Local explicitly correlated second-order perturbation theory for the accurate treatment of large molecules

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Local explicitly correlated second-order perturbation theory for the accurate treatment of large molecules

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A local explicitly correlated LMP2-F12 method is described that can be applied to large molecules. The steep scaling of computer time with molecular size is reduced by the use of local approximations, the scaling with respect to the basis set size per atom is improved by density fitting, and the slow convergence of the correlation energy with orbital basis size is much accelerated by the introduction of terms into the wave function that explicitly depend on the interelectronic distance. The local approximations lead to almost linear scaling of the computational effort with molecular size without much affecting the accuracy. At the same time, the domain error of conventional LMP2 is removed in LMP2-F12. LMP2-F12 calculations on molecules of chemical interest involving up to 80 atoms, 200 correlated electrons, and 2600 contracted Gaussian-type orbitals, as well as several reactions of large biochemical molecules are reported. © *2009 American Institute of Physics.*
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I. INTRODUCTION

The slow convergence of the electron correlation energy with basis set size can be accelerated by including terms into the wave function that depend explicitly on the interelectronic distances r_{ij}. This leads to very numerous and expensive many-electron integrals, but pioneering work of Kutzelnigg and co-workers[1–4] showed that these can be well approximated by resolutions of the identity (RIs). The original R12-methods included only linear r_{12} terms,[1–3,5,6] but more recently it has been found that much better accuracy can be achieved by using a short-range correlation factor. In particular, a simple Slater function $F(r_{12})=\exp(-\gamma r_{12})$ turns out to be particularly efficient in correcting for the basis set error.[7–9] Methods that include such terms are now denoted F12 methods.

In the past few years much progress has been made in the development of F12 theories and their efficient implementation. Not only various MP2-F12[5–7,10–18] but also coupled-cluster[19–28] approximations have been described in literature. One of the key findings of all these methods is that using aug-cc-pVnZ (Ref. 29) basis sets, the results show at least the quality of conventional aug-cc-pV$(n+2)$Z calculations, e.g., with triple-zeta basis sets quintuple zeta quality is reached.[9,14–17,24,25,28,30]

Whereas in conventional MP2 theory the computer time scales as $\mathcal{O}(\mathcal{N}^5)$, where $\mathcal{N}$ stands for the number of atoms or electrons in the molecule, MP2-F12 theory can show a scaling up to $\mathcal{O}(\mathcal{N}^8)$, depending on the approximation and implementation.[5,13,14,16] For the treatment of large molecules of chemical interest a reduction in the scaling is therefore of major importance. For instance, the QM shell in mixed quantum mechanical/molecular mechanics (QM/MM) treatments of enzymes often comprises 50–100 atoms so that really large systems could be treated accurately as soon as the calculation of the QM part is possible within a reasonable time.[31]

Low-order or even linear scaling of the computational resources with the molecular size can be achieved by exploiting the fact that electron correlation is essentially a short-range effect.[32–35] By localizing the orbitals it is possible to classify the correlated electron pairs according to their distance; neglecting very distant pairs then eliminating the quadratic dependence of the number of pairs on the molecular size. Furthermore, the excitations from a pair of localized occupied molecular orbitals (LMOs) can be restricted to subsets (domains) of local virtual orbitals that are spatially close to the LMOs, thereby making the computational effort for each electron pair independent of the molecular size. Ultimately, these two approximations lead to linear scaling, and this has been demonstrated already for the whole hierarchy of closed-shell single-reference electron correlation methods.[36–42]

In the current work we aim to develop low-order scaling algorithms for explicitly correlated second-order Møller–Plesset perturbation theory, MP2-F12.[13–15] In order to reduce scaling, local RI approximations can be introduced.[13,14] Furthermore, the necessary two-electron integrals can be efficiently computed using density fitting (DF) approximations, which involve another auxiliary basis set. Again, local approximations can be used to reduce the scaling (local DF).[43,44] Of course, each of these approximations introduces a certain error, and one must be careful that these errors are not larger than the gain of accuracy one aims to achieve with the F12 treatment. In conventional calculations, the basis set error is usually much larger than the error caused by local approximations. This is reversed when explicitly correlated

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methods are used. The accuracy of the local approximations will therefore be systematically investigated in the current paper.

II. THEORY

In the current work, we will only consider closed shells but extension to open-shell cases[17] is straightforward. MP2-F12 theory has been discussed in many previous papers,[5,14,16–18] and will therefore be reviewed here only briefly. Our formulation will be based on the general MP2-F12 formulation we presented earlier,[16] but a number of approximations will be introduced in order to reduce the computational effort and the scaling with molecular size. First of all, the *diagonal* ansatz[2,16] will be used throughout this work. Previous benchmarks have shown that it mostly yields better results than the full orbital-invariant ansatz[45] because geminal basis set superposition errors (BSSEs) are avoided.[16,17] However, since the diagonal ansatz is not orbital invariant, localized orbitals must be used to ensure size consistency. In the present context this is no disadvantage since we are aiming at a localized description anyway. The orbital localization has been carried out using the method of Pipek and Mezey.[46]

In the following $i,j,\ldots$ will denote occupied orbitals, $a,b,\ldots$ are virtual orbitals, $r,s,\ldots$ are any orbitals, and α',β' are orbitals of an orthogonal infinite basis. The latter contains the orbital basis as a subset. α,β denote orthogonal auxiliary basis functions that are used in the RI approximations. Summation over repeated dummy indices (Einstein summation rule) will be implied in most expressions.

A. The wave function ansatz and the energy expression

The first-order wave function $|\Psi^{(1)}\rangle$ used in closed-shell MP2-F12 theory can be written as

$$|\Psi^{(1)}\rangle = \frac{1}{2}\sum_{p=\pm 1}\sum_{i,j}\left[\sum_{a,b}T_{ab}^{ij,p}|\Phi_{ij,p}^{ab}\rangle + T_{ij,p}|\Phi_{ij,p}\rangle\right], \quad (1)$$

where

$$|\Phi_{ij,p}^{ab}\rangle = \frac{1}{2}(\hat{E}_{ai}\hat{E}_{bj} + p\hat{E}_{bi}\hat{E}_{aj})|0\rangle \quad (p = \pm 1) \quad (2)$$

are conventional doubly excited configurations; $p=1$ and $p=-1$ denote singlet and triplet coupling of the two excited electrons, respectively. $\hat{E}_{ai} = \eta_a^\dagger\eta_i + \bar{\eta}_a^\dagger\bar{\eta}_i$ are the usual spin-summed one-particle excitation operators, and $|0\rangle$ is the closed-shell Hartree–Fock reference function. Here and in the following, (ij,p) indicates that the corresponding quantity has been symmetrized ($p=1$) or antisymmetrized ($p=-1$) in the labels i and j, e.g., $|ij,p\rangle = \frac{1}{2}(|ij\rangle + p|ji\rangle)$. Note that the configurations have the symmetries $\Phi_{ij,p}^{ab} = p\Phi_{ij,p}^{ba}$, $\Phi_{ij,p} = p\Phi_{ji,p}$, and this implies similar symmetries for the amplitudes $T_{ab}^{ij,p} = pT_{ba}^{ij,p}$ and $T_{ij,p} = pT_{ji,p}$. The inclusion of the full summations in Eq. (1) is convenient to eliminate any normalization factors in the working equations.

The explicitly correlated configurations $|\Phi_{ij,p}\rangle$ are defined as

$$|\Phi_{ij,p}\rangle = |\Phi_{ij,p}^{\alpha'\beta'}\rangle\langle\alpha'\beta'|\hat{Q}_{12}\hat{F}_{12}|ij,p\rangle, \quad (3)$$

where $\hat{F}_{12}(r_{12}) \equiv F(r_{12})$ is the nonlinear correlation factor, and $\hat{Q}_{12}$ a strong-orthogonality projector (ansatz **3**),

$$\hat{F}_{12} = -\gamma^{-1}\exp(-\gamma r_{12}), \quad (4)$$

$$\hat{Q}_{12} = 1 - |ab\rangle\langle ab| + |mn\rangle\langle mn| - |m\alpha\rangle\langle m\alpha| - |\alpha m\rangle\langle\alpha m|. \quad (5)$$

The projector ensures that the explicitly correlated configurations are orthogonal to the Hartree–Fock wave function and to the conventional configurations $\Phi_{ij,p}^{ab}$.

In order to simplify the theory as much as possible we use approximation **3***A, in which (i) the extended Brillouin conditions (EBC) are assumed to be valid ($f_{rx}=0$, where x is any function that is orthogonal to the orbital basis), and (ii) exchange terms $\hat{k}$ are neglected.[5] Furthermore, small terms involving the overlap matrix $X_{ij,kl}^{(p)}$ of the explicitly correlated configurations are neglected. This corresponds to approximation MP2-F12/**3***A(D,NOX), as defined in Ref. 16. These approximations lead to a slight overestimation of the MP2-F12 correlation energies (relative to an exact treatment with the same basis set), but as has been shown in previous work,[16] this has very little impact on energy differences such as reaction energies.

