Energetics of Large Water Clusters [up to (H_2O)_{20}] by means of Explicitly Correlated, Localized Coupled Cluster Methods

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ABSTRACT We consider the performance of combined PNO-F12 approaches for the dissociation energy of water clusters as large as (H_2O)_{20} by comparison to canonical CCSD(T)/CBS reference values obtained through n-body decomposition of post-MP2 corrections. We find that PNO-LCCSD(T)-F12b approaches with “Tight” cutoffs are generally capable of reproducing canonical CCSD(T) results to within ~0.25%, while requiring only a fraction of the computational cost associated with the latter. However, basis set convergence patterns and effect of counterpoise corrections are more erratic than for canonical calculations, highlighting the need for canonical benchmarks on closely related systems.
Introduction

Noncovalent interactions (NCIs) are well-known to significantly influence various physical and chemical properties of many (supra)molecular systems.[1,2] In biochemistry, for instance, NCIs are known to play important roles in protein folding, protein-ligand interaction, and nucleobase packing and stacking.[3,4] They are also of great importance in various chemical contexts such as organocatalysis, supramolecular chemistry, and conformational stability. That being said, individual NCIs (which may amount to as little as a few tenths of a kcal/mol; see, e.g., Ref.[5]) are extremely difficult to measure experimentally. For this reason, systematically-convergent wavefunction \textit{ab initio} methods constitute a crucial, well-nigh exclusive source of information on such individual NCIs. As such, these methods are extensively used for calibration of approximate computational approaches, such as molecular mechanics force fields, semiempirical MO methods, and DFT functionals.

Biochemically relevant NCIs are generally taking place in aqueous solutions. NCIs between biomolecules and water molecules, and between the latter among themselves, are therefore essential for understanding vital biochemical mechanisms, such as binding of substrates/inhibitors to their corresponding enzymes, maintaining 3-dimensional structures of organic complexes, and so forth. In this context, water clusters have long been the subject of basic scientific interest because they dictate water’s singular bulk properties (including but not limited to a remarkably high boiling point, low thermal expansion coefficient, and unusual density behavior). Thus, a great many experimental and theoretical studies have been carried out on the structure and properties of water in both the gas and liquid phases,[6–10] and wavefunction \textit{ab initio} methods have already provided valuable insight into the structures and energetics of small water clusters.[11–15]

One of our group’s recent ventures[16] was the re-evaluation of large water cluster benchmarks using conventional and explicitly-correlated (F12) coupled cluster methods: the latter were effectively used to accelerate the notoriously slow 1-particle basis set convergence for the MP2 and CCSD energetic components (see Refs.[17–20] for reviews on F12 methodology). Canonical CCSD(T)-F12b calculations on larger water clusters such as (H\textsubscript{2}O)\textsubscript{20}, however, are currently beyond the reach of commodity high-performance computing (HPC) hardware – except for woefully inadequate small basis sets like aVDZ. For this reason, pair natural orbital (PNO) local correlation approaches[21–24] may constitute an attractive, affordable alternative. PNO-type approaches may additionally be combined with
the F12 ansatz in order to provide the best of both worlds –accelerated basis set convergence as well as nearly-linear CPU time scaling with system size.

Despite enabling *ab initio* methods to ever-larger systems of interest, practical implementations of both PNO-type and F12 approaches involve many cutoffs, screening thresholds, and other details ‘under the hood’; these are hidden from the end user as tuned collections invoked through keywords like, e.g. in ORCA,[25] LoosePNO, NormalPNO (the default), and TightPNO: for details see Table 1 of Ref.[26] (The MOLPRO equivalents are specified in Tables 1-4 of Ref.[24] and the accompanying discussion.) For this reason, and especially in chemical territories where PNO-type approaches have not yet proven to be consistent and robust, comparing calculated results with a canonical benchmark is necessary to ensure the latter’s reliability.

For water clusters, or indeed any cluster $A_n$ for large enough $n$, such cutoffs put an additional fly in the ointment. While they do lead to substantial pruning in $A_n$, the monomer $A$ is so small that nothing is screened out and the PNO calculation becomes functionally equivalent to a canonical one. This creates an intrinsic imbalance for a cluster dissociation energy.

