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Theory and range of modern semiempirical molecular orbital methods

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Abstract. Semiempirical molecular orbital methods have a long history. They serve to tackle large systems and complicated processes beyond the reach of ab initio or density functional methods. Although their setup is derived from Hartree–Fock theory, the design of approximate energy expressions and the empirical parameters are used to achieve higher accuracy than the underlying ab initio theory. In this way the effect of larger basis sets or correlation can be partially simulated. All widely used semiempirical methods establish their accuracy by error statistics for molecular properties with experimental and high-level ab initio or density functional theory calculations as a reference. Their computational efficiency makes them suitable for the study of biochemical systems and solid materials. The present review presents a variety of applications which demonstrate the need for and success of semiempirical methods.

Keywords: Semiempirical molecular orbital methods — Semiempirical parameterization — Semiempirical applications

1 Introduction

Semiempirical methods appeared from the 1930s to the 1950s on the π electron level. Most prominent are the famous Hückel method [1] and the Pariser–Parr–Pople method [2, 3]. From the mid-1960s a variety of all-valence electron methods was developed [4, 5, 6, 7, 8, 9]. They have been widely used for the prediction of structural, energetic and spectroscopic properties of molecular and solid-state systems. The development of new semiempirical methods, their improvement and application to larger and more complex systems has continued until now [10, 11, 12, 13].

Owing to advances in computer hardware and software efficiency, the applicability of first-principles methods has been extended to systems with a few hundred atoms. Yet, there is still a need for semiempirical methods for the treatment of problems beyond the capabilities of ab initio or density functional theory (DFT) methods [10]. This is particularly true for large biomolecules with hundreds to thousands of atoms, computer-aided drug design, adsorption studies on complex surfaces, and molecular dynamics simulations at long time scales. In some cases approximate methods have been shown to provide similar accuracy as more sophisticated approaches with a very small fraction of the computational effort [11]. Even if the quantitative accuracy of semiempirical methods is usually limited, they can give insights into qualitative trends that are sometimes lost with more accurate methods [14].

This review gives a brief summary of the basic features of some of the most popular semiempirical methods together with examples of their use in modern chemical, biological and pharmaceutical research, demonstrating their wide range of applicability.

2 Theory

The basic features of semiempirical methods are

1. Explicit treatment of valence electrons.
2. Pseudominimal basis sets.
3. Neglect of three- and four-center integrals.
4. Use of parameterized expressions for two-center integrals.

A few exceptions to these above points exist and are discussed in subsequent sections.

There are basically four types of semiempirical approximations: the extended Hückel theory (EHT) [15, 16], complete neglect of differential overlap (CNDO) [5, 17, 18, 19], intermediate neglect of differential overlap (INDO) [5, 20] and neglect of diatomic differential overlap (NDDO) [5, 17].

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In EHT the basis functions are only used for the calculation of overlap integrals. All other contributions to the Fock matrix elements are based on empirical parameters. The latter three methods use the zero differential overlap (ZDO) approximation to reduce the number of multicenter integrals. In CNDO and INDO methods only two-center electron repulsion integrals of Coulomb type $(\mu\mu|\nu\nu)$ and two-center core–electron attraction integrals $\langle\mu|V_{\mathrm{B}}|\mu\rangle$ are retained. Here μ, ν are atomic orbitals on atoms A and B, and V_{B} is the core potential of atom B. NDDO is an improvement over the INDO approximation, since the ZDO approximation is applied only for orbital pairs centered at different atoms. Consequently, additional types of two-center integrals, $(\mu\mu'|\nu\nu')$ and $\langle\mu|V_{\mathrm{B}}|\mu'\rangle$, are taken into account. Orbitals μ, μ' are centered on atom A and ν, ν' on atom B. In this way not only two-center monopole–monopole interactions are retained, as in INDO, but also higher multipole interactions. In principle the NDDO approximation should describe long-range electrostatic interactions more accurately than INDO.

Due to deficient parameterization the original NDDO method [17] did not represent a significant improvement over the original INDO implementation [20]. A successful INDO implementation was the third version of the modified INDO (MINDO/3) [21]. Shortly afterwards the modified neglect of diatomic overlap (MNDO) method [22] led to improved agreement with experiment. Later, two modifications of MNDO were introduced. The most prominent of these are the Austin model 1 (AM1) by Dewar et al. [23] and the parametric method 3 (PM3) by Stewart [24]. These three methods are included in popular program packages such as Gaussian [25], CERIUS [26], SPARTAN [27] and MOPAC [28].

2.1 MNDO/d, OM1 and OM2

MNDO-type methods use a multipole expansion [22] for the calculation of two-center two-electron integrals $(\mu\mu'|\nu\nu')$ which can be reduced to empirical formulas for two-center Coulomb integrals [29, 30]. This is computationally more efficient than an exact evaluation, for example by the Harris algorithm [31]. The Pauli repulsion which is not included in the CNDO or INDO method has been incorporated into the core–core repulsion V_{nn}. In order to obtain a balance between attractive and repulsive terms, the analytical $1/R_{\mathrm{AB}}$ dependence has been replaced by a Coulomb integral $\gamma_{\mathrm{AB}} = (s_{\mathrm{A}}s_{\mathrm{A}}|s_{\mathrm{B}}s_{\mathrm{B}})$, plus a correction term f_{AB}

$$\begin{aligned} V_{nn} &= \sum_{\mathrm{A}>\mathrm{B}} Z^*_{\mathrm{A}} Z^*_{\mathrm{B}} \gamma_{\mathrm{AB}} + f_{\mathrm{AB}} \\ f_{\mathrm{AB}} &= Z^*_{\mathrm{A}} Z^*_{\mathrm{B}} \gamma_{\mathrm{AB}} \left(e^{-\alpha_{\mathrm{A}} R_{\mathrm{AB}}} + e^{-\alpha_{\mathrm{B}} R_{\mathrm{AB}}}\right) \end{aligned} \tag{1}$$

Z^* is the effective core charge. MNDO was originally developed for first-row elements (H, C, N, O, F) [22]. Later it was extended by Thiel and coworkers to some second-row elements and some elements from higher rows after inclusion of *d* functions (MNDO/d) [32, 33]. At present the elements H, Li–F, Al–Cl, Zn, Ge, Br, Sn, I, Hg and Pb are parameterized.

The one-electron integrals U_μ and $H_{\mu\nu}$ and the core–core repulsion V_{nn} are calculated and parameterized in a similar way as in MINDO/3 [21]. The two–center two–electron integrals $(\mu\mu'|\nu\nu')$ are expanded in multipole–multipole interactions, initially for *s* and *p* functions [22] and later for *d* functions [32]. These interactions are subsequently expanded in semiempirical expressions related to the Klopman approximation. The absolute value of these approximate integrals is considerably smaller than the exact value in the bond region. This has been interpreted as an intrinsic inclusion of electron correlation in the MNDO method [22]. It should finally be pointed out that the zero-point energy is neglected and the binding energy is identified with the heat of formation at room temperature in MNDO and related methods.