The EBC approximation (indicated by the star in the method designation) has the advantage that the first-order equations for the amplitudes $T_{ij,p}$ of the explicitly correlated configurations and the conventional amplitudes $T_{ab}^{ij,p}$ decouple entirely. The conventional amplitudes and energy contribution can then be obtained by standard canonical MP2 theory; optionally, local approximations can be introduced; in this case the first-order LMP2 equations have to be solved iteratively.[36,37,47] The amplitudes $T_{ij,p}$ can simply be obtained as

$$T_{ij,p} = -V_{ij,p}/B_{ij,p}, \quad (6)$$

where

$$V_{ij,p} = \langle ij,p|r_{12}^{-1}\hat{Q}_{12}\hat{F}_{12}|ij,p\rangle, \quad (7)$$

$$B_{ij,p} = \langle ij,p|[\hat{F}_{12},\hat{t}_{12}]\hat{Q}_{12}\hat{F}_{12}|ij,p\rangle, \quad (8)$$

where $\hat{t}_{12} = \hat{t}_1 + \hat{t}_2$ is the kinetic energy operator. The F12-energy correction is then given by

$$E_{\mathrm{F12}} = -\sum_{p=\pm 1}(2-p)\sum_{i\geq j}(2-\delta_{ij})V_{ij,p}^2/B_{ij,p}. \quad (9)$$

Explicit expressions for the quantities $V_{ij,p}$ and $B_{ij,p}$ can be found in Refs. 14 and 16.

B. Local approximations

As outlined in Sec. I, electron correlation in nonmetallic systems is a short-range effect, and therefore the correlation of distant pairs can be neglected if a local orbital basis is used. Due to the short-range character of the $\hat{F}_{12}$ correlation factor, the energy contributions of the explicitly correlated

terms can be expected to decay even faster than the conventional ones, and it may therefore be sufficient to compute these terms only for orbital pairs that are relatively close (*strong* or *close* pairs). For this purpose the pairs are classified as usual in local correlation methods: first, to each LMO a subset of atoms is assigned. This assignment can be based on some sort of population analysis, as discussed, e.g., in Refs. 48 and 49. In the current work we have applied the method of Boughton and Pulay[48] with a completeness criterion of 0.985. The functions selected for a LMO i comprise an *orbital domain* $[i]$. The pair classification can then be based on distance criteria: pairs are neglected if the minimum distance R between any function in the domain $[i]$ and any function in the domain $[j]$ is larger than a given threshold. We distinguish strong pairs ($R=0$), close pairs ($1<R\leq3$), weak pairs ($3<R\leq8$), distant pairs ($8<R\leq15$), and very distant pairs ($R>15$) (all distances in a_0). Thus, in strong pairs the domains of i and j share at least one atom, and in close pairs the closest atoms in i and j are typically separated by one bond. Asymptotically, the number of pairs in each class, except for the very distant pairs, scales linearly with molecular size, which is one of the requirements for achieving linear scaling of the computational cost.

The pair approximations outlined above are used in the MP2-F12(loc) method, which will be summarized in Sec. II C. In addition, domain approximations can be introduced. These will be discussed in Sec. II D.

C. The MP2-F12(loc) method

In the MP2-F12(loc) method as introduced in Ref. 14, local pair approximations are only used in the F12 energy contribution [cf. Eq. (9)], while the conventional MP2 energy contribution is computed with standard canonical MP2 methods. No domain approximations are employed, and therefore the MP2-F12(loc) correlation energy becomes equal to the full MP2-F12 correlation energy if all pairs are included in the F12 treatment.

In addition to the pair approximation made in the wave function ansatz, local RI and DF approximations can be introduced in order to reduce the effort to compute the matrix elements $V_{ij,p}$ and $B_{ij,p}$. These approximations will be discussed in Secs. II E and II F, respectively.

Since for small- and medium-size molecules the calculation of the F12-energy contribution is much more expensive than the canonical MP2 calculation, significant savings can be achieved by using these approximations. However, for very large molecules the MP2 part will dominate since it scales with $\mathcal{O}(\mathcal{N}^5)$, while the F12 calculation without distant pairs scales at most with $\mathcal{O}(\mathcal{N}^4)$ (or less if local DF and RI approximations are used). In order to reduce the scaling of the MP2 part, domain approximations must be introduced. This will be discussed in Sec. II D.

D. The LMP2-F12 method

In the LMP2-F12 method proposed recently[15] local domain approximations[32,36] are used in the conventional part of the first-order wave function, which then takes the form

$$|\Psi^{(1)}\rangle = \frac{1}{2}\sum_{p=\pm1}\sum_{i,j}\left[\sum_{\tilde{a},\tilde{b}\in[ij]}T^{ij,p}_{\tilde{a}\tilde{b}}|\Phi^{\tilde{a}\tilde{b}}_{ij,p}\rangle + T_{ij,p}|\Phi_{ij,p}\rangle\right]. \quad (10)$$

For each pair ij the indices $\tilde{a},\tilde{b}$ refer to a set of orthonormal orbitals that span the pair domain $[ij]$. Each domain is initially defined by a subspace of (nonorthogonal) projected atomic orbitals (PAOs) that are spatially close to the orbitals i and j. For each domain, this subset of PAOs is symmetrically orthonormalized to obtain the pair-specific functions $\tilde{a},\tilde{b}$.

The domain approximation introduces an error in the conventional MP2 energy that may be much larger than the remaining basis set error of the MP2-F12 method. Fortunately, this error can be largely removed by modifying the projector $\hat{Q}_{12}$ used in the definition of the explicitly correlated configurations $|\Phi_{ij,p}\rangle$ so that the summation over $\alpha'\beta'$ in Eq. (3) is extended by the virtual orbital pairs that are excluded by the domain approximation in the conventional part. This means that for a pair ij the projector becomes

$$\hat{Q}^{ij}_{12} \approx 1 - \sum_{\tilde{a},\tilde{b}\in[ij]}|\tilde{a}\tilde{b}\rangle\langle\tilde{a}\tilde{b}| + \sum_{m,n}|mn\rangle\langle mn|$$
$$- \sum_m\sum_\alpha(|m\alpha\rangle\langle m\alpha| + |\alpha m\rangle\langle\alpha m|). \quad (11)$$

The essential difference to the full projector is that the contribution $|ab\rangle\langle ab|$ in Eq. (5) has been replaced by its local counterpart. Thus, for a given pair ij only the contribution $\sum_{\tilde{a},\tilde{b}\in[ij]}T^{ij,p}_{\tilde{a}\tilde{b}}|\Phi^{\tilde{a}\tilde{b}}_{ij,p}\rangle$ in the conventional LMP2 wave function is projected out from the explicitly correlated part, and the explicitly correlated configurations can (partly) compensate the domain error made by restricting the summation $\tilde{a},\tilde{b}$ in the latter term. In a recent communication[15] it was demonstrated for the correlation energies of a number of small molecules and for reaction energies involving these molecules that this modification of the wave function and the projector yields as accurate results as obtained with the full (nonlocal) MP2-F12 ansatz. In the current paper it will be shown that this also holds for large molecules.

Apart from the reduction of the domain error, this ansatz has the advantage that the number of matrix elements such as $K^{ij,p}_{\tilde{a}\tilde{b}}=\langle ij,p|r_{12}^{-1}|\tilde{a}\tilde{b}\rangle$, $F^{ij,p}_{\tilde{a}\tilde{b}}=\langle ij,p|\hat{F}_{12}|\tilde{a}\tilde{b}\rangle$, and $U^{ij,p}_{\tilde{a}\tilde{b}}=\langle ij,p|[\hat{F}_{12},\hat{t}_{12}]|\tilde{a}\tilde{b}\rangle$, that arise by inserting $\hat{Q}^{ij}_{12}$ into Eqs. (7) and (8), is strongly reduced. In fact, if distant pairs are neglected, their number scales only linearly with molecular size. Still, the number of integrals $K^{ij}_{m\alpha}$, $F^{ij}_{m\alpha}$, etc., that arise from the last three terms of the projector, scales as $\mathcal{O}(\mathcal{N}^3)$, and without further approximations their evaluation using DF even scales as $\mathcal{O}(\mathcal{N}^4)$. In Sec. II E we will introduce local RI approximations that reduce this scaling as well.

E. Local resolution of the identity

As an example we consider terms like $K^{ij,p}_{\alpha m}F^{ij,p}_{\alpha m}$, where i, j, and m are localized orbitals. In order to fully exploit locality, it is necessary to use local RI functions α as well. Unfortunately, a single set of well localized orthogonal functions α cannot be obtained. However, for each individual

pair ij it is possible to generate a subspace of orbitals $\tilde{\alpha}^{ij} \in [ij]_{RI}$ that are localized in the same region of space as the orbitals i and j. This can be achieved by selecting for each pair ij a subspace of RI basis functions $\mu' \in [ij]_{RI}$ that are spatially close (within a predefined distance) of the localized orbitals i and j. For each individual pair the selected basis functions are then symmetrically orthonormalized to yield the corresponding set of orthonormal functions $\tilde{\alpha}^{ij}$. Since these orbitals are different for each pair [and orbitals $\tilde{\alpha}^{ij}$ and $\tilde{\alpha}'^{kl}$ belonging to different pairs $(ij) \neq (kl)$ are nonorthogonal] the total number of functions $\tilde{\alpha}^{ij}$ is much larger than the number of RI basis functions, i.e., we use a highly redundant set of localized orbitals. This makes it formally necessary to add the superscript ij to these functions. However, since it will always be obvious from the context to which pair the orbitals belong, we will omit these labels in the following.