So how do we validate our PNO calculations for clusters as large as $(H_2O)_{20}$? As stated above, canonical CCSD(T) calculations in adequate basis sets are not a practical option (or we need not resort to PNO in the first place). However, we learned from our earlier work[16] that in an $n$-body expansion (see methods section below), the high-level correction, $HLC = [CCSD(T) – MP2]$, converges fairly rapidly with $n$. Hence, a very good approximation to the canonical CCSD(T)/CBS energetics can be obtained from combining canonical whole-system MP2-F12/CBS with at most 4-body HLCs. Such a calculation involves thousands of single-point CCSD(T) energy calculations, but on at most tetramers, and of course it is embarrassingly parallel. This offers us a practical route toward nearly exact canonical benchmark results as a touchstone for the PNO approaches.

For smaller clusters like $(H_2O)_6$, we of course need not resort to such approximations. In the present paper, dissociation energies of water clusters from the BEGDB[27] and WATER27[28] datasets will be considered in ascending order of size: (a) eight $(H_2O)_6$ structures, for which we were able to obtain canonical CCSD (T)/CBS reference values; (b) one $(H_2O)_{10}$ system; and (c) four $(H_2O)_{20}$ clusters.

**Computational Methods**

All calculations were carried out on the Faculty of Chemistry’s Linux cluster ‘chemfarm’ at the Weizmann Institute of Science. Single-point PNO-LCCSD(T)-F12b[24,29] calculations
were carried out using default and “domopt=tight” options, as defined in Ref.[24] and implemented in the Molpro2018 program package.[30] All PNO-based calculations discussed in this paper employ tight PNO domains unless explicitly stated otherwise.

CCSD(T)-F12b[31,32] and DF-MP2-F12[33] calculations (apart from those ran as a by-product of the former ones) were also used for the purpose of obtaining reliable canonical reference values.

For the explicitly correlated [i.e., CCSD(T)-F12b and PNO-LCCSD(T)-F12b] calculations, the correlation-consistent cc-pVnZ-F12 basis sets (a.k.a VnZ-F12) of Peterson et al.[34] were used in conjunction with the appropriate auxiliary basis sets for JKfit[35] (Coulomb and exchange), MP2fit[36,37] (density fitting in MP2), and OptRI[38,39] (complementary auxiliary basis set, CABS) basis sets. We also employed our own aug-cc-pVnZ-F12 (or aVnZ-F12) basis sets, introduced in Ref.[40]; the issue of the appropriate CABS basis set in such calculations is investigated in detail in Ref.[41] As recommended in Ref. [42], the geminal exponent (β) value was set to 1.0 for all basis sets used in explicitly-correlated calculations under consideration.

Conventional (i.e., orbital-based) ab initio CCSD(T)[43,44] calculations were performed using correlation-consistent[45] basis sets. In general, we used the combination of diffuse function-augmented basis sets aug-cc-pVnZ (n = T,Q,5) on non-hydrogen atoms and regular cc-pVnZ basis sets on hydrogen – to be denoted haVnZ for short.

Basis set extrapolations were carried out using the two-point formula:

\[ \frac{E_{\infty} = E(L) - [E(L)-E(L-1)]\left[\frac{L}{L-1}\right]^\alpha - 1}{2} \]

where L is the highest angular momentum present in the basis set for elements B–Ne and Al–Ar and α an exponent specific to the level of theory and basis set pair. The basis set extrapolation exponents (α) were taken from Table 2 of Ref.[46].

Aside from Boys-Bernardi counterpoise corrections[47] and the uncorrected values, we also apply the average of both (so-called “half-CP”), as rationalized by Sherrill and coworkers[48] for orbital-based ab initio methods and by our group[49] for F12 calculations. In short, such practice exploits the balance between basis set superposition error (which causes overbinding) and intrinsic basis set incompleteness (which causes underbinding).[49]

As mentioned in the introduction, decomposing water cluster dissociation energies (for which MP2 is a good approximation) into MP2 and HLC, and then applying an n-body expansion to the latter, may offer a route towards accurate energetics for large water clusters, where all-atom HLCs are computationally too costly.[16,50] (For brief overviews of the n-
body decomposition scheme, see Refs.[51,52].) Indeed, multiple levels of theory may be nested, with the 2-body HLCs treated at the highest level, the 3-body HLCs at a lower one, etc. By way of illustration, our reference value for \((\text{H}_2\text{O})_{10}\) below consists of:

\[
\text{REF}_{\text{water10}} = \text{half-CP-MP2-F12/a'V\{T,Q\}-F12 } \{\text{half-CP, whole system}\}
+ 2\text{-body}\left( [\text{CCSD(T)} - \text{MP2}] / \text{AV\{Q,5\}Z} \right) + 3\text{-body}\left( [\text{CCSD(T)} - \text{MP2}] / \text{AV\{T,Q\}Z} \right)
+ 4\ldots10\text{-body}\left( [\text{CCSD(T)} - \text{MP2}] / \text{AVTZ} \right)
\] (2)