The MNDO method has been continually modified and improved by Thiel and coworkers. The most important aspects of these modifications are the use of effective core potentials for the inner orbitals and the inclusion of orthogonalization corrections in a way as it has been suggested and implemented a long time ago in the SINDO1 method (see Sect. 2.3). This led to the two models OM1 and OM2 (orthogonalization model 1 and 2), respectively [11, 34, 35]. These corrections were found to be important for the description of torsion angles in organic compounds.

A modified NDDO method, NDDO-G, was proposed for the calculation of optical spectra [36]. A revised multireference configuration interaction (MRCI) algorithm was incorporated in the OM2 method [37] and applied to calculations of excited state surfaces of all-trans butadiene [38]. The graphical unitary group approach was used in an implementation of a multireference configuration interaction method for use with small active molecular orbital spaces in the OM2 framework [39].

Recently the NDDO approximation was re-examined on the basis of nonempirical frozen-core calculations on small molecules [40]. A nonsystematic variation of the absolute errors in the total energy calculations was found and was attributed to the fact that the core–electron and the electron–electron interactions are not treated in a balanced way in the NDDO approximation. A modification was proposed.

2.2 AM1, PM3 and PM5

In principle MNDO, AM1 and PM3 differ only in the parameterization and in the empirical function f_{AB} in Eq (1). PM5 [41] is a modification of PM3 with an improved parameter set.

Owing to the ZDO approximation the evaluation of molecular integrals is an N^2 process in semiempirical methods as compared with N^3 in DFT and N^4 in Hartree–Fock (HF) theory. The bottleneck for the calculation of larger systems with $N \geq 10000$ electrons is the linear algebra connected with the Hartree–Fock–Roothaan equations

$$\mathbf{F}^\lambda \mathbf{C}^\lambda = \mathbf{C}^\lambda\ \epsilon \tag{2}$$

This involves an N^3 process. λ refers to an orthogonalized basis set. Several methods have been developed to remove this bottleneck. This is particularly important for semiempirical methods, because all other parts involve at most N^2 processes. Stewart et al. [42] proposed a simplified diagonalization procedure for PM3 which is based on the Jacobi method. It still scales with N^3, but is 1 or 2 orders of magnitude faster than conventional diagonalizers, because the rotations are performed only once. A technique based on localized molecular orbitals has been developed by Stewart [43] for biomolecules. The time required for a single self-consistent-field (SCF) calculation can be made almost proportional to the size of the system. It was demonstrated that proteins with several thousand atoms can be optimized. Shortly afterwards Daniels et al. [44] introduced a conjugate-gradient density matrix search procedure for the AM1 treatment of huge polymers. They also used a divide-and-conquer technique which separates a large system into smaller subsystems that can be treated at much lower cost. A technical solution for the problem of large systems is the development of parallelized program codes that can be used on modern parallel computers. Efficient parallel implementations exist for MOPAC [45, 46]. Another group [47, 48] presented a parallel implementation of MNDO, AM1, PM3 and modified versions of these techniques for calculations of large molecular systems.

A variety of modifications of the original methods is now available. AM1 and PM3 have been extended for the treatment of transition metal compounds by inclusion of *d* orbitals in the valence basis [49, 50, 51]. The Green's function technique has been implemented in MNDO–type methods [52] for the calculation of ionization potentials and electron affinities. A parameterized variational technique is used for the calculation of molecular polarizabilities and hyperpolarizabilities within the MNDO, AM1 and PM3 methods [53, 54]. AM1, PM3 and MNDO have been modified by Repasky et al. [55, 56]. In a first approach, a correction scheme based on bond and group equivalents (BGE) was applied to the conversion of semiempirical molecular energies to heats of formation [55]. Using the BGE scheme with standard semiempirical molecular energies, mean absolute errors of calculated heats of formation were reduced for AM1, PM3 and MNDO from 6.6, 4.2 and 8.2 kcal/mol to 2.3, 2.2 and 3.0 kcal/mol, respectively, for a set of 583 neutral molecules containing H, C, N and O. This approach was soon replaced by a more general formalism of the same authors [56]. The core repulsion function V_{nn} of Eq (1) was augmented with up to four weighted pairwise distance directed Gaussian functions (PDDG). After complete reparameterization of the methods, the mean absolute errors in the calculated heats of formation were reduced for PM3 and MNDO from 4.4 and 8.4 kcal/mol to 3.2 and 5.2 kcal/mol, respectively, for 622 neutral molecules containing H, C, N and O. The improvement is less pronounced than for the previous BGE scheme, which is more empirical in nature. The PDDG approach also affects all other molecular properties, such as ionization potentials, bond lengths and angles and dipole moments. The modified methods, PDDG/PM3 and PDDG/MNDO, have also been parameterized for halogens [57]. For 442 halogen-containing molecules, the mean absolute errors in the heats of formation with PDDG/PM3 and PDDG/MNDO are 5.6 and 6.6 kcal/mol, respectively, compared with PM3 (8.1 kcal/mol), AM1 (11.1 kcal/mol) and MNDO (14.0 kcal/mol). However, in a recent comparative study of the energy and geometry of the supramolecular system 2-(2′-hydroxyphenyl)-4-methyloxazole, MNDO was found to generate more reliable geometries than AM1, PM3 or the two recently developed schemes PDDG/MNDO and PDDG/PM3 [58]. The two latter modifications exhibit a large number of short to very short and unphysical H...H intermolecular distances.

A modified AM1/d version with reoptimized phosphorus parameters developed with emphasis on biological phosphate hydrolysis reactions has been reported [59]. In another study the elements P, S and Cl have been reparameterized in AM1 with an emphasis on Mo-containing compounds. An additional set of *d* orbitals in the basis set is used together with two-center core–core parameters rather than the usual Gaussian functions [60].

2.3 SINDO1 and MSINDO

In 1973 Coffey and Jug [61] presented a new formula for the β parameter based on symmetrically orthogonalized orbitals and showed that this method was conceptually and practically superior to the original INDO method in all respects. A few years later [62] it was named symmetrically orthogonalized INDO (SINDO). Shortly afterwards the much improved SINDO1 method [63] was developed for organic compounds of first-row elements. It was later extended to elements of the second and third row [64, 65].