Due to the Gaussian product theorem, the integrals $K^{ij}_{\tilde{\alpha}m}$ and $F^{ij}_{\tilde{\alpha}m}$ decrease exponentially with the distance between i and $\tilde{\alpha}$ or j and m. Due to the (anti)symmetrization in i and j the integrals $K^{ij,p}_{\tilde{\alpha}m}$ will be small if m or α are far from i and j. We can therefore approximate the matrix elements in Eq. (7) as

$$V_{ij,p} = \left[K^F_{ij,p} - \sum_{\tilde{a},\tilde{b} \in [ij]} K^{ij,p}_{\tilde{a}\tilde{b}} F^{ij,p}_{\tilde{a}\tilde{b}} \right.$$
$$\left. + \sum_{m,n \in [ij]_{MO}} K^{ij,p}_{mn} F^{ij,p}_{mn} - 2 \sum_{m \in [ij]_{MO}} \sum_{\tilde{\alpha} \in [ij]_{RI}} K^{ij,p}_{\tilde{\alpha}m} F^{ij,p}_{\tilde{\alpha}m} \right],$$
$$(12)$$

where $[ij]_{MO}$ denotes a domain of localized orbitals m that are spatially close to the orbitals i or j. The sizes of the RI domains $[ij]_{RI}$ and the MO domains $[ij]_{MO}$ are asymptotically independent of the molecular size, and therefore the number of required integrals $K^{ij,p}_{\tilde{\alpha}m}$ scales as $\mathcal{O}(\mathcal{N})$ (always assuming that the number of pairs ij scales linearly). A similar expression holds for the quantities $B_{ij,p}$.

Thus, asymptotically the computational effort per pair becomes independent of the molecular size, and the overall effort for evaluating the RIs will scale linearly. This can lead to enormous savings in calculations for large molecules. Since the number of occupied orbitals m is much smaller than the number of RI functions, we currently include all occupied orbitals in the domains $[ij]_{MO}$. This introduces an $\mathcal{O}(\mathcal{N}^2)$ overhead, but with a small prefactor.

Similar local RI approximations can be made for the MP2-F12(loc) method. In this case the projector is approximated as

$$\hat{Q}^{ij}_{12} \approx 1 - \sum_{\tilde{r},\tilde{s} \in [ij]_{AO}} |\tilde{r}\tilde{s}\rangle\langle\tilde{r}\tilde{s}|$$
$$+ \sum_{m \in [ij]_{MO}} \sum_{\tilde{r} \in [ij]_{AO}} (|m\tilde{r}\rangle\langle m\tilde{r}| + |\tilde{r}m\rangle\langle\tilde{r}m|)$$
$$- \sum_{m \in [ij]_{MO}} \sum_{\tilde{\alpha} \in [ij]_{RI}} (|m\tilde{\alpha}\rangle\langle m\tilde{\alpha}| + |\tilde{\alpha}m\rangle\langle\tilde{\alpha}m|), \quad (13)$$

where the orthonormal orbitals $\tilde{r}, \tilde{s}$ span the AO pair domains $[ij]_{AO}$. These domains include all atomic orbitals at the same

atoms as used for the RI domains $[ij]_{RI}$. As will be shown in Sec. III C, the major part of the error caused by the local RI approximation arises from local approximations in the representation of $-|rs\rangle\langle rs|$, and large domains are necessary to achieve sufficient accuracy. This means that the crossover point to low-order (linear) scaling will be reached only for very large molecules.

F. Local density fitting

DF approximations are widely used nowadays in electronic structure theory. Originating from density functional theory (DFT)[50–52] their usage spreads today from MP2[43,53–56] and CC2 (Ref. 57) over (local) CCSD(T) (Ref. 58) to MP2-F12.[11,13,14,16,17,59] The overall scaling with respect to system size is not affected by standard DF, but it significantly reduces the prefactor and reduces the scaling with respect to N_{AO}/N_{atoms} from quartic to cubic. If other than Coulomb integrals are computed, it is essential to use robust fitting approximations[11,60] to ensure integral accuracy.

For the AO integrals such as $K^{ij}_{\mu\nu}$ or $F^{ij}_{\mu\nu}$ a local variant of DF can be applied.[13,43] The summation over the inherently local fitting functions A, B can be restricted to domains $[i]_{fit}$, very similar as in the RI summations discussed in Sec. II E. Only those fitting functions are included in these domains which are within a distance R_{fit} (or a certain number of bonds) from the AOs in the orbital domain $[i]$,

$$F^{ij}_{\mu\nu} \approx \sum_{A \in [i]_{fit}} D^A_{\mu i} F^A_{\nu j} + \sum_{B \in [j]_{fit}} F^B_{\mu i} D^B_{\nu j}$$
$$- \sum_{A \in [i]_{fit}} \sum_{B \in [j]_{fit}} D^A_{\mu i} F_{AB} D^B_{\nu j}. \quad (14)$$

The fitting coefficients $D^B_{\mu i}$ are obtained by solving the linear equations

$$\sum_{B \in [i]_{fit}} J_{AB} D^B_{\mu i} = J^A_{\mu i} \quad (\forall A \in [i]_{fit}). \quad (15)$$

Similar but slightly more complicated expressions hold for the commutator integrals $U^{ij}_{\alpha\beta}$. For details see Refs. 11, 13, 14, and 59.

In this case the overhead of the local fitting is that for each orbital domain $[i]_{fit}$ the Coulomb submatrix J_{AB}, with $A, B \in [i]_{fit}$ must be inverted (or the corresponding LU-decomposition be performed). Thus, as for the local RI, there will be a certain molecular size below which local DF will be more expensive than standard DF. The accuracy and efficiency of local DF will be investigated in Sec. III B.

G. Screening of three-index integrals

The cost of integral evaluation is reduced through conventional Schwarz screening. However since the F12-specific integrals all have short-range kernels $\hat{w}_{12} = \hat{F}_{12}, \hat{F}_{12} r^{-1}_{12}, \nabla^2_1 \hat{F}_{12}$ it is also very advantageous to screen on the distance between the orbital product $|\alpha\beta\rangle$ and the fitting function $|A\rangle$. In our integral package all integrals are generated from two-index intermediates. If we assume that the zero-angular momentum integral offers a reasonable estimate of the magnitude of general integrals, we can use bounds on

$(s|\hat{w}_{12}|s)$ integrals for approximate screening of the general integrals. This assumption will certainly not lead to a rigorous bound on the three-index integrals, but we find captures enough of the short-ranged nature of the kernels to be useful. A rigorous extension to arbitrary angular momentum could be made, based on the work of Lambrecht and co-workers.[61,62]

The correlation factor in this work is a Slater-type function fitted to an optimized Gaussian expansion.[14] Screening could be performed based either on the asymptotic form of the approximated Slater or on that of the most diffuse Gaussian. After tests we have settled on the former. To establish bounds on the $(s|\hat{w}_{12}|s)$ integrals we first define relevant notation: the two Gaussian atomic orbitals have exponents α and β and sit on centers a distance x apart. We define the variables $\zeta = \alpha + \beta$, $\xi = \alpha\beta/\zeta$, $\eta = \alpha\beta + \alpha\gamma + \beta\gamma = \zeta(\xi + \gamma)$, $\rho = \alpha\beta\gamma/\eta = \xi\gamma/(\xi + \gamma)$, $T = \xi x^2$, and $U = \gamma^2/(4\xi)$. We also use Ten-no's function[7]

$$G_m(T,U) = \int_0^1 dt\, t^{2m} e^{-Tt^2 + U(1-t^{-2})}. \qquad (16)$$

For the case $\hat{w}_{12} = e^{-\gamma r_{12}}$ we follow Ten-no and write

$$(s|e^{-\gamma r_{12}}|s) = \frac{\pi^{5/2}\gamma}{\xi^2\zeta^{3/2}}[G_{-1}(T,U) - G_0(T,U)]. \qquad (17)$$

The difference in square brackets is given by

$$G_{-1}(T,U) - G_0(T,U) = \int_0^1 dt(t^{-2} - 1)e^{-Tt^2 + U(1-t^{-2})}. \qquad (18)$$

In the limit of large T, the inequality

$$G_{-1}(T,U) - G_0(T,U) \le \int_0^\infty dt(t^{-2} - 1)e^{-Tt^2 + U(1-t^{-2})} \qquad (19)$$

holds, and rapidly becomes tight, supplying the approximate bound

$$(s|e^{-\gamma r_{12}}|s) \lesssim \frac{\pi^3}{(\alpha\beta)^{3/2}}e^{\gamma^2/4\xi}e^{-\gamma x}\left(1 - \frac{\gamma}{2x\xi}\right). \qquad (20)$$

For a generally looser (but completely rigorous) bound we can use

$$G_{-1}(T,U) - G_0(T,U) \le \int_0^1 dt\, t^{-2}e^{-Tt^2 + U(1-t^{-2})}$$
$$\le \int_0^\infty dt\, t^{-2}e^{-Tt^2 + U(1-t^{-2})}. \qquad (21)$$

Evaluating this last integral gives the bound

$$(s|e^{-\gamma r_{12}}|s) \le \frac{\pi^3}{(\alpha\beta)^{3/2}}e^{\gamma^2/4\xi}e^{-\gamma x}. \qquad (22)$$

For the case $\hat{w}_{12} = e^{-\gamma r_{12}}r_{12}^{-1}$ we have

$$(s|r_{12}^{-1}e^{-\gamma r_{12}}|s) = \frac{2\pi^{5/2}}{\xi^2\zeta^{3/2}}G_0(T,U). \qquad (23)$$

For the special function we can use the inequality

$$G_0(T,U) \le \int_0^\infty dt \exp[-Tt^2 + U(1 - t^{-2})]$$
$$= \frac{1}{2}\left(\frac{\pi}{T}\right)^{1/2}e^{U-2\sqrt{TU}} \qquad (24)$$

and the bound becomes tight for large T. This leads to

$$(s|r_{12}^{-1}e^{-\gamma r_{12}}|s) \le \frac{\pi^3}{(\alpha\beta)^{3/2}}e^{\gamma^2/4\xi}\frac{e^{-\gamma x}}{x}. \qquad (25)$$

For the final case of $\hat{w}_{12} = \nabla_1^2 e^{-\gamma r_{12}}$ we note that

$$(s|\{\nabla_1^2 e^{-\gamma r_{12}}\}|s) = \gamma^2(s|e^{-\gamma r_{12}}|s) - 2\gamma(s|e^{-\gamma r_{12}}r_{12}^{-1}|s) \qquad (26)$$

so the bound on the integral can be built based on the preceding inequalities.