For the avoidance of doubt, all calculated dissociation energies considered in this work are “vertical” – that is, the isolated monomer geometries are the same as those found within the cluster, and the dissociation energy does not include monomer relaxation terms. To facilitate comparisons with earlier work (e.g., Ref.[16]), reference geometries were taken verbatim from the BEGDB and WATER27 datasets and not optimized further.

Results and Discussion

a. \((\text{H}_2\text{O})_6\) structures

For our reference level, we were able to obtain both \(\text{CCSD(T)}/\text{A'V\{Q,5\}Z}\) and \([\text{CCSD-F12b/a'V\{T,Q\}Z-F12} + (\text{T})/\text{A'V\{Q,5\}Z}]\) half-CP energetics for the hexamers under consideration. However, as can be seen in Table S1 (found in the ESI), the latter turned out to be virtually indistinguishable from the former \((\pm 0.01 \text{ kcal/mol RMSD})\) – which indicates that 1-particle basis set convergence has been achieved.

Error statistics for the \((\text{H}_2\text{O})_6\) structures (Table 1) reveal that PNO-based methods are capable of reproducing canonical results to within less than 0.1 kcal/mol (arguably within the uncertainty of the reference values). However, it can be seen that basis set convergence patterns are quite erratic. Using both \(\text{VnZ-F12}\) and \(\text{a'VnZ-F12}\) basis set families, neither CP corrections nor basis set extrapolations consistently reduce error. (Indeed, since basis set extrapolation is itself subject to a certain degree of empiricism, some might argue that PNO-based methods require a dedicated set of extrapolation exponents for the procedure to be fruitful. On the flip side, strong sensitivity to extrapolation exponents is in our experience a sign that the basis sets being extrapolated from are still too far from the CBS limit.[53,54])
|        | n=         | T | T* | Q  | Q* | 5  | {T/Q} | {Q/5} |
|--------|------------|---|----|----|----|----|-------|-------|
| RMSD   | Raw        |   |     |    |    |    |       |       |
|        | VnZ-F12    | 0.102 | 0.228 | 0.063 | 0.024 | - | 0.109 | - |
|        | a'VnZ-F12  | 0.024 | 0.313 | 0.173 | 0.021 | - | 0.240 | - |
|        | conv. haVnZ | 0.099 | -   | 0.030 | -   | 0.150 | 0.032 | 0.249 |
|        | CP         |   |     |    |    |    |       |       |
|        | VnZ-F12    | 0.507 | 0.389 | 0.242 | 0.187 | - | 0.164 | - |
|        | a'VnZ-F12  | 0.390 | -   | 0.206 | -   | - | 0.140 | - |
|        | conv. haVnZ | 3.152 | -   | 1.188 | -   | 0.609 | 0.247 | 0.139 |
|        | half-Cp    |   |     |    |    |    |       |       |
|        | VnZ-F12    | 0.206 | 0.097 | 0.151 | 0.095 | - | 0.135 | - |
|        | a'VnZ-F12  | 0.189 | -   | 0.189 | -   | - | 0.189 | - |
|        | conv. haVnZ | 1.615 | -   | 0.608 | -   | 0.379 | 0.130 | 0.194 |
|        | MSD        |   |     |    |    |    |       |       |
|        | Raw        |   |     |    |    |    |       |       |
|        | VnZ-F12    | 0.098 | 0.227 | -0.057 | 0.000 | - | -0.104 | - |
|        | a'VnZ-F12  | 0.013 | 0.313 | -0.171 | 0.019 | - | -0.238 | - |
|        | conv. haVnZ | -0.080 | -   | -0.027 | -   | -0.149 | 0.011 | -0.247 |
|        | CP         |   |     |    |    |    |       |       |
|        | VnZ-F12    | -0.506 | -0.388 | -0.187 | -0.187 | - | -0.163 | - |
|        | a'VnZ-F12  | -0.389 | -   | -0.206 | -   | - | -0.139 | - |
|        | conv. haVnZ | -3.149 | -   | -1.186 | -   | -0.608 | 0.247 | -0.139 |
|        | half-Cp    |   |     |    |    |    |       |       |
|        | VnZ-F12    | -0.204 | -0.095 | -0.150 | -0.094 | - | -0.133 | - |
|        | a'VnZ-F12  | -0.188 | -   | -0.188 | -   | - | -0.188 | - |
|        | conv. haVnZ | -1.615 | -   | -0.607 | -   | -0.378 | 0.129 | -0.193 |