This method has several distinct features. The most important one is that an orthogonalization transformation of the basis functions is taken into account explicitly in solving the Hartree–Fock–Roothaan equations Eq. (2).

$$\boldsymbol{\lambda} = \mathbf{S}^{-1/2}\,\boldsymbol{\chi} \tag{3}$$

$\mathbf{S}^{-1/2}$ can be expanded in a series

$$\mathbf{S} = \mathbf{E} + \boldsymbol{\sigma}$$

$$\mathbf{S}^{-1/2} = \mathbf{E} - \frac{1}{2}\,\boldsymbol{\sigma} + \frac{3}{8}\,\boldsymbol{\sigma}^2 - \frac{5}{16}\,\boldsymbol{\sigma}^3 + \cdots \tag{4}$$

Here $\mathbf{E}$ is the unit matrix and $\boldsymbol{\sigma}$ the remaining two-center overlap matrix. The one–electron integral matrix $\mathbf{H}$ is transformed

$$\mathbf{H}^{\lambda} = \mathbf{S}^{-1/2}\mathbf{H}\mathbf{S}^{-1/2} \tag{5}$$

and the expansion is truncated in such a way that only terms up to second order in the overlap are retained. A discussion of the consequences of finite-order expansion on molecular integrals has been given by Brown and Roby [66]. Another special feature of SINDO1 is the treatment of inner orbitals by a local pseudopotential introduced by Zerner [67]. Two-center one-electron integrals $H^{\lambda}_{\mu\nu}$ are calculated by the following empirical formula:

$$H^{\lambda}_{\mu\nu} = L_{\mu\nu} + \Delta H_{\mu\nu} \qquad \mu \in A,\ \nu \in B. \tag{6}$$

Here L is a correction to the Mulliken approximation for the kinetic energy, and ΔH is entirely empirical and contains adjustable bond parameters. These are optimized in order to minimize the deviation from experiment for a set of reference compounds. Two sets of Slater orbital exponents are used. One (ζ^{U}) for intra-atomic integrals, and the other (ζ) for interatomic integrals. Experimental heats of formation are calculated from binding energies E_{B}, which are corrected by the zero-point energies obtained from vibration analyses. This is theoretically more sound than in MNDO, AM1 and PM3, where binding energies are parameterized directly to reproduce experimental heats of formation without reference to zero-point energies.

Recently a new version MSINDO was developed by substantial modifications in the SINDO1 formalism. The parameterization was initially published for the elements H, C–F, Na–Cl, Sc–Zn, and Ga–Br [68, 69, 70, 71], but now parameters are also available for Li–B and K–Ca [72].

In MSINDO the standard basis set for elements Al–Cl has been changed from $\{3s, 3p\}$ to $\{3s, 3p, 3d\}$ in order to account for hypervalent compounds [68]. For compounds containing Na and Mg an inclusion of $3d$ functions was considered inconsistent, because these atoms already contain $3p$ functions for polarization. Moreover, test calculations showed that the $3d$ functions on these atoms had only insignificant effects on the molecular properties. As for SINDO1 the H basis set can be augmented with a $2p$ shell for the treatment of hydrogen bonds. All Slater–Condon parameters ($F^{0}, G^{1}, F^{2}, \ldots$) are calculated analytically for the one-center two-electron integrals and one–electron integrals U_{μ}. For the higher multipole terms, $G^{1}, F^{2}, \ldots$, this differs from SINDO1, where these terms were taken from experimental spectra. The present procedure is more consistent since all parameters were derived at the same level of theory. To maintain rotational invariance a number of one-center hybrid integrals have to be included in the case of d functions [73]. This was already implemented in SINDO1 and was kept in MSINDO. The core integrals U_{3d} of second- and third-row elements were scaled by a screening potential K_{sc} in order to avoid unrealistically high populations for the $3d$ shell.

$$U'_{3d} = (1 - K_{\mathrm{sc}})U_{3d} \tag{7}$$

For second-row elements a fixed value of $K_{\mathrm{sc}} = 0.15$ is used. For third–row elements U_{3d}, U_{4s}, and U_{4p} were scaled with different screening potentials [71].

The most important change in MSINDO with respect to SINDO1 is a modification of the approximate Löwdin orthogonalization of the basis [68]. Only the first-order terms in overlap are retained in Eq (5). In SINDO1 the expansion was to second order [74]. If only first-order terms are taken into account, no transformation of the two-electron integrals is necessary. The one-electron integrals are transformed:

$$H^{\lambda}_{\mu\mu'} = H^{\lambda}_{\mu\mu'} - f^{\mathrm{B}}\frac{1}{2}\sum_{\mathrm{B}\neq\mathrm{A}}\sum_{\nu}^{\mathrm{B}}\left(L_{\mu\nu'}S_{\nu\mu'} + S_{\mu\nu'}L_{\nu\mu'}\right). \tag{8}$$

The correction factor, f^{B}, accounts for the neglect of higher–order terms in the truncated expansion (Eq. 4). Its value depends on the number of basis functions on atom B. f^{B} is 1 for an $\{s\}$ basis, $\frac{3}{4}$ for an $\{s, p\}$ basis and $\frac{1}{2}$ for an $\{s, p, d\}$ basis.

All semiempirical methods are parameterized for the elements H, C, N, F and O. Here it is possible to compare the statistical errors for some of the more recent methods. In Table 1 the statistics for energetic, structural and electronic properties for first–row elements are compared for MSINDO, MNDO, AM1 and PM3. Apparently there is no significant difference in the average errors for these four methods. It has to be noted that the reference set of MNDO, AM1 and PM3 is almost twice as large as the MSINDO reference set. Complete statistics for all second-row elements Na–Cl have so far only been published for two methods, MSINDO and MNDO/d. These are given in Tables 2 and 3. Both methods perform equally well for the calculation of heats of formation. The agreement with experimental bond lengths seems to be slightly better with MSINDO than with MNDO/d, but as for first-row elements the size of the reference molecule set is considerably larger for MNDO/d, so a direct comparison is hampered. The average errors for both methods are slightly larger for second-row elements compared with first-row ones. This is due to the occurrence of more complex binding situations (ionic complexes, hypervalent compounds) with elements S and Cl. In both semiempirical methods it was necessary to augment the minimal $\{3s, 3p\}$ basis with $3d$ polarization functions to describe these compounds with reasonable accuracy.

Table 1. Mean absolute errors for ground-state properties of first-row elements with the number of values in parentheses [69]. Comparison of MSINDO, MNDO, AM1 and PM3.

	Group	MSINDO		MNDO		AM1		PM3	
$\Delta_{\mathrm{f}}H$ (kcal/mol)	HCNO	5.12	(64)	6.26	(133)	5.52	(133)	4.23	(133)
	F	5.59	(25)	10.51	(43)	6.76	(43)	6.45	(43)
R (Å)	HCNO	0.011	(164)	0.015	(228)	0.017	(228)	0.011	(228)
	F	0.022	(46)	0.037	(124)	0.027	(124)	0.022	(124)
θ (°)	HCNO	1.84	(72)	2.69	(92)	2.01	(92)	2.22	(92)
	F	1.20	(22)	3.04	(68)	3.11	(68)	2.72	(68)
IP (eV)	HCNO	0.44	(67)	0.47	(51)	0.36	(51)	0.43	(51)
	F	0.37	(16)	0.34	(40)	0.54	(40)	0.40	(40)
μ (D)	HCNO	0.34	(32)	0.32	(57)	0.25	(57)	0.27	(57)
	F	0.33	(17)	0.38	(40)	0.31	(40)	0.29	(40)

Table 2. Mean absolute errors for heats of formation (kcal/mol) of second-row elements with the number of values in parentheses [69]. Comparison of MSINDO and MNDO/d.

Element	MSINDO		MNDO/d	
Na	8.37	(13)	7.57	(23)
Mg	5.80	(25)	9.61	(46)
Al	6.76	(16)	4.93	(29)
Si	6.69	(41)	6.33	(84)
P	4.83	(21)	7.62	(43)
S	7.49	(24)	5.57	(99)
Cl	7.13	(37)	3.76	(178)

Table 3. Mean absolute errors for bond lengths R (Å) of second-row elements with the number of values in parentheses [69]. Comparison of MSINDO and MNDO/d.