III. RESULTS AND DISCUSSION

For simplicity we denote the (aug-)cc-pVnZ orbital basis sets[29,63] as (A)VnZ. In some calculations the diffuse basis functions on hydrogen atoms have been omitted and these basis sets will be denoted AVnZ'.

All calculations employed DF approximations in the HF, MP2, and MP2-F12 steps. This strongly reduces the computational effort for the integral-direct evaluation of the integrals. For the DF in the MP2 and MP2-F12, the AVnZ/MP2FIT fitting basis sets of Weigend et al.[56] were used. For the DF-HF calculations[64] we used the VnZ/JKFIT fitting basis sets[65] (without local approximations). The latter basis sets were also used as RI basis sets in the explicitly correlated calculations. The cardinal number n in the fitting sets was always the same as in the orbital basis sets. Unless otherwise noted, for all MP2-F12(loc) and LMP2-F12 calculations the aug-cc-pVTZ orbital basis, the VTZ/JKFIT RI basis, and the AVTZ/MP2FIT DF basis sets have been used. As in our previous work[14,15] the exponent γ in the correlation factor $\hat{F}_{12}$ has been chosen to be $1.4a_0^{-1}$. In general, the results are not very sensitive to the choice of this parameter.

The geometries of glutathionedisulphide (GSSG) and borrelidin have been optimized using DFT with the BP86 functional and the TZVP basis sets.[66–71] All other geometries have been optimized at the DF-LMP2 (Ref. 43) level using the VTZ basis sets and all pairs.

Since the residual equations for conventional and explicitly correlated double amplitudes are not coupled, the F12/**3***A(loc) energy corrections E_{F12} can be added to conventional MP2 or LMP2 correlation energies (depending on which projector is used). Since for the AVTZ orbital basis the HF errors are not entirely negligible, only correlation energies or contributions of the correlation energy to reaction energies will be considered. We note that the basis set error of the HF energy can be strongly reduced by including single excitations into the complementary auxiliary orbitals and computing the corresponding energy correction perturbatively.[17,25,30] This correction has not been applied in the current work since in the local method the CABS approach is not used. However, it would be possible to evaluate the correction at the expense of one Fock matrix evaluation in the union of the AO and RI basis sets.

TABLE I. Effect of pair approximations on the F12 energy contribution E_{F12} (in −mH). The projector in Eq. (13) without local DF or local RI approximations has been used. For the definition of the pair classes see text.

Pairs	Progesterone			Cholesterol			Borrelidin			GSSG		
	N_{pair}[a]	E_{F12}	ΔE[b]	N_{pair}[a]	E_{F12}	ΔE[b]	N_{pair}[a]	E_{F12}	ΔE[b]	N_{pair}[a]	E_{F12}	ΔE[b]
All[c]	2016	397.680	—	3240	470.551	—	4851	653.991	—	3276	872.406	—
Strong+close+weak	1191	397.645	−0.035	1472	470.498	−0.053	1694	653.909	−0.082	1978	872.266	−0.140
Strong+close	433	394.406	−3.274	521	466.237	−4.314	618	648.677	−5.314	727	866.348	−6.058
Strong	206	384.655	−13.025	247	454.070	−16.481	317	634.178	−19.813	384	847.749	−24.657

[a]Number of pairs treated in F12.
[b]Deviation from the calculation with all pairs in millihartree.
[c]Very distant pairs were neglected.

A. Accuracy of weak pair approximations

Table I lists the effects of different pair approximations on the F12 contributions E_{F12} to the correlation energies for four test molecules, namely, cholesterol $C_{27}H_{46}O$, progesterone $C_{21}H_{30}O_2$, borrelidin $C_{28}H_{43}NO_6$, and GSSG $C_{20}H_{32}N_6O_{12}S_2$ (cf. Figs. 1–4).

The pair classes are defined as described in Sec. II B. As expected, distant and very distant pairs contribute only a negligible amount to the energy correction E_{F12}, e.g., 0.035 mH for progesterone. If weak pairs are neglected, the error increases to a few millihartree, if also close pairs are neglected to more than 10 mH. Obviously, the absolute errors increase with the molecular size. However, it is anticipated that the errors cancel to a large amount when energy differences are computed. The effect of these approximations for reaction energies will be investigated in Sec. III F.

B. Accuracy of local DF

In Table II the errors of E_{F12} due to local DF approximations are shown for the same molecules and basis sets as in Table I. The orbital fitting domains $[i]_{fit}$ contain all fitting functions of the auxiliary fitting basis set that are located at

the atoms in the orbital domain $[i]$ (cf. Sec. II B), and in addition at all centers that are separated by at most L_{DF} bonds from these atoms. The deviation from the conventionally density-fitted result (full DF) decreases quickly with the domain size determined by L_{DF}. For $L_{DF}=3$, which is the default in our program, it does not amount to more than a few hundreds of millihartree for a large molecule such as pregnenolone ($C_{21}H_{32}O_2$). As will be shown in Sec. III F, the effect of the local DF approximation on energy differences is even smaller. Hence errors of local DF approximations are negligible, whereas the time savings in the fitting and subsequent assembly steps are considerable, as will be demonstrated later.

C. Accuracy of local RI

In this section we will study the effects of local approximations in the strong-orthogonality projector $\hat{Q}_{12}$ as described in Sec. II E. First, we will consider the MP2-F12(loc) case, in which the conventional MP2 contribution is unaffected by local approximations, and domains will only be introduced in the projector $\hat{Q}_{12}$. The pair-specific local AO and RI domains $[ij]_{AO}$ and $[ij]_{RI}$, respectively, are comprised of all AO and RI basis functions located within a radius R_{RI} from any atom in the pair domain $[ij]$. This is similar to the local RI approximations used in our previous work.[13,14]

The effect of this local RI approximation on the absolute MP2-F12(loc) correlation energies of our test molecules is
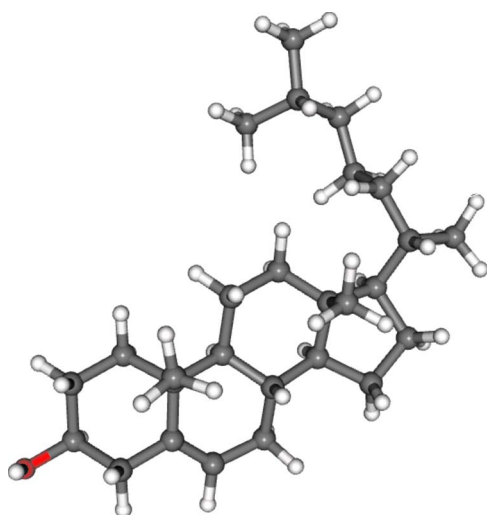

FIG. 1. (Color online) Cholesterol $C_{27}H_{46}O$ is the major precursor for the steroidogenesis in the body and plays hence a fundamental role in the synthesis of sex hormones. In the first reaction step the side chain of cholesterol is cleaved by an enzyme. Furthermore cholesterol is essential in building and maintaining cell membranes and affects the channeling of signal molecules.
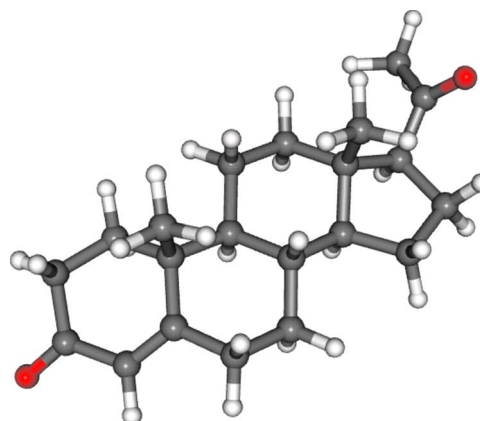