* = Constant scaling of triples (Ts), cf. Table 3 of Ref.[55]

Table 1. \((\text{H}_2\text{O})_6\): Error statistics for PNO-LCCSD(T)-F12b dissociation energies obtained using various basis sets; half-CP corrected, canonical CCSD(T)/A’V{Q,5}Z is used as a reference.

However, it should also be kept in mind that the (T) contributions — which we have seen in past work[16] are quite nontrivial — do not benefit at all from F12 as (T) is a 3-body, not a 2-body effect. Marchetti and Werner[56] in the past proposed scaling of the (T) contribution by the \(E_{\text{corr}}[\text{MP2-F12}]/E_{\text{corr}}[\text{MP2}]\) ratio as a workaround. In Ref.[55] we considered both this
approach, and scaling by the $E_{\text{corr}}[\text{CCSD-F12b}]/E_{\text{corr}}[\text{CCSD}]$ ratio, and found that constant scaling by a fixed ratio determined for a small training set [given in Table 3 of Ref.[55], denoted (Ts) there] yields better results for thermochemistry (besides being trivially size-consistent). For the problem at hand, triples scaling (denoted by an asterisk) does seem to offer an improvement over unscaled results – with the exception of raw triple-zeta options, which are arguably too far from the basis set limit anyway (thus, unscaled results obtained in this manner seem to benefit from a fortuitous error compensation). Indeed, that (Ts) scaling of the largest basis set is more effective than basis set extrapolations for PNO-F12 methods may be a useful finding with broader implications for thermochemistry of larger systems. We intend to explore this issue further in a future paper.

Ineffectiveness of CP corrections may be associated with the fundamental principles on which PNO methodology rests: while ‘strong pairs’ that exceed a certain energetic cutoff, fully benefit from the availability of added basis functions, ‘weak pairs’ are only treated at a lower level of theory, or are simply neglected, thus not making optimal use of the added functions and creating an imbalance for the overall calculated energy. Unlike for the canonical F12 case,[40] where a′VnZ-F12 offers considerably faster and smoother basis set convergence than VnZ-F12, we see no obvious advantage in PNO-F12 calculation on $(\text{H}_2\text{O})_6$ isomers. This can, however, be an artifact of the smallness of these clusters (see below).

Mean signed deviations for the methods under consideration indicate that PNO-based results are generally underbound relative to canonical reference values (except for VTZ-F12, a′VTZ-F12 and scaled VQZ-F12 and a′VQZ-F12 raw dissociation energies).

\textit{b. $(\text{H}_2\text{O})_{10}$}

Unlike for the hexamers, fully canonical CCSD(T) energetics with sufficiently large basis sets were previously found to be computationally prohibitive.[16] Thus, we have employed the n-body decomposition scheme in Eq.(2).

Results obtained for $(\text{H}_2\text{O})_{10}$ (Table 2) display a somewhat similar picture to $(\text{H}_2\text{O})_6$, except that this time around, a′VnZ-F12 seems to be generally preferable over VnZ-F12. Like for the hexamers, it can be seen that PNO-based methods can reproduce the canonical values to within $\sim0.1$ kcal/mol (equivalent to $\sim0.1\%$ percent of the overall interaction, which amounts to 98.5 kcal/mol). In this case, however, some of the errors – and specifically those for the raw dissociation energies – are larger in magnitude. This fact illustrates the thermochemical imbalance in PNO association energies pointed out in the introduction: This
problem is expected to be exacerbated for $A_n$ clusters as $n$ increases. Unlike for $(H_2O)_6$, mean signed deviations testify that PNO-based results are, in fact, overbound in this case (except for the CP-corrected VTZ-F12 and $a'$VTZ-F12 options); unfortunately, this finding precludes using an ad hoc, a posteriori correction for PNO-based results – such as a constant scaling factor – in order to eliminate biases from corresponding canonical limits. Again, basis set extrapolations do not seem to bring us closer to the canonical reference, and while (Ts) scaling does offer an improvement for some CP-corrected results, it is not as useful since values of comparable quality may be obtained using CP-uncorrected (and therefore less computationally costly) alternatives. (For instance, raw $a'$VQZ-F12 is of similar quality to scaled, CP-corrected quadruple zeta options).