Element	MSINDO		MNDO/d	
Na	0.051	(12)	0.120	(16)
Mg	0.030	(32)	0.120	(55)
Al	0.031	(13)	0.067	(20)
Si	0.018	(57)	0.047	(68)
P	0.019	(37)	0.048	(58)
S	0.022	(37)	0.040	(77)
Cl	0.037	(45)	0.038	(117)

Until now, no complete error statistics have been published for third–row transition metals Sc–Zn except for SINDO1 [65] and MSINDO [71]. MNDO/d, AM1/d and PM3tm [50, 51] have so far only been parameterized for a small number of transition elements.

The main group elements of the third row have been parameterized in a way similar to the transition metals [70]. A $\{4s, 4p\}$ valence basis has been given to K and Ca, while a set of 4d polarization functions has been added to the basis set of Ga–Br. As for the second-row elements Al–Cl this should improve the results for hypervalent compounds. For most elements the average deviation from experiment is comparable or slightly smaller with MSINDO as compared to that with AM1 [75, 76, 77], PM3 [78], and MNDO/d [32].

In order to better describe long–range interactions, in particular at surfaces, dipole–monopole and dipole–dipole terms were added to the MSINDO formalism following an early suggestion by Voigt [79]. The radial part of the two–center integrals has been taken from Dewar and Thiel [80]. After modification of the formalism a complete reparameterization of all elements had to be performed. The new version, called MSINDO+, was tested for some cases where SINDO1 and MSINDO gave results in disagreement with experiment. One example is the surface structure of MgO. In MSINDO studies [81, 82] the MgO(001) surface structure has been studied with embedded cluster and cyclic cluster models (CCM). The surface relaxation obtained is in agreement with recent experiments, but the calculated rumpling is negative, while the experimental value is positive. Earlier attempts to improve this MSINDO result by modifying the parameters failed. It was concluded that dipole–dipole interactions are responsible for the outward movement of first-layer O atoms from the surface. This is confirmed by an improved agreement of the modified MSINDO+ version for both structure parameters δd_{12} and Δ_1 with experiment [72]. It is expected that the modified version will give a generally improved description of intermolecular interactions.

2.4 ZINDO

ZINDO is a program package developed by the group of Zerner [83]. It contains a variety of semiempirical programs, among them INDO/1 and INDO/S. Whereas INDO/1 can be used to obtain geometries, INDO/S was designed for the calculation of electronic spectra of organic molecules and complexes containing transition metals. The latter model was calibrated at the configuration interaction with single excitations (CIS) level for energy differences with fixed geometries. The latter were taken from experiment. No attempts were made to optimize geometries or total ground-state energies in this model.

ZINDO starts from the original INDO Fock matrix terms together with an analytic expression for the core–core repulsion V_{nn}. Special attention has been given to the calculation of one-center two-electron integrals from Slater–Condon factors F and G and the evaluation of $U_{\mu\mu}$ from experimental ionization energies [84]. For example, the ionization process that removes an s electron of an atom with an $\{s^l p^m d^n\}$ electronic configuration can be expressed in terms of $U_{\mu\mu}$, F and G:

$$\begin{aligned} I_s &= E(s^{l-1}p^m d^n) - E(s^l p^m d^n) \\ &= -U_{ss} - (l-1)F^0_{ss} - m\left[F^0_{sp} - \frac{1}{6}G^1_{sp}\right] \\ &\quad - n\left[F^0_{sd} - \frac{1}{10}G^2_{sd}\right]. \end{aligned} \tag{9}$$

The one-center Coulomb integrals $(\mu\mu|\mu'\mu') = F^0_{\mu\mu'}$ are calculated analytically while the G integrals are taken as parameters. The ionization potentials I are taken from atomic spectra. After rearranging Eq. (9) the U_{ss} are obtained. A special feature of ZINDO is the use of distance-dependent Slater exponents ζ for the calculation of two-center integrals [84].

$$\begin{aligned} \zeta(R) &= a + b/R \qquad \text{for } \zeta(R) < \zeta(0) \\ \zeta(R) &= \zeta(0) \qquad \text{elsewhere} \end{aligned} \tag{10}$$

This procedure mimics to some extent the use of multiple–zeta basis sets in high–quality ab initio calculations. Later also charge–dependent orbital exponents that are more flexible with respect to the chemical environment were implemented in INDO/S [85]. For transition metal atoms, one-center hybrid integrals of the form $(\mu\mu'|\mu''\mu''')$ are taken into account which do not appear in the original INDO method. They are necessary to maintain rotational invariance [64, 73], if d orbitals are involved.

For the two-center one-electron integrals a conventional INDO formalism is applied. There are two sets of optimized parameters for ZINDO. One set was optimized for molecular geometries, and the other one for electronic spectra. So in principle two successive ZINDO calculations would be necessary: a geometry optimization with the first parameter set, and then a calculation of spectroscopic properties at fixed geometry with the second parameter set. Since it is known that the ZINDO geometries are not very accurate, usually experimental data or another semiempirical method is used for the structure optimization. Recently, a modification of the original INDO/1 method has been introduced [86] and an improvement in the structure determination of a number of small molecules was reported.

Other recent developments are the inclusion of the local spin formalism within the Heisenberg spin model [87], and the extension to the calculation of Rydberg states by adding a shell of diffuse orbitals at a single center on the molecule [88]. New integral approximations were introduced to take into account that a Rydberg orbital has a much greater radial extent than the valence basis functions and to allow mixing between the valence and Rydberg excited states.

From the original limitations of the method, which were discussed by Zerner [9], the Rydberg orbital problem seems to be removed. Others included the problems with higher excitations due to the lack of double and triple excitations. It was also observed that double excitations improve results, whereas triple excitations usually destroy them, in contrast to ab initio calculations. Oscillator strengths of the more intense bands were overestimated by a factor of 2 or 3, which is typical for CIS calculations. INDO/S can accurately predict low-lying π–π^* bands and n–π^* bands for molecules with hydrogen and first- and second-row elements except for compounds containing oxygen. The d–d* spectrum of transition metal complexes is accurately given.

2.5 Hybrid methods

Hybrid methods are usually combinations of quantum mechanical (QM) methods and molecular mechanics (MM) methods. The essential inner part of a system is studied with the more accurate QM method and the outer part with the MM method. The latter provides an embedding for the inner part. This allows the study of large systems with more than 1000 atoms. This is particularly true if the QM method is a semiempirical method. Bakowies and Thiel [89] described the implementation of models for MNDO-type wavefunctions and MM3 force fields. Their applications included protonations, deprotonations, hydride transfer reactions, nucleophilic additions and nucleophilic ring cleavage reactions. Antes and Thiel [90] derived semiempirical connection atom parameters for MNDO, AM1 and PM1 for the simulation of the geometric and electronic properties of a methyl group in the sense of a united pseudoatom. In a study of triosephosphate isomerase [91] it was demonstrated that the extension of the QM region at the expense of the MM region affects the results and causes structural changes. Semiglobal potential energy surfaces of reactive systems were generated by a combination of MM force fields, ab initio electronic structure calculations, DFT, and semiempirical molecular orbital theory [92]. For the calculation of rate constants of enzyme-catalyzed reactions the potential energy surface has been modeled by a combined generalized hybrid orbital/QM/MM/semiempirical valence bond method [93]. A hybrid approach that treats the active part of large reactive systems with a high-level QM approach and the environment with AM1 has been presented by Cui et al. [94].