FIG. 2. (Color online) Progesterone $C_{21}H_{30}O_2$ is one of the sex hormones derived from cholesterol. It is involved in the female menstrual cycle, pregnancy and embryogenesis of humans and other species.
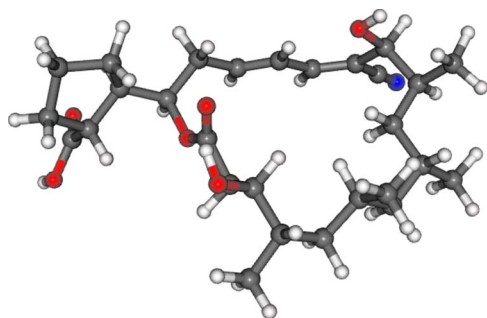
FIG. 3. (Color online) Borrelidin $C_{28}H_{43}NO_6$ is a potent inhibitor of angiogenesis, and the enantioselective synthesis of this polyketide macrolide has attracted increasing attention during the last years (Refs. 77 and 78). As a highly potential anticancer drug it can inhibit the spontaneous formation of lung metastases.

shown in the left part of Table III. It is found that in the current calculations with a Slater function as correlation factor the local RI slightly overestimates the correlation contributions relative to the results with full RI domains, whereas in our previous calculations with a linear correlation factor,[13] the correlation contribution was always underestimated. Furthermore, in comparison to linear R12 theory the F12 results converge much faster with respect to the domain size. Typically, for a given domain size, the errors are an order of magnitude smaller. For example, with a RI domain radius $5a_0$ the MP2-F12(loc) results do not deviate by more than 2%–3% from the full RI result, while our previous R12 results showed errors of about 20%.[13]

Despite the better convergence of the local RI approximations in F12 theory, the errors are still much larger than those caused by the local DF approximations, and they turn out to be quite critical when energy differences are computed (cf. Sec. III F). Therefore, rather large RI domains (e.g., $R_{RI}=13a_0$) must be used to obtain converged results. This means that local RI approximations in the MP2-F12(loc) method will be useful only in calculations for large molecules.

In order to investigate this error further, we have tested the effect of the domain approximation on the different contributions in the projector, cf. Eq. (13). The correlation energies for a linear glycine polypeptide, $(gly)_8$, are shown in
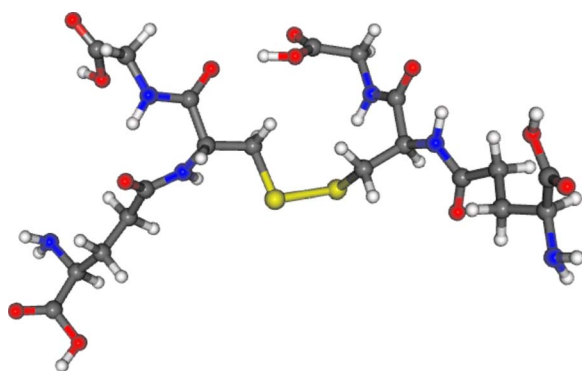

FIG. 4. (Color online) GSSG $C_{20}H_{32}N_6O_{12}S_2$ is the oxidized form of Glutathione (GSH). As reducing agent the thiol group of the cysteine fragment in GSH is able to donate a reducing equivalent ($H^+ + e^-$) to reactive radical species. Hence GSH is an antioxidant and protects cells from those free radicals.

TABLE II. Error of E_{F12} (in millihartree) caused by local fitting for different orbital fitting domains L_{DF} (see text). The projector in Eq. (13) without local RI approximations has been used. Strong, close, and weak pairs were included. The total F12 energy contributions without local DF can be found in the second row of Table I.

L_{DF}	Progesterone	Cholesterol	Borrelidin	GSSG
1	0.364	0.493	0.483	0.479
2	0.129	0.183	0.192	0.192
3	0.049	0.075	0.087	0.092
4	0.015	0.029	0.035	0.053
5	0.005	0.014	0.015	0.034

Fig. 5 as a function of the RI domain size. When domains are introduced in all terms (circles), convergence is very slow, and the correlation energy is overestimated, as also seen in Table III. The domains have to be extended by about $13a_0$ in order to get close to the exact result. However, if domains are only used for $\tilde{\alpha}$ in the RI contribution $-|m\tilde{\alpha}\rangle\langle m\tilde{\alpha}| -|\tilde{\alpha}m\rangle\langle\tilde{\alpha}m|$ (diamonds), convergence with the domain size is very much improved, and already with $R_{RI}=3a_0$ a rather accurate correlation energy is obtained. This result somewhat deteriorates if also the terms $|m\tilde{r}\rangle\langle m\tilde{r}|+|\tilde{r}m\rangle\langle\tilde{r}m|$ are approximated (triangles).

From these results it follows that the largest effect comes from the contributions $-|\tilde{r}\tilde{s}\rangle\langle\tilde{r}\tilde{s}|$. This term contains the projector $-\hat{v}_1\hat{v}_2$, which removes the contributions of the conven-

TABLE III. F12 energy contributions E_{F12} and total correlation energies (in $-mH$) as a function of the cutoff radius R_{RI} (in a_0, see text). All pairs were included, and no local DF approximations were applied. In the MP2-F12(loc) case the projector in Eq. (13) and in the LMP2-F12 case the projector in Eq. (11) with local RI [cf. Eq. (12)] has been used.

	MP2-F12(loc)		LMP2-F12		
R_{RI}	E_{F12}	E_{tot}^{corr}	R_{RI}	E_{F12}	E_{tol}^{corr}
		Progesterone			
0^a	—	4069.198	0^a	—	3982.665
7	403.387	4472.584	3	478.433	4461.097
9	399.461	4468.658	5	477.942	4460.607
11	398.361	4467.559	7	477.888	4460.552
13	397.927	4467.124	9	477.865	4460.530
∞	397.680	4466.877	∞	477.860	4460.524
		Cholesterol			
0^a	—	4986.499	0^a	—	4872.430
7	478.640	5465.139	3	577.049	5449.478
9	473.503	5460.003	5	576.389	5448.818
11	471.948	5458.448	7	576.304	5448.734
13	471.109	5457.609	9	576.282	5448.712
∞	470.551	5457.051	∞	576.275	5448.705
		Borrelidin			
0^a	—	6446.416	0^a	—	6328.649
7	663.416	7109.832	3	764.052	7092.701
9	658.068	7104.483	5	763.277	7091.926
11	655.780	7102.196	7	763.167	7091.816
13	654.795	7101.211	9	763.148	7091.798
∞	653.991	7100.407	∞	763.142	7091.792

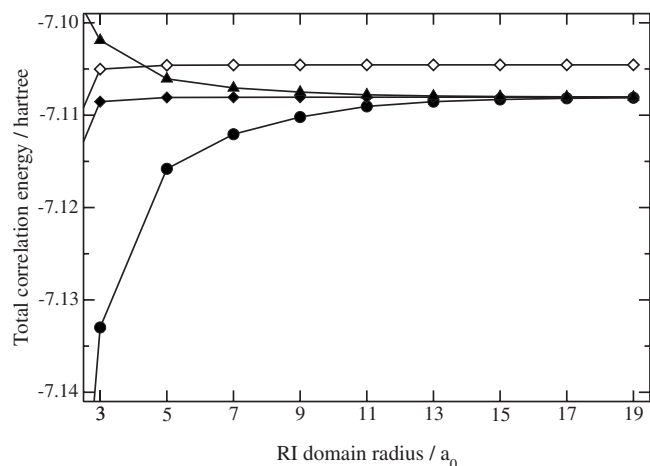[a]Pure MP2 and LMP2 correlation energies.

FIG. 5. MP2-F12(loc) and LMP2-F12 correlation energies for $(gly)_8$ as a function of the cutoff radius R_{RI} (see text). All pairs (including very distant pairs) were correlated. Full symbols: MP2-F12(loc) using the projector in Eq. (13). Open symbols: LMP2-F12 using the projector in Eq. (11); circles: all terms of the projector (13) treated with local approximations; diamonds: only $-|m\tilde{\alpha}\rangle\langle m\tilde{\alpha}| - |\tilde{\alpha}m\rangle\langle\tilde{\alpha}m|$ in Eq. (13) is treated with local approximations; triangles: only $|m\tilde{r}\rangle\langle m\tilde{r}| + |\tilde{r}m\rangle\langle\tilde{r}m| - |m\tilde{\alpha}\rangle\langle m\tilde{\alpha}| - |\tilde{\alpha}m\rangle\langle\tilde{\alpha}m|$ in Eq. (13) is treated with local approximations.

TABLE IV. Accuracy and CPU times (in minutes on opteron 2.4 GHz processors) for integral evaluation depending on the prescreening threshold THRF12 (in a.u.), using MP2-F12(loc).

	$-\log(\text{THRF12})$	$-E_{F12}/\text{mH}$	CPU time
$(gly)_7$	6	617.4828	67.3
	7	617.4441	73.8
	8	617.4441	85.4
	Off	617.4441	203.5
GSSG	6	849.9058	177.3
	7	849.8761	202.0
	8	849.8759	225.7
	Off	849.8759	563.7

D. Accuracy of prescreening

The accuracy and the savings due to prescreening based on a Slater-type geminal (see Sec. II G) are demonstrated in Table IV. Depending on the screening threshold THRF12, the CPU times for integral evaluation are reduced by a factor of 2–3. With a threshold THRF12 $= 10^{-8}$ the error in the energy is less than 10^{-7} hartree, and stable and accurate results are also obtained for other systems. Therefore this value has been used as default in all further calculations.

