389–0.393
S30L-CHNOF	24	interaction energies ^c	OM3-D3T	3.59	OM3-D3	4.36
AF6	6	folding energies ^c	OM2-D2	0.20	OM2-D3T	0.34
	6	folding enthalpies ^c	OM2-D2	0.18	OM2-D3, OM2-D3T	0.34–0.44
	27	selected interatomic distances ^d	PM7	0.090	OM3-D2	0.121
	74	selected angles ^d	OM2-D2	5.17	all other	6.42–7.05

^aOnly the OMx-Dn and PM7 methods are considered here since the other SQC methods do not adequately describe noncovalent interactions. If MAEs differ by less than 0.1 kcal/mol for energies or 0.01 Å for distances or 1.0° for angles, the corresponding methods are listed together. ^bWithout the HF...HF complex; see text. ^cSingle-point calculations on reference geometries. ^dDeviations upon optimization with SQC methods.

relative orientation of the monomers in a complex. The associated minima on the potential energy surface are usually rather extended and flat, and hence the deviations of the SQC results for the geometrical parameters from the *ab initio* reference values are expected to be much larger than in the intramolecular case. Inspection of Table 14 confirms that this is indeed the case: the MAEs are typically of the order of 0.3 Å for the intermolecular distances and 10° for the angles.

The overall statistics in Table 14 for the OMx-Dn methods indicate that the OM3-based results are mostly superior to the OM2-based results, the D3 correction normally performs better than the D2 correction, and the three-center dispersion correction usually has no significant influence on the geometries of the rather small complexes considered here (D3 vs D3T). Hence, we will focus on the OM3-D3 results in the following.

In an overall assessment, OM3-D3 outperforms PM7 for the A24-CHNOF set (MAEs of 0.26 vs 0.38 Å and 8.7 vs 12.9°) and the S66 set (MAEs of 0.32 vs 0.41 Å and 13.2 vs 15.8°), while it shows somewhat larger errors for the S7L set (MAEs of 0.39 vs 0.33 Å) and the AF6 set (MAEs of 0.17 vs 0.09 Å and 7.1 vs 6.6°). OM3-D3 works especially well for the dispersion-dominated complexes in the A24-CHNOF set (MAEs of 0.02 Å and 1.2°).

We now address individual sets and complexes. In the case of the A24-CHNOF set, all SQC methods considered give qualitatively reasonable complex geometries in general (realistic shape and intermolecular distances within ±1 Å of the reference values), except for MNDO which often fails qualitatively and yields much too large intermolecular separations.

A problematic case is the HF dimer: the reference geometry has a linear hydrogen bond (F–H...F), which is also found with PM7 (but much too long) whereas the OMx and OMx-Dn methods give cyclic hydrogen-bonded structures (SI Figure S2). If the angle F–H...F is constrained to the reference value, the HF molecules drift apart upon SQC geometry optimization: the hydrogen bond is too long by 0.16–0.18 Å at OM2 and OM2-Dn, by 0.51–0.56 Å at OM3 and OM3-Dn, and by 1.04–1.05 Å at PM6 and PM7. Thus, when calculations are run

on the reference geometry, the SQC methods either underestimate the binding energy (OM2 and OM2-Dn) or even predict a repulsive interaction (OM3, OM3-Dn, and especially PM6 and PM7; see section 5.1). As discussed previously,⁴² the methane dimer is also problematic: OM3-D3 gives a qualitatively correct geometry, while other SQC methods fail in this regard.

The reference interaction energies are derived in the original work on the A24 set¹²⁴ without accounting for the deformation of the monomers (i.e., from single-point calculations on monomers at the geometry of the respective complex). However, for small monomers such as those in the A24 set, these deformation energies are negligible, and the interaction energies computed with and without them are essentially the same for all tested SQC methods (SI Table S27).