| n= | T   | T*  | Q   | Q*  | {T/Q} |
|----|-----|-----|-----|-----|-------|
| VnZ-F12 | 0.561 | 0.856 | 0.412 | 0.543 | 0.304 |
| a'VnZ-F12 | 0.409 | 0.757 | 0.204 | 0.358 | 0.054 |

| n= | T   | T*  | Q   | Q*  | {T/Q} |
|----|-----|-----|-----|-----|-------|
| VnZ-F12 | -0.505 | -0.233 | 0.035 | 0.162 | 0.429 |
| a'VnZ-F12 | -0.273 | 0.053 | 0.094 | 0.245 | 0.362 |

| n= | T   | T*  | Q   | Q*  | {T/Q} |
|----|-----|-----|-----|-----|-------|
| VnZ-F12 | 0.028 | 0.311 | 0.224 | 0.353 | 0.367 |
| a'VnZ-F12 | 0.068 | 0.405 | 0.149 | 0.302 | 0.208 |

* = Constant scaling of triples (Ts), cf. Table 3 of Ref. [55]

**Table 2.** $(H_2O)_{10}$: Signed deviation (kcal/mol) for PNO-LCCSD(T)-F12b dissociation energies obtained using various basis sets; $REF_{water10}$, eq. (2), is used as a reference.

c. $(H_2O)_{20}$ structures

As for our $n$-body-based strategy used for $(H_2O)_{10}$, we have managed to obtain benchmark, fully-canonical results using the following level of theory:

$REF_{water20} = MP2-F12/a'V\{T,Q\}-F12 \{raw, whole system\}$

+ 2-body \( \left( [CCSD-F12b - MP2-F12]/a'VQZ-F12 + (T)/AV5Z \right) \)

+ 3-body \( \left( [CCSD-F12b - MP2-F12]/a'VTZ-F12 + (T)/a'V\{D,T\}Z \right) \)

+ 4-body \( \left( [CCSD(T) - MP2]/a'VTZ \right) \) \( (3) \)
As can be seen in Table S2 in the ESI, this reference level represents an improvement over the one previously established in Ref.[16] (see ESI-2 of same paper), which corresponds to:

\[
\text{REFOLD}_{\text{water}20} = \text{MP2-F12/V}\{T,Q\}-F12 \ \{\text{raw, whole system}\}
\]

\[
+ 2\text{-body}\left( [\text{CCSD-F12b} - \text{MP2-F12}]/\text{VQZ-F12} + (T)/\text{A'}V\{T,Q\}Z \right) \\
+ 3\text{-body}\left( [\text{CCSD-F12b} - \text{MP2-F12}]/\text{VTZ-F12} + (T)/\text{a'}V\{D,T\}Z \right)
\]

which neglected 4-body HLC contributions entirely. Primarily because of the latter, old and new total interaction energies differ by up to 0.86 kcal/mol.

Error statistics for the four structures of \((\text{H}_2\text{O})_{20}\) (Table 3) further confirm our hypothesis regarding accumulation of errors in PNO-based calculations, depending on chosen PNO cutoffs — as some of the errors for the raw calculations now approach 1 kcal/mol.

Nevertheless, PNO-based methods can still be used to reproduce canonical reference values to within 0.5 kcal/mol, which at about 0.25% of the cluster association energy might be deemed negligible in relative terms. Once again, CP corrections prove to be quite ineffectual, and do not justify the required additional computational cost (i.e., using the entire cluster’s basis functions for calculating monomer energies). (Ts) scaling, on the other hand, does seem to improve most calculated results — even \(\text{a'}\text{VTZ-F12}\), which is relatively compact and computationally economical, comes close to the reference. Thus, a PNO-LCCSD(T)-F12b calculation with tight PNO settings on the edge-sharing \((\text{H}_2\text{O})_{20}\) structure took 6 days and 14 hours CPU time (with nearly perfect parallelization), whereas our n-body-based canonical reference calculation according to eq. (3) required more than a year (!) for the same system. This is indeed good news, as PNO-based methods can now be recognized as both remarkably economical and fairly accurate for the systems under consideration.