E. Timings and scaling with molecular size

The diagonal ansatz with the neglect of distant pairs in combination with the approximations discussed in Secs. II B and II F leads to either linear or quadratic scaling of the transformation, fitting, and assembly steps. The dependence of the CPU times on the molecular size is demonstrated in Figs. 6 and 7 for linear glycine chains $(gly)_n$ as a function of the number n of glycine residues, $n = 1, \dots, 12$. The calculation for $(gly)_{12}$ included 87 atoms, 3128 basis functions, and 272 electrons were correlated. The onset of linear scaling can

tional double excitations from the explicitly correlated part of the wave function. Apparently, if approximations are introduced into this term, these contributions are incompletely removed, and the remainder leads to the observed overestimation of the correlation energy.

This problem of double counting can be avoided by restricting the conventional double excitations for a given pair ij to the same domains as used to approximate the projector $-\hat{v}_1\hat{v}_2$, cf. Eq. (11). Thus, the domain error of the LMP2 wave function, which typically reduces the correlation energy by 1%–2%, can be (partly) compensated by contributions of the explicitly correlated terms,[15] which contain a fixed contraction of the missing configurations, cf. Eq. (3).

The result for this approximation is shown in the right part of Table III as well as in Fig. 5 (open diamonds). It is seen that the convergence with the RI domain size radius R_{RI} is much faster than in the left column of Table III since in this case the RI domains vary only in the terms $-|m\tilde{\alpha}\rangle\langle m\tilde{\alpha}| - |\tilde{\alpha}m\rangle\langle\tilde{\alpha}m|$.

For a value $R_{RI} = 5a_0$ the energies are converged to about 0.1 mH. Furthermore, Table III also demonstrates that the domain error in the LMP2 (i.e., the difference of the pure MP2 and LMP2 correlation energies) is dramatically reduced by the F12 correction. While for pure LMP2 the correlation energies are smaller by about 100 mH (2%) than the MP2 correlation energies, the difference in the total MP2-F12(loc) and LMP2-F12 correlation energies only amounts to 6–10 mH (0.1%–0.2%). Similarly, in Fig. 5 the LMP2-F12 correlation energy is very close to the MP2-F12(loc) one. Thus, one can expect that the MP2-F12(loc) and LMP2-F12 methods give very similar results. The effect of the local RI approximations on energy differences will be further investigated in Sec. III F, while the effect of the local approximations on the CPU times will be demonstrated in Sec. III E.
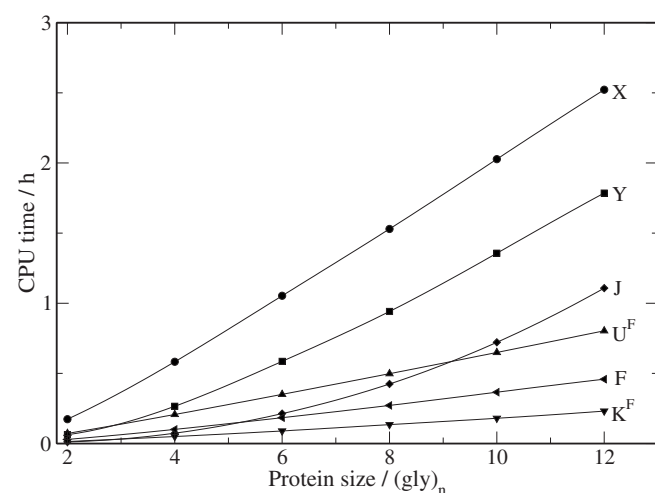

FIG. 6. CPU times for three-index integral evaluation for linear glycine polypeptides $(gly)_n$ (in hours on MACPRO with Xeon Woodcrest 3.0 GHz processor). The integral kernels are $J = r_{12}^{-1}$, $F = \hat{F}_{12}$, $K^F = r_{12}^{-1}\hat{F}_{12}$, $U^F = [\hat{t}_{12}, \hat{F}_{12}]\hat{F}_{12}$, $X = [\hat{t}_1, \hat{F}_{12}]$, and $Y = [\hat{t}_1, r_{12}^{-1}]$. The latter two integral types are required to compute $U_{\alpha\beta}^{ij}$, cf. Ref. 11.
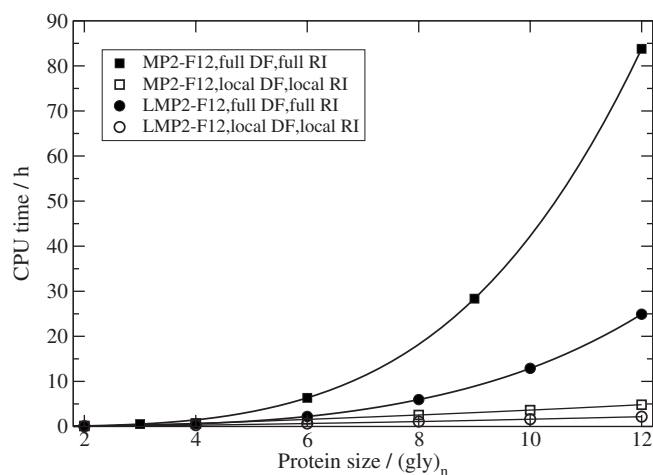
FIG. 7. CPU times of transformation, fitting, and assembly steps of the F12 calculations for glycine polypeptides $(gly)_n$ (calculated as total CPU times minus the times for integral evaluation and MP2/LMP2, in hours on MACPRO with Xeon Woodcrest 3.0 GHz processor). Strong, close, and weak pairs were included in the F12 treatment. In the MP2-F12(loc) and LMP2-F12 calculations with local RI the cutoff radius R_{RI} was set to $13a_0$ and $5a_0$, respectively.

be expected early in such one-dimensional systems, and therefore they are suitable test systems, though rather unrealistic models for real applications.

The number of significant three-index integrals with short-range kernels such as $\hat{F}_{12}$ scales linearly with molecular size, and due to the screening the CPU time for evaluating these integrals scales linearly as well (cf. Fig. 6). Only the number of Coulomb integrals over r_{12}^{-1} as well as the integrals over the commutator $\hat{Y}=[\hat{t}_1, r_{12}^{-1}]$ scale quadratically with molecular size, and therefore linear cost scaling is not reached by integral screening for these integrals. The scaling for $\hat{Y}$ integrals is better than for Coulomb integrals because the kernel has a shorter range form. It can be expressed as[11] $[\hat{t}_1, r_{12}^{-1}]=2\pi\delta(r_{12})-(\vec{\nabla}_1 r_{12}^{-1})\cdot\vec{\nabla}_1$; the first term is manifestly short range, and the second decays like r_{12}^{-2}. This leads to the lower-scaling integral evaluation for $\hat{Y}$ integrals, seen in Fig. 6.

If distant pairs are neglected and both local DF and local RI approximations are activated, only three-index integrals $(\mu'\nu|\hat{w}_{12}|A)$ are needed for which the RI basis functions μ' and the fitting functions A are within a certain distance. This is because for a pair ij the functions in the domain $[ij]_{RI}$ are close to either i or j. If distant pairs are neglected, j is close to i, and thus μ' must be within a certain distance of i. A similar argument can be applied to the fitting functions A. Thus, for each orbital i, one can determine which μ' and A contribute. The corresponding pair of centers is stored. Repeating this for all orbitals i yields all center pairs which must be considered. Asymptotically, this will lead to linear cost scaling for all integrals involving RI basis functions. The savings will be the larger the smaller the RI and DF domains, and the more pairs are neglected.

For the integrals $(\mu\nu|r_{12}^{-1}|A)$ such a test is not possible since we need the integrals $(mn|r_{12}^{-1}|A)$ for all occupied orbitals mn, and therefore all μ, ν. Thus, linear scaling cannot be reached for these integrals. If finite domains $[ij]_{MO}$ would be

used, one could construct appropriate test densities and apply screening techniques similar to those described earlier[43] for LMP2 in order to reach linear scaling. However, this has not been implemented so far.

The first integral transformation step, e.g., $(\mu i|\hat{F}_{12}|A)$ $=(\mu\nu|\hat{F}_{12}|A)C_{\nu i}$, is done for each individual fitting function A in terms of blocks over the indices μ, ν. Normally, a block contains all functions at a given center, but merging of the functions at neighboring centers is possible if the block size becomes too small, e.g., for hydrogen atoms. For each block of indices μ, ν the maximum values of the integrals and orbital coefficients $C_{\mu i}$ (for each i) are determined, and the transformation of the block is skipped if the product of the integral and coefficient maximum values is smaller than a threshold. For the integrals with short-range kernels such as $\hat{F}_{12}$ the number of integrals as well as the number of significant molecular orbital coefficients $C_{\mu i}$ scale linearly with molecular size, and then the CPU time for the transformation scales linearly as well. For the remaining integral types the transformation scales quadratically.

Figure 7 shows the total CPU times of the MP2-F12(loc) and LMP2-F12 calculations, excluding the times for the integral evaluation; the latter (cf. Fig. 6) is almost the same in both cases. In both cases, the times with and without local RI and local DF approximations are compared. We first consider the case without local RI approximations (full symbols). Even then the CPU times for the LMP2-F12 calculation with the local projector (11) are significantly smaller than the ones with the full projector (13) since instead of all integrals K_{rs}^{ij}, F_{rs}^{ij}, and U_{rs}^{ij}, only the corresponding integrals with $\tilde{a}\tilde{b}\in[ij]$ are needed. The number of the latter integrals scales linearly with molecular size, while the number of all F_{rs}^{ij} scales cubically (always assuming that very distant pairs are neglected). Accordingly, the time for assembly of the integrals such as F_{rs}^{ij} [cf. Eq. (14)] should scale as $\mathcal{O}(\mathcal{N}^4)$, while the time for assembly of the integrals such as $F_{\tilde{a}\tilde{b}}^{ij}$ scales only quadratically. If local DF approximations are activated, the scaling for the assembly step is reduced to $\mathcal{O}(\mathcal{N}^3)$ and $\mathcal{O}(\mathcal{N})$, respectively, since asymptotically the size of the fitting domains becomes independent of the molecular size.