A multilevel treatment of transition metal containing organic compounds based on NDDO and DFT methods has been proposed and applied to histidine and porphyrin complexes [95]. The semiempirical methods were reparameterized for the transition metals using genetic algorithms. The importance of a correct partitioning of the organic substrate was stressed.

2.6 Other methods

The semiempirical method semi-ab initio model 1 (SAM1) by Dewar et al. [96] is based on AM1. The two-electron integrals $(\mu\mu'|\nu\nu')$ are calculated analytically over Gaussian-type functions, and scaled empirically. Up to the present, no comprehensive list of SAM1 parameters and error statistics is available [11]. A comparison between AM1 and SAM1 for the calculation of vibrational frequencies was carried out for 41 organic molecules by Holder and Dennington [97]. Both methods showed reasonable agreement with the experimental values, and SAM1 performed slightly better than AM1.

Another semiempirical method with the acronym SINDO, but with completely different features from those described in Sect. 2.3, was developed by Golebiewski et al. [98] some time ago, but was later not rigorously improved.

The capabilities of semiempirical methods for the treatment of chemical reactions were assessed as long ago as 1980 [99]. A discussion of problems and features of current semiempirical molecular orbital techniques and a test of some of the approximations and assumptions used appeared recently [100]. There the importance of orthogonalization corrections, effective core potentials and an implicit dispersion term was outlined. The inadequacy of the Gaussian potentials added to the core–core terms in AM1 and the PM*n* methods for the description of hydrogen bonding was pointed out.

3 Range

The following subsections will present a selection of applications of the most frequently used semiempirical methods MNDO and MNDO/d, AM1, PM3/PM5, MSINDO (or SINDO1), INDO/S (or ZINDO), and SAM1, and adaptations of these methods for problems in current chemistry, biochemistry and pharmacology. This choice cannot be expected to be complete, given the fact that every year several hundred studies are published in this area.

3.1 Organic and biochemical systems

Several reviews about the use of semiempirical methods in the field of organic chemistry, biochemistry and pharmacology are available [11, 12, 101, 102, 103].

3.1.1 MNDO/d

MNDO/d and the more recent orthogonalization models OM1 and OM2 have been used for the structure optimization of large organic molecules, in particular where high accuracy is required for the description of weak interactions that determine the conformation of long carbon chains. Some of the most recent applications are a conformation analysis of cyclic ADP–ribose in connection with an experimental NMR study [104], the binding of methylguanidinium to a methylphosphate entity in a combined ab initio and semiempirical model study of the thymidylate synthase G52S mutation [105] and the potential surface for the approach of the carcinogen *N*-2-acetylamino-fluorene to the carbon $C_{(8)}$ of deoxyguanosine [106]. A comparison between the new MNDO versions OM1 and OM2 with AM1 and PM3 for the secondary structure in peptides and proteins showed [107] that the description of the peptide conformers is considerably improved by OM1 and OM2 compared with AM1 and PM3, although in some cases there still were discrepancies with available ab initio data. MNDO-PSDCI molecular orbital theory has recently been used to calculate the spectroscopic properties of sensory rhodopsin from *Natronobacterium pharaonis* [108].

3.1.2 AM1, PM3 and PM5

The application of semiempirical methods in organic chemistry and molecular biology can be classified in three categories: structure determination, electronic properties and reaction energies. A detailed knowledge of the molecular structure is a necessary prerequisite for subsequent studies of reactivity, for example, in computer-aided drug design. The electron density can be used as basis for the parameterization of simple electrostatic field methods. In particular AM1 is widely applied to the structure determination and electronic structure calculation of large and very large organic molecules. Some of the most impressive calculations in this field are on a 19995-atom polymer of glycine and a 6304-atom RNA molecule [52], where the Millam–Scuseria conjugate-gradient density matrix search was applied instead of conventional matrix diagonalization.

A recent example of structure determination at the semiempirical level is the study of the conformational flexibility of the ibuprofen molecule with AM1 in combination with crystallography database searching [109]. A conformation analysis of anhydrotetracycline (AHT), a toxic decomposition product of the widely used antibiotic tetracycline, was also performed with AM1 [110]. The results were used to explain the toxic effects of the anhydride. The interaction of AHT with aluminum was studied with AM1 and HF and good agreement of semiempirical and ab initio reaction energetics was observed [111]. The toxic equivalence factors of polycyclic aromatic hydrocarbons were investigated in a combined AM1 and PM3 study [112]. Modern semiempirical methods can reproduce structure parameters obtained with ab initio techniques. This has been shown in a comparative study on the structure of α- and β- galactose [113]. In this study AM1 yielded best agreement with a RHF/6-31G* reference calculation.

A modification of the Broyden–Fletcher–Goldfarb–Shanno procedure was used for a PM3 calculation of the small protein crambin with more than 700 atoms [114]. PM3 has been modified for geometry optimization of large organic molecules as exemplified for a 1226-atom plasminogen [115]. The original PM3 method is frequently used for smaller molecules, for example, in a combined experimental and theoretical study of epibatidine analogues and their positional isomers [116, 117], or more recently for a study of Schiff base ligands [118]. The complexation of H^+, Li^+, Ca^{2+} and Ba^{2+} cations by a Schiff base of gossypol with *n*-butylamine was studied with the new PM5 method [119]. PM5 is used in the field of organic chemistry, in many cases for the calculation of reaction energies. One recent example is a study on the relation between the reactivity of phenylazonaphthol sulfonates and azo-hydrazone tautomerism [120]. PM5 was also used to optimize structures of magnesium–bacteriochlorine, magnesium–chlorine, magnesium–porphine, mesochlorophyll a, chlorophylls a, b, c(1), c(2), c(3) and d, and bacteriochlorophylls a, b, c, d, e, f, g and h with all homologous structures [121]. The tautomerism of another class of compounds, N-substituted benzohydroxamic acids and their anions, was investigated with AM1 [122] in order to estimate the pK_a values of these molecules. Even with semiempirical methods, a full geometry optimization of DNA molecules is not feasible with present computer power. But there are a number of semiempirical studies on DNA fragments. Examples are PM3 studies of DNA binding sites of the *Escherichia coli* DNA-binding protein OmpR [123] and of the geometry of short double helices composed of nucleotides [124]. Recently, the electronic structure of a mutagene, chloroimide 3,3-dichloro-4-(dichloromethylene)-2,5-pyrrolidinedione, has been calculated for correlation with its known bacterial mutagenicity value [125].