In the S66 set, the OMx-Dn methods again give the lowest MAEs for the distances and angles, but there are some notable outliers, in particular the benzene...AcOH (OH-π), H₂O...MeOH, C₆H₆...MeNH₂, peptide...peptide, and T-shaped pyridine dimer complexes (for their optimized reference and SQC structures see SI Figures S3–S7). The PM7 geometries are reasonable for some of these complexes, presumably due to the inclusion of special H-bond correction terms (see SI Figures S3–S7). Finally, a severe failure of the OM3 and OM3-Dn methods is that they give symmetric structures for carboxylic acid dimers, in which two hydrogen atoms are equidistant to the oxygen atoms in the corresponding hydrogen bonds. This is found for the acetic acid dimer in the S66 set and for the formic acid dimer in the validation of OMx and OMx-Dn methods.⁴² Since the monomer moieties in such dimers are strongly distorted, their interaction energies are strongly overestimated (see SI Table S28 for acetic acid dimer).

In the S7L set, PM7 gives overall the best intermolecular distances; OM3-D3 has slightly smaller errors for the H...H distances. A specific problem is that PM7 optimizes the parallel displaced naphthalene dimer to the sandwich conformation, contrary to OMx-Dn.

In the AF6 set, the overall statistical errors of the PM7 and OMx-Dn methods are rather similar, with slight advantages for PM7. All SQC methods without explicit dispersion corrections

fail qualitatively since MNDO, AM1, PM6, and the OM x methods predict the most favorable conformation to be linear for all alkanes while PM3 predicts the opposite. Only the OM2-D2 and OM3-D n methods give the correct result that the linear conformation dominates for short chain lengths and that the hairpin conformation becomes more favorable for alkanes with 17 ± 1 carbon atoms, in agreement with experiment.¹³⁹

6. CONCLUSIONS

At the end of such a large and diverse benchmark study, it is impossible to provide a single unbiased “grand error estimate” for each SQC method. The chosen benchmark sets strongly differ in their size and in the quality of the reference data, and they address different properties. Thus, instead of attempting to provide such grand error estimates, we summarize the results for all subsets and identify the methods which are best for a given subset/property combination and which are most robust in general. This information can be used as a guide for selecting the SQC method that performs best for applications of the kind considered here.

Tables 15 and 16 present the benchmark results for ground-state properties and noncovalent interactions, respectively; they list the two top-performing methods with their MAEs for all data sets and subsets (as described in Tables 1 and 2).

Most of the entries in Table 15 involve one of the OM x or OM x -D n methods, which appear to perform best overall for the large variety of ground-state molecules and properties considered presently. As a rule of thumb, the OM x and OM x -D n methods can thus be recommended as default for ground-state SQC studies, especially when a specific validation against experimental data or high-level calculations is not feasible. Common organic molecules are also described with good accuracy by PM6 and PM7 because of their extensive parametrization. This indicates that SQC methods with orthogonalization corrections still have a large potential for improvement when larger data sets are used for their parametrization; this is one target of our current research.

The OM x -D n and PM7 methods have similar overall accuracy for noncovalent binding energies and geometries of noncovalent complexes. The OM x -D n methods generally outperform PM7 for dispersion-dominated complexes and mixed electrostatic/dispersion interactions, while PM7 is normally superior for hydrogen-bonded complexes; the latter can be attributed to special hydrogen-bond corrections that are present in PM7 but not in the OM x -D n methods. While it has been shown for water clusters that the description of hydrogen bonds can be improved by a special parametrization of OM x methods,¹⁴⁰ it would seem more promising to target a complete reparametrization at the OM x -D n level that includes noncovalent interaction energies and geometries as reference data.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jctc.5b01047.

Details on converting semiempirical heats of formation at 298 K to ZPVE-exclusive energies at 0 K, extensive tables with numerical results for individual molecules and properties in all data sets covered presently, tables with additional statistical evaluations not included in the main text, figures with error distributions and with reference

and optimized SQC geometries of selected noncovalent complexes (309 pages) (PDF)

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Notes

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NOTE ADDED AFTER ASAP PUBLICATION

This paper was published ASAP on January 29, 2016, with errors in Table 15. The corrected version was reposted on February 2, 2016.