If local RI approximations are activated as well (open symbols), the scaling of the most expensive integral types is further reduced: The CPU time for the integrals $F_{\tilde{r}\tilde{s}}^{ij}$ [MP2-F12(loc)] or $F_{\tilde{a}\tilde{b}}^{ij}$ (LMP2-F12) scales linearly, the one for $F_{m\tilde{\alpha}}^{ij}$ quadratically, and the one for F_{mn}^{ij} cubically. However, the time for the latter integrals is very small so that the apparent scaling for medium molecular sizes is between linear and quadratic. Strict linear scaling could be achieved by defining MO domains $m\in[ij]_{MO}$ (cf. Sec. II E). However, this has not been attempted so far. It should be noted that even if local RI approximations are used in projector (13), the number of integrals $F_{\tilde{r}\tilde{s}}^{ij}$ ($\tilde{r}, \tilde{s}\in[ij]_{AO}$) is much larger than the number of integrals $F_{\tilde{a}\tilde{b}}^{ij}$ ($\tilde{a}, \tilde{b}\in[ij]$) needed with projector (11) since in order to get accurate results, the domains $[ij]_{AO}$ must be much larger than the pair domains $[ij]$.

Even though the scaling of our implementation is not yet fully linear, the reduction of the overall CPU times by the

TABLE V. CPU times (in hours on opteron 2.4 GHz processors) for cholesterol, $C_{27}H_{46}O$ using different local approximations in MP2-F12(loc) or LMP2-F12. The RI domain sizes were $15a_0$ and $5a_0$ for MP2-F12(loc) and LMP2-F12, respectively.

Pairs	RI	DF	U	J	$F+U^F+K^F$	Assembly[a]
			MP2-F12(loc)			
All[b]	full	full	11.7	1.2	5.1	121.8
			LMP2-F12			
All[b]	full	full	10.9	1.0	16.6	27.6
Strong	full	full	10.8	1.0	4.8	10.2
Strong	loc	full	10.7	1.0	4.8	7.5
Strong	loc	loc	10.2	0.8	4.7	3.2

[a]CPU-times for F12 energy correction, excluding integral evaluation and MP2/LMP2.
[b]All apart from very distant pairs.

local DF and RI approximations is very significant, as seen in Fig. 7. For $(Gly)_{12}$, the CPU time (without integral evaluation) is reduced by a factor of about 17 [MP2-F12(loc)] or 11 (LMP2-F12). In the latter case the saving is smaller since the use of the local projector without any further local approximation saves already a factor of about 3.5, and so overall the local projector plus the local RI and DF approximations save a factor of nearly 40. Even if the integral time is included, the overall saving is about a factor of 7 [MP2-F12(loc)] or 10 (LMP2-F12) relative to MP2-F12 with the same pairs but no other local approximations.

Timings for a more realistic case, the molecule cholesterol (74 atoms, 2346 basis functions, and 160 correlated electrons) are presented in Table V. Dramatic savings are achieved for the "assembly" steps, i.e., the time needed for the F12 calculation apart from integral evaluation. The local approximations allow here for savings by a factor of about 38. On the other hand, the savings for the integrals are small since the same integrals over AOs are required in MP2-F12 and LMP2-F12. For the integral sets involving RI basis functions some savings are possible if local RI and local DF approximations are used (see above), but the onset of linear scaling occurs rather late and with a large prefactor.

From Figs. 6 and 7 as well as from Table V it is seen that in full MP2-F12 calculations for large systems, most CPU time is spent in the fitting and assembly steps, which scale with $\mathcal{O}(\mathcal{N}^5)$. However, if LMP2-F12 with local DF and RI approximations is used, the assembly time scales linearly and becomes very small, and then most of the time is required for the integral evaluation.

By far most of the time is spent for the commutator integrals over $\hat{X}=[\hat{t}_1,\hat{F}_{12}]$ and $\hat{Y}=[\hat{t}_1,r_{12}^{-1}]$, which are needed to compute the matrices $\mathbf{U}^{ij}$ [cf. Eq. (38) in Ref. 11]. We note that in approximation **3C**,[16,72] these integrals are not required, and further savings in the integral evaluation might be possible by using this method. However, in approximation **3C** various additional integral transformations to intermediate orbital spaces are necessary, which may compensate part of the savings. The development of a **3C**(loc) program is currently under way in our group.

F. Reactions involving large molecules

In this section we will demonstrate the performance of MP12-F12(loc) and LMP2-F12 for reactions involving large molecules (up to 65 atoms) of biochemical and pharmacological interest. When computing reaction energies using local methods it is essential to make sure that the domains in the reactants and products are consistent.[49,73,74] The Pipek–Mezey localization often yields artificially large contributions of diffuse basis functions at hydrogen atoms that are bound to aromatic rings. Therefore, we used in the androstendione reaction (cf. Fig. 8) for the hydrogen atoms the VTZ basis without diffuse functions (basis AVTZ′). The contributions of the two most diffuse functions of each angular momentum at each atom were eliminated in the localization criterion, which further improves the localization.[73,74] Furthermore, the domains of the π-orbitals in the aromatic systems were merged.[74] It was carefully checked that the resulting domains were consistent for the reactants and products of all reactions studied. In the calculations with AVQZ basis sets, the domains obtained with the AVTZ basis set were used. The structures of reactants and products were optimized using DF-LMP2/VTZ and all pairs (apart from very distant ones).

As a first example we consider a ring closure reaction yielding androstenedione, which is the precursor of male and female sex hormones. This reaction (cf. Fig. 8) is the last step in an androstenedione total synthesis. The cleavage of the protecting group o-hydroxy phenol and the C–C bond formation takes place in aqueous solution under the catalytic influence of H_2O and H^+. However, since purpose of the current calculations is solely to test the accuracy of the local approximations on reaction energies, we did neither consider zero-point energies nor solvent and other environmental effects in this work.

MP2, LMP2, MP2-F12(loc), and LMP2-F12 correlation contributions to the reaction energy are summarized in Table VI. The basis set limit was estimated by extrapolating the MP2/AVTZ′ and MP2/AVQZ′ correlation energies using the two-point extrapolation formula $E_n=E_{CBS}+A/n^3$ ($n=3$, 4).
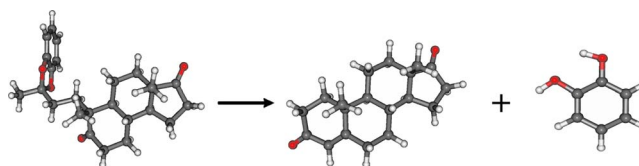

FIG. 8. (Color online) A ring closure reaction yielding androstenedione.

TABLE VI. The effect of local approximations on the correlation contributions ΔE_{corr} (in kcal mol^{-1}) to the reaction energy of the androstenedione ring closure. In LMP2 and LMP2-F12, very distant pairs were always neglected. The HF/AVTZ and AVQZ values are -0.73 and -1.29 kcal mol^{-1}, respectively.

Pairs	DF	RI	ΔE_{corr}
	DF-LMP2		
AVTZ$'$	full	$\cdots$	4.78
AVQZ$'^{a}$	full	$\cdots$	4.84
	DF-MP2		
AVTZ$'$	full	$\cdots$	7.80
AVQZ$'$	full	$\cdots$	6.64
CBS[34]			5.80
	DF-MP2-F12(loc)/AVTZ$'$		
All^{b}	full	full	6.17
Strong+close+weak	full	full	6.17
Strong+close+weak	loc	full	6.17
Strong+close+weak	loc	loc	6.31
Strong+close	full	full	5.96
Strong+close	loc	full	5.97
Strong+close	loc	loc	6.10
Strong	full	full	5.60
Strong	loc	full	5.61
Strong	loc	loc	5.74
	DF-LMP2-F12/AVTZ$'$		
All^{b}	full	full	5.81
Strong+close+weak	full	full	5.78
Strong+close+weak	loc	loc	5.81
Strong+close	full	full	5.26
Strong+close	loc	loc	5.27
Strong	full	full	4.68
Strong	loc	loc	4.68

[a]The orbital domains for the AVQZ$'$ basis were taken from the AVTZ$'$ calculation.
[b]Without very distant pairs.

The correlation contribution of the reaction energy using conventional MP2 is rather strongly basis set dependent. The MP2/AVTZ$'$ result differs from the extrapolated MP2/CBS[34] value by 2.0 kcal mol^{-1}, and the MP2/AVQZ$'$ value still deviates by 0.84 kcal mol^{-1} from the MP2/CBS[34] one.

On the contrary, the DF-LMP2 calculations show a much weaker basis set effect, but as compared to the CBS[34] estimate, the LMP2/AVQZ$'$ correlation contribution to the reaction energy is underestimated by approximately 1 kcal mol^{-1}. Very likely, this "domain error" is partly due to the much reduced intramolecular BSSE in LMP2 calculations, which leads to a destabilization of the reactants and thus to a reduction of the (positive) correlation contribution to the reaction energy.