The computational efficiency of semiempirical methods enables the study of a series of molecules in a reasonable amount of time. An important application is the development of quantitative structure–activity relationships (QSAR). As an example, the molecular electron density calculated with AM1 has been used to obtain QSAR for a series of substituted amines, benzoic acids and other bioactive substances [126, 127]. For a reliable modeling of biomolecules the accuracy of calculated dipole moments and electrostatic potentials of the consistent molecular subunits is important. For a set of 71 simple dye molecules a comparison of calculated dipole moments with AM1, PM3, INDO/S, CNDO/S, DFT and CISD was performed [128]. It was reported that AM1 and PM3 modified with an empirical correction procedure yield dipole moments at the same level of accuracy as ab initio or DFT methods. However, in an analysis of the accuracy of AM1 and PM3 for the calculation of molecular electrostatic potentials and dipole moments of natural amino acids it was concluded that these methods do not yield sufficiently accurate results compared with ab initio or DFT methods [129].

PM3 is used in drug design, for example, in a study on the effect of dinitro–substitution on the methylation reaction of catechol and endogeneous catechol derivates catalyzed by catechol *O*-methyltransferase [130]. The oxidation decomposition of 2,4,6-tri-tert-butylphenol and of related compounds was investigated with PM3 in order to study the cytotoxic activity of these compounds [131]. Owing to its applicability to large organic systems, PM3 can also be used to examine the reliability of QM/MM hybrid methods, for example, in calculations of the hydride ion transfer reaction of the enzyme dihydrofolate reductase [132]. A PM3 study of the interactions of a collagen-like peptide with polyphenolics important in leather chemistry [133] serves to demonstrate the wide range of semiempirical applications in modern chemistry. Finally, the variation of the band gap in peptide α-helices has been studied with AM1 on the singles CI level [134].

3.1.3 SINDO1 and MSINDO

SINDO1 has been comprehensively applied to excited states and photochemical reaction mechanisms of organic systems with an emphasis on aromatic and antiaromatic molecules. A selection of this work will be presented. After it became clear that the optimization of excited states of aromatic systems on CI surfaces is feasible and resulted in nonplanar rings [135], it seemed challenging to study photoprocesses. One such process is the photoisomerization and photofragmentation of cyclopentanone [136], where photoexcitation could lead to three different products. The excitation and subsequent nonradiative decay via diabatic crossing of states could be explained by state diagrams along particular reaction coordinates. Other studies on diazirines [137], methylfuran [138], di-π-methane [139], cyanopyrrole [140], thiophenes [141], tetramethylene sulfide [142] and tetramethylene sulfoxide [143] followed. All these studies showed that schemes designed for such reactions by organic chemists are insufficient for an explanation. Rather it could be shown that such mechanisms are more complicated and involve many intermediates and transition structures. A complementary study in this line [144] showed that the so–called adiabatic reactions are exceptions with a low percentage of occurence.

A new line of work was started shortly afterwards which was concerned with the synthesis of antiaromatic compounds via photochemical processes. The idea was that antiaromatic compounds would become more aromatic in some excited states and therefore more amenable. In this way the mechanism of the photochemical formation of cyclobutadiene [145] and azacyclobutadiene [146, 147] could be explained via excited state diagrams via detailed reaction pathways. A new pathway for the formation of pentalene [148] was proposed. A complementary study on the cycloaddition of ethylene to benzene [149] concluded this work.

Newer work with MSINDO gave results of similar or even better quality than NDDO–type methods for spectra of organic systems such as amines [150].

3.1.4 ZINDO

As mentioned before, the strength of the ZINDO package is the accurate calculation of optical spectra; therefore most applications make use of this feature. Some of the most recent examples of INDO/S calculations are given here.

The spectroscopy of 4-hydroxy-1-methylstilbazolium betaine including solvent effects was studied with INDO/S and good agreement with experimental data in water and methanol was obtained [151]. A theoretical model for the active site of an enzyme (*Azotobacter vinelandii*) FeMo cofactor for the fixation of nitrogen has been investigated by Stavrev and Zerner [152]. A small subsystem of the cofactor with the Fe and Mo atoms was selected for ZINDO and DFT calculations of possible reaction pathways. The electronic excitations in monomers and aggregates of bacteriochlorophylls were calculated by means of INDO/S-CI calculations [153] as a model for photosynthetic processes in organisms and the results were generalized by means of an effective Hamilton operator. ZINDO and HF theory were used in a study of electronic properties of the DNA base guanine [154]. Emphasis was given to the sequence–specific regions of lowest ionization potentials that were calculated using Koopmans' theorem. The structures, stabilities and electronic spectra of the heterofullerenes $C_{59}N$ and $C_{69}N$ and the formation of dimers with N–N bonds were examined with INDO/S [155]. An example of the strength of INDO/S for the calculation of optical spectra is given where spectroscopic redshifts due to dissolution of benzene in liquid cyclohexane are obtained in excellent agreement with the experimentally observed shifts [156]. The static and dynamic polarizability, α, the first hyperpolarizability, β, and the second hyperpolarizability, γ, of substituted (*M*)-tetrathia-[7]-helicenes were studied with ZINDO and DFT methods [157].

Electronic spectra of organic compounds were calculated by a modified ZINDO version where the two-center integrals were approximated by a parametric function [158]. The proposed modification significantly improved the calculated wavelengths of linear polyenes and of polycyclic aromatic hydrocarbons [159].

3.1.5 SAM1

This method is intended to bridge the gap between semiempirical and ab initio methods. For this reason it was used in comparative studies of energetic and structural properties together with ab initio and DFT methods. The number of SAM1 applications is small compared with those of AM1, PM3 and INDO/S. Some typical recent examples are given in this section.

Three systems of isomeric fullerenes, C_{88}, C_{36} and C_{72}, were optimized at semiempirical SAM1 and ab initio levels [160], and the calculated structural data are related to observed data. A combined DFT and SAM1 study was performed to describe the interaction between nitric oxide and the active site of ferric cytochrome P450 [161]. Reactions of the same system, cytochrome P450, with alkanes were studied with SAM1 using a model system consisting of unsubstituted porphyrin, iron and methylthiolate [162]. SAM1 was also used to calculate optimized structures and complexation enthalpies for a variety of organic ligands to a methyl diester protoporphyrin IX complex as a model system for examining cytochrome P450 Fe-binding inhibitors [163]. Finally, the reaction path for nitric oxide reduction in nitric oxide reductase was investigated with SAM1 using an active site model consisting of nonresidue porphyrin, iron and methylthiolate [164].