Would switching to default PNO domains come at a substantial cost in accuracy? As can be seen in Table 4, employing such settings leads to further under-binding: for the \(\text{a'}\text{VnZ-F12}\) \((n=\text{T},\text{Q})\) basis sets considered here, applying default PNO domains results in an error two to six times as large than that obtained using tight PNO settings. That being said, it should once more be noted that default PNO settings are more computationally economical, and may thus be preferable for larger systems for which tight PNOs are too demanding. Again, a PNO-LCCSD(T)-F12b calculation with tight PNO settings on the edge-sharing \((\text{H}_2\text{O})_{20}\) structure required 6 days and 14 hours CPU time, compared to only 23 hours with default PNOs (6.843:1 ratio). This finding may indeed be useful for, say, still larger water clusters [such as \((\text{H}_2\text{O})_{100}\)]. However, the associated compromises on accuracy are not quite justified for the case under consideration.
To sum up: we have seen that PNO-based methods can be used to reproduce accurate canonical dissociation energies of water clusters up to (H\textsubscript{2}O)\textsubscript{20}. This further corroborates that such methods are a viable alternative to canonical calculations for calculating NCIs of biologically relevant systems. That being said, and since systematic convergence is perhaps the key benefit of wavefunction \textit{ab initio} calculations, the somewhat erratic behavior of PNO-based regarding CP corrections and basis set extrapolations is indeed somewhat troubling. Thus, we can again see that results obtained using such methods should be treated with some caution in cases where no calibration against canonical values is available.

**Conclusions**

In this paper, we have investigated the performance of combined PNO and F12 methodologies [i.e., PNO-LCCSD(T)-F12b] for reproducing high-quality, canonical

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**Table 3.** (H\textsubscript{2}O)\textsubscript{20}: Error statistics for PNO-LCCSD(T)-F12b dissociation energies obtained using various basis sets; Ref\textsubscript{water20} is used as a reference.

|        | n= | T   | T*  | Q   | Q*  | {T/Q} |
|--------|----|-----|-----|-----|-----|-------|
| RMSD   |    |     |     |     |     |       |
| raw    |    |     |     |     |     |       |
| VnZ-F12|    | 0.309 | 0.430 | 0.504 | 0.225 | 0.533 |
| a'VnZ-F12 |    | 0.511 | 0.271 | 0.942 | 0.605 | 1.092 |
| CP     |    |     |     |     |     |       |
| n=     |    |     |     |     |     |       |
| VnZ-F12|    | 2.556 | 1.408 | 1.323 | 0.756 | 0.641 |
| a'VnZ-F12 |    | 1.938 | 0.764 | 1.190 | 0.619 | 0.753 |
| half-CP |    |     |     |     |     |       |
| n=     |    |     |     |     |     |       |
| VnZ-F12|    | 1.407 | 0.518 | 0.911 | 0.485 | 0.586 |
| a'VnZ-F12 |    | 1.221 | 0.261 | 1.065 | 0.612 | 0.922 |

* = Constant scaling of triples (Ts), cf. Table 3 of Ref.[55]

**Table 4.** (H\textsubscript{2}O)\textsubscript{20}: Error statistics for PNO-LCCSD(T)-F12b dissociation energies obtained using a'VnZ-F12 (n=T,Q) basis sets with tight and default PNO domains; Ref\textsubscript{water20} is used as a reference.

|        | n= | T   | T*  | Q   | Q*  | {T/Q} |
|--------|----|-----|-----|-----|-----|-------|
| RMSD   |    |     |     |     |     |       |
| Raw    |    |     |     |     |     |       |
| a'VnZ-F12 |    | 0.361 | 0.191 | 0.666 | 0.428 | 0.772 |
| tightDomain | | 1.689 | 1.203 | 1.716 | 1.494 | 1.641 |
| default     |    |     |     |     |     |       |

|        | n= | T   | T*  | Q   | Q*  | {T/Q} |
|--------|----|-----|-----|-----|-----|-------|
| MSD    |    |     |     |     |     |       |
| raw    |    |     |     |     |     |       |
| a'VnZ-F12 |    | -0.498 | 0.258 | -0.940 | -0.603 | -1.091 |
| tightDomain