The MP2-F12(loc)/AVTZ$'$ value without any local approximations differs from the CBS[34] reference value by only 0.37 kcal mol^{-1}. The corresponding LMP2-F12/AVTZ$'$ result is even closer to the CBS[34] value. The deviation merely amounts to 0.01 kcal mol^{-1}, but this may be fortuitous since the CBS[34] could also be in error by a few tens
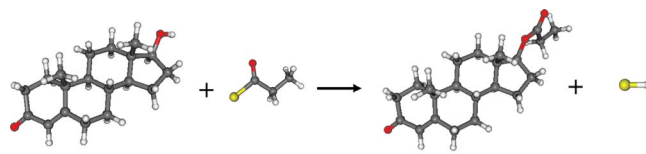

FIG. 9. (Color online) Esterification of propionic acid chloride with testosterone.

of a kcal mol^{-1}. In any case, it is obvious that the effect of the domain approximation is much reduced in the LMP2-F12 calculations as compared to the corresponding LMP2 calculations, and the MP2 basis set limit is reached within "chemical accuracy."

The neglect of distant and very distant pairs in the F12 treatment has virtually no effect on the computed reaction energy. The further neglect of weak pairs causes deviations of 0.21 and 0.55 kcal mol^{-1} for MP2-F12(loc) and LMP2-F12, respectively, from the all-pair result. The error for LMP2-F12 is larger than for MP2-F12(loc) since the domain error of the weak pairs is not compensated by the F12 terms. If also close pairs are neglected, these errors even increase to 0.57 and 1.13 kcal mol^{-1} for MP2-F12(loc) and LMP2-F12, respectively. Thus, somewhat unexpectedly, the F12 correction also significantly affects the contributions of close and weak pairs, and therefore it is recommended to include all strong, close, and weak pairs into LMP2-F12 calculations if one aims for high accuracy.

In all cases the effect of local DF is negligible (≈ 0.01 kcal mol^{-1}). In the case of local RI the situation for MP2-F12(loc) and LMP2-F12 is quite different. In MP2-F12(loc) a distance criterion R_{RI} of at least $13a_0$ is needed to obtain an accurate reaction energy; using this value, the error caused by the local RI still amounts to 0.13 kcal mol^{-1}. LMP2-F12 requires much smaller RI domains of just $R_{RI} = 5a_0$, and the deviation then amounts to at most 0.03 kcal mol^{-1}. With $R_{RI} = 3a_0$ we obtain $\Delta E_{corr} = 5.92$ kcal mol^{-1} (strong+weak+close pairs included in the F12 treatment), i.e., the error increases to 0.14 kcal mol^{-1}.

As a second example we consider the esterification of propionic acid chloride with testosterone (cf. Fig. 9). Esters of different carboxylic acid chain length play an important role in hormone therapy. The larger the chain of the carboxylic acid in the ester, the longer the testosterone derivative stays in body tissues because of increased lipophilicity.

The results are presented in Table VII. The conclusions are rather similar to the androstenedione reaction. The MP2/AVTZ value differs from the MP2/CBS[34] reference by 1.42 kcal mol^{-1}, the MP2/AVQZ result still by 0.60 kcal mol^{-1}. Again the MP2 basis set dependence is probably affected by intramolecular basis set superposition effects: the smaller the basis set the larger is the BSSE in the product propionic acid ester, which artificially lowers the correlation contribution of the (again positive) correlation contribution to the reaction energy. The almost BSSE-free LMP2 results lie much closer to the CBS value; the differences amount to just 0.26 kcal mol^{-1} (AVTZ) and 0.21 kcal mol^{-1} (AVQZ).

The MP2-F12(loc)/AVTZ all pairs result deviates from

TABLE VII. The effect of local approximations on the correlation contribution ΔE_{corr} (in kcal mol^{-1}) to the reaction energy of the testosterone esterification reaction. In the LMP2, very distant pairs were neglected. The HF/AVTZ and AVQZ values are -6.50 and -6.26 kcal mol^{-1}, respectively.

Pairs	DF	RI	ΔE_{corr}
	DF-LMP2		
AVTZ	full	⋯	1.41
AVQZ[a]	full	⋯	1.88
	DF-MP2		
AVTZ	full	⋯	0.25
AVQZ	full	⋯	1.07
CBS[34]			1.67
	DF-MP2-F12(loc)/AVTZ		
All[b]	full	full	1.66
Strong+close+weak	full	full	1.66
Strong+close+weak	loc	full	1.68
Strong+close+weak	loc	loc	1.59
Strong+close	full	full	1.69
Strong+close	loc	full	1.68
Strong+close	loc	loc	1.60
Strong	full	full	1.28
Strong	loc	full	1.28
Strong	loc	loc	1.19
	DF-LMP2-F12/AVTZ		
All[b]	full	full	1.96
Strong+close+weak	full	full	1.99
Strong+close+weak	loc	loc	1.97
Strong+close	full	full	2.14
Strong+close	loc	loc	2.13
Strong	full	full	1.78
Strong	loc	loc	1.77

[a]The orbital domains for the AVQZ basis were taken from the AVTZ calculation.
[b]Without very distant pairs.

the MP2/CBS[34] value by only 0.01 kcal mol^{-1}, whereas LMP2-F12 yields a difference of 0.29 kcal mol^{-1}. Due to the limited accuracy of CBS[34], it is not possible to decide which is more accurate. Again, the RI and DF errors for LMP2-F12 are very small (the total errors amount to 0.01–0.02 kcal mol^{-1}), and distant pairs can be safely neglected. Despite the much larger RI domains in the MP2-F12(loc) method, the error of the local RI approximation is much larger than in the LMP2-F12 case.

We have also computed reaction energies for a number of other reactions, and the conclusions were similar as for the ones presented here. In order to obtain results that are close to the basis set limit, the inclusion of strong and close pairs in the MP2-F12(loc) or LMP2-F12 treatment is usually sufficient to achieve chemical accuracy. If only strong pairs are included, errors over 1.0 kcal mol^{-1} can occur, and this is therefore not recommended. Errors caused by local DF approximations were negligible.

IV. CONCLUSIONS

New MP2-F12(loc) and LMP2-F12 methods have been presented which involve pair approximations, efficient pre-

screening techniques for short-ranged integrals, local DF, and local RI approximations. The effect of these approximations was systematically studied for correlation and reaction energies of large molecules.

If all pairs are correlated and no local DF and RI approximations are applied, the MP2-F12(loc) method is equivalent to MP2-F12 and should therefore approach the MP2 basis set limit. This is not so obvious for LMP2-F12 since in the underlying LMP2 wave function the excitations are restricted to domains, and therefore the LMP2 correlation energies are somewhat smaller than the MP2 ones. This may substantially affect energy differences, and in the current study LMP2/AVTZ and MP2/AVTZ correlation contributions to reaction energies differed by up to 3 kcal mol^{-1}. However, as shown earlier[15] for small molecules, these domain errors are to a large extent eliminated by the additional F12 terms in the LMP2-F12 first-order wave function. The present work shows that this also holds for reactions involving large molecules: in all cases that we studied so far, the MP2-F12(loc) and LMP2-F12 values agreed within about 0.3 kcal mol^{-1}. Thus, the LMP2-F12 method does not only correct for basis set errors but also for the domain errors in LMP2. At the same time, it leads to dramatic savings of CPU time, as compared to full MP2-F12 calculations, in particular, if the contributions of distant pairs are neglected. Using local DF and RI approximations, which have a negligible effect on the accuracy, almost linear scaling of the overall computational effort with molecular size can be reached. LMP2-F12 is therefore the method of choice for large molecules.

Our results demonstrate that the LMP2-F12 calculations with triple-zeta basis sets can now be carried out for reactions involving molecules with up to 100 light atoms, which means that many reactions of interest in organic, biochemical, or pharmacological chemistry can be studied. For the first time, near-basis-set-limit accuracy can be reached for such extended systems. The methods are easy to use and available in the current release of the MOLPRO quantum chemistry package.[75] As already shown earlier[31,49] it is also possible to use such methods in QM/MM hybrid methods, using electrostatic embedding to describe the effect of a protein environment.

Of course, our current results apply only to the MP2 approximation, which in many cases is insufficient in order to obtain quantitative results. The next goal is therefore to extend the local approximations to coupled-cluster methods. Recently, we have shown that highly accurate results can be obtained using very simple CCSD(T)-F12 approximations, in which MP2-F12 is the first step.[25,28,30] In order to be able to treat large molecules at this level, it is highly desirable to develop a corresponding explicitly correlated local coupled-cluster [LCCSD(T)-F12] method. Previous work has shown that the domain error in LMP2 and LCCSD(T) calculations is very similar.[73,76] It can therefore be anticipated that the domain error will also be small in LCCSD(T)-F12 calculations when the same local projector as in LMP2-F12 is used. Another very important advantage of employing this projector in LCCSD(T)-F12 calculations is that exactly the same transformed integrals involving four external (virtual) orbit-

als as in the LCCSD(T) method[38–42] will be needed. The number of these integrals scales linearly with molecular size. Thus, as compared to standard LCCSD(T) calculations, the additional effort for the F12 treatment will be small. Further work in this direction is currently in progress in our laboratory.

ACKNOWLEDGMENTS

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