3.2 Combinations of methods

Since the methods MNDO, AM1 and PM3 are available together in several program packages (e.g., MOPAC, Gaussian, SPARTAN), they are frequently used together in combined and comparative studies. An important issue in the theoretical treatment of biomolecules and the reactivity of enzymes is intramolecular and intermolecular hydrogen-bonding interaction. The hydrogen-bonding interactions calculated with AM1, PM3 and SAM1 were compared with accurate ab initio results and experiments [165]. It was found that AM1 performs better than the other two methods, but still is not satisfactory for O–H···O interactions. A similar comparison of the same methods was performed for the normal modes in several local anesthetics of amino–ester type [166]. MOPAC calculations were used in a computer–aided conformational analysis in order to characterize the pharmacophore for the intestinal peptide carrier [167]. The gastrin CCK antagonist activity of 67 benzodiazepines was studied by molecular modeling using MOPAC [168]. Conformationally constrained analogues of the potent muscarinic agonist 3-(4-(methylthio)-1,2,5-thiadiazol-3-yl)-1,2,5,6-tetrahydro-1- methylpyridine (methylthio-TZTP, 17) were designed and synthesized in a combined experimental and theoretical study using MOPAC 6.0 [169]. The AMPAC program package was used to obtain QSAR in dental monomers that influence their mutagenicity [170]. AM1, PM3 and MNDO electrostatic-potential-derived atomic charges were compared in correlations with solvatochromic hydrogen-bonding acidity for QSAR studies [171]. Here best correlation was obtained with the AM1 and MNDO methods. A theoretical investigation into the possibility of designing bioreductive analogues of cyclophosphamides as anticancer drugs was undertaken with AM1 and PM3 as included in MOPAC93 [172], and gave results in agreement with experiment. These methods were also used to calculate molecular vibration modes as a basis for a three-dimensional QSAR using the eigenvalue analysis paradigm applied to 41 HIV-1 integrase inhibitors [173].

An example for a combination of different semiempirical methods is the investigation of structural, electronic and spectroscopic properties of all-trans and 1,3-cis retinoic aldehydes [174]. The absorption spectra of these molecules were calculated with ZINDO with geometries fully optimized by the PM3/CI method.

3.3 Solvent effects

A good account of solvation models in connection with semiempirical methods is given by Cramer and Truhlar [175, 176]. These authors contributed the SMx ($x = 1$–5) series of solvation models [177, 178, 179, 180, 181]. Their models rely on the suitable definition of atomic partial charges. They are based on generalized Born electrostatics augmented by first-hydration-shell effects. They were linked to the AM1 and PM3 methods. There is a wealth of applications for compounds containing H, C, N, O, F, S, Cl, Br and I atoms [182, 183]. The SM5.4 solvation model was extended to calculate free energies in almost any organic solvent. The model was developed with an input of 1786 experimental solvation free energies for 206 solutes in one or more of 90 solvents [184]. Other widely used continuum models based on electrostatics only are the polarizable continuum model (PCM) [185] and the conductor-like screening model (COSMO) [186].

Henry's law constants for triazine-derived herbicides were calculated using quantum chemical solvation models SM2 and SM3 based on PM3 [187]. Surprisingly the agreement between the semiempirical results and experiment was better than for those values obtained with DFT methods. The dipole moment of α-chymotrypsin at pH 7.0 was computed with the PM5/COSMO method [188]. The value of 492 D obtained compared well with experiments. However, when explicit solvent models were used, the magnitude of the calculated dipole was dependent upon the number of discrete water molecules added to the protein.

AM1 CI calculations with a continuum solvent treatment have been used to investigate the geometry of two nearly isoenergetic stereoisomers of phenothiazine–pyrene dyads and to calculate the properties of their excited Franck–Condon states [189].

The intermolecular interaction energies between solvent molecules and a polymer were simulated for the polystyrene and methylcyclohexane system using ethylbenzene as a model compound for the repeating unit of the polymer [190]. The mechanism of polymerization reactions of tetramethylenes and trimethylenes via diradicals or zwitterions could be clarified by SINDO1 combined with the PCM [191]. Another important study identified the most favorable interaction sites of magnesium ions with tetracycline in aqueous solution with AM1 and the COSMO continuum solvent model in a systematic surface scan [192].

3.4 Nanoparticles

Among the nanoparticles the fullerenes are the most prominent. Structure determination of fullerenes of different symmetry groups [193] was extended to systems with 960 atoms [194]. Nowadays even more complicated problems are attacked. Structural, energetic and spectroscopic properties of C_{78} isomers, various $C_{60}F_{36}$ species, the complete set of 134 isolated-pentagon-rule isomers of C_{94}, and of 259 isolated-pentagon-rule isomers of C_{98} were described with MNDO, AM1, PM3 and SAM1 [195,196,197,198]. MNDO, AM1 and PM3 calculations were performed to estimate the bowl-to-bowl inversion barriers and equilibrium geometries for 15 buckybowl molecules, including corannulene, sumanene, canastanes and semibuckminsterfullerenes [199]. The mechanism of carbon nanotube fracture was studied with MSINDO and PM3 [200]. A proposed mechanism based on empirical potentials involves an aggregation of Stone–Wales defects followed by a ring–opening step whereby a bond between two five-membered rings is weakened. The semiempirical studies instead predict that this bond is a particularly strong one, and that the weak bonds lie within the pentagons. Semiempirical MNDO, AM1 and PM3 calculations of relative energies and nucleus–independent chemical shifts were reported for 153 fullerene isomers in an attempt to assess the reliability of these methods through comparisons with ab initio and density functional results [201]. AM1 and OM2 calculations were combined with ^{1}H–NMR spectroscopy in a study of optically active adducts of C_{60} with bis-malonates [202].

An iterative genetic optimization procedure for both cluster structures and empirical parameters of AM1 has been presented and applied to the Si_6H_2 and Si_6H_6 clusters [203]. The training set for the AM1 parameters was formed by results from ab initio calculations.

A systematic theoretical study on the equilibrium geometries, harmonic vibrational frequency analyses, enthalpies of formations and electronic properties of Si_n ($n = 26$–$36,60$) cages was performed using AM1 [204]. A growth pattern of hybridosilsesquioxanes $Si_nO_{3n/2}H_n$ was proposed [205] analogous to the fullerene growth and the structure of such precursors of nanotubes with up to 840 atoms was determined with MSINDO [206]. The growth mechanism was clarified via classical [207] and nonclassical [208] multistep processes.

3.5 Solids and Surfaces

3.5.1 Solids

The simulation of solids can be achieved in various ways. Starting from the molecular approach free clusters of large size are suitable. In this way SINDO1 calculations of NaCl and MgO clusters [209] with up to 800 atoms showed a quasilinear dependence of the binding energy and bond distances on the relative average coordination number of the cluster. An extrapolation to the bulk was therefore feasible. Cluster simulations of the bulk properties of the stoichiometric rutile showed a similar trend [210]. To avoid the large size of clusters an embedding procedure for the cluster calculation of ionic crystals was proposed [211] which improved the relative order of intralayer and interlayer TiO distances. However, since an embedding procedure cannot restore the full equivalence of atoms in a periodic crystal, a cyclic cluster model is superior. Such a model was implemented on the INDO level [212]. This model was improved for ionic systems [82] and implemented in MSINDO. It was found that for noncubic lattices, long-range effects had to be taken into account [213].

In another INDO method [214] the large unit cell (LUC) model was implemented. The lattice energies of α- and β-oxalic acid have been calculated as the sum of the semiempirically calculated intermolecular dispersion, induction, repulsion and electrostatic energy obtained with a modified MINDO/3 version [215]. A molecular theory to determine thermodynamic properties of isotropic and nematic phases of liquid crystals has been proposed, based on a convex pegmodel and PM3 calculations [216]. Periodic INDO calculations using the CCM were employed to study the structural and electronic properties of the fluorine intercalated graphite compound $(C_2F)_n$ [217].

The spectroscopic properties and lattice relaxation of $KNbO_3$, $KTaO_3$ and $BaTiO_3$ crystals were studied at the INDO level using the LUC model [218]. The effect of crystal packing on the electronic structure of organic molecules was modeled by incorporation of the external electrostatic potential into the Hamiltonian within the ZINDO formalism [219].

3.5.2 Surfaces

The studies in the previous subsection are useful also for the simulation of surfaces and adsorption processes. A review on such questions and the modeling of surfaces for some ionic systems was given several years ago [220]. The free cluster approach was used for the adsorption of water on rutile and anatase surfaces with SINDO1 [221]. The adsorption of CO, CO_2 and H_2O on NaCl and MgO was compared on the basis of free cluster models [222]. A sequence of MSINDO studies was concerned with the adsorption of NO, NH_3 and H_2O on TiO_2 [223] and V_2O_5/TiO_2 [224] and with the reaction mechanism of the selective catalytic reduction of NO with NH_3 and O_2 to N_2 and H_2O on V_2O_5/TiO_2 [225]. The latter involves 24 steps. Embedded clusters were chosen for the study of adsorption of water on Cr_2O_3 [226]. The surface relaxation of MgO (100) [81] was studied with the same model. An MSINDO adsorption study of Cu cluster with up to 52 atoms on the MgO (100) surface simulated by a three–layer cluster of 192 atoms [227] demonstrates the versatility of this line of work.

Besides the MSINDO and SINDO studies described previously, there are some other semiempirical investigations on surface properties and adsorption. The modified INDO version of Stefanovich et al. [214] was applied to adsorption studies of organic molecules at the rutile (110) and anatase (101) surfaces [228, 229]. The surfaces were modeled with the LUC model. A special parameterization of carbon and nitrogen was necessary to improve INDO results for bi–isonicotinic acid adsorption on rutile (110) [228] as a prototype system for solar cells. Later the adsorption of the same molecule on the anatase (101) surface was studied [229]. Other semiempirical studies make use of molecular clusters as models for surfaces, a technique that is also frequently applied in ab initio and DFT studies. A modified MINDO/3 version, MINDO/3-HB, was used in an investigation of different synthesis routes of zinc phosphates [230] and the adsorption of CO on the Lewis acid sites. Small clusters of 8–46 atoms were used to model the Cu (110) surface [231]. The adsorption of a formate ion, CO and acetate on Cu (110) was studied with SAM1, B3LYP and HF. Close agreement between SAM1 and B3LYP was observed for adsorption geometries, whereas calculated vibration frequencies showed larger deviations. An example of a combined QM/MM approach is the study of HCl adsorption on an ice surface [232]. A modified PM3 version with system-specific parameters, PM3-SSP, was used to describe the central adsorption region with the HCl molecule and 21 surface water molecules. This arrangement was embedded in a periodic water slab where the molecules are described with a classical force field. It was found that HCl dissociation strongly depends on the number and the positions of dangling surface hydrogens.

3.6 *Molecular dynamics*

The high computational efficiency of semiempirical methods has made them attractive for molecular dynamics simulations where a large number of SCF and force calculations have to be performed. A comparison of semiempirical, HF, DFT and classical approaches for molecular dynamics simulations was recently given [233].

A method for direct dynamics calculations of unimolecular and bimolecular rate constants of gas-phase chemical reactions involving atoms, diatomic or polyatomic species was introduced by Hu et al. [234]. All semiempirical methods available in MOPAC, in particular MINDO/3, MNDO, AM1 and PM3, were employed to calculate the potential, gradient or Hessian, as required at various steps of the dynamics calculations. MNDO, AM1 and PM3 were used in direct dynamics calculations to describe the product energy partitioning for formaldehyde dissociation into hydrogen and carbon monoxide [235]. Trajectory results with system-specific reparameterized NDDO Hamiltonians, however, were in poor agreement with the experimental product energy partitioning. The photodissociation of ClOOCl has been investigated with a modified MNDO/d version and direct semiclassical dynamics simulations [236]. A direct dynamics approach for the semiclassical simulation of photochemical reactions in the condensed phase was implemented in MOPAC [237]. Semiempirical NDDO calculations with fractional orbital occupation numbers were employed to describe excited states. The environment was approximated with a classical force field.

The defect formation and migration in small clusters of water molecules containing one or more defects in hydrogen bonding was studied with direct molecular dynamics simulations using PM3 [238]. The PM3 method was reparameterized in order to construct a reliable potential energy surface in a molecular dynamics investigation of the intramolecular proton transfer in malonaldehyde [239].

The Born–Oppenheimer molecular dynamics has recently been implemented in MSINDO [240]. In this implementation the velocity Verlet algorithm is used for the integration of the equation of motion. Simulated annealing has been used for the study of various isomers of the Si_{45} and Si_{60} clusters [240]. A new compact network structure was found which is stabler than a fullerene–like structure for Si_{60}. This is in agreement with DFT calculations. The melting behavior of the Si_7 cluster was investigated and good agreement with experiment was obtained for the calculated melting temperature [240].

The $O(^3P) + C_2H_6$ reaction has been studied with stationary CCSD(T)/cc-pVTZ and MSINDO and B3LYP/6-31G* direct dynamics calculations [241]. It was found that with MSINDO the errors of the calculated reaction energies are reduced by not less than 50 % compared with those obtained by earlier PM3 calculations. A similar improvement was found for the activation barriers. A similar trend was found in a comparative B3LYP, MSINDO and PM3 study of the dynamics of the $O(^3P) + CH_4$ reaction [242]. It was concluded that MSINDO results compare well with more accurate B3LYP/6-31G* calculations, noticeably improved over PM3 for most of the dynamics properties studied. The reactions of $O(^3P)$ with CH_4, CH_3CH_3 and $CH_3CH_2CH_3$ at center-of-mass collision energies in the range 2.8 – 3.9 eV were investigated with crossed–beams experiments and with MSINDO direct dynamics calculations [243]. The experiments and calculations both provide evidence for previously unobserved reaction pathways which principally lead to O atom addition and subsequent H atom elimination or C–C bond breaking: $O(^3P) + RH \rightarrow RO + H$ or $R'O + R''$.

4 Concluding remarks

The development of semiempirical methods and their extension to a growing number of research areas has been a continuous process over the last 4 decades and there is apparently no end to be seen. This is demonstrated by the large number of semiempirical studies in organic, inorganic and physical chemistry, biochemistry, drug design, crystallography and surface science. The present review gives an overview on these activities. A selection of representative studies was discussed in order to illustrate how semiempirical methods are applied to current chemical problems. The accuracy of traditional semiempirical methods has been continuously improved. New methods with special features have been developed. Hybrid approaches combining ab initio or density functional and semiempirical approaches have been introduced for studies of large systems and become popular. Their high computational efficiency still makes semiempirical methods an attractive alternative to ab initio or DFT methods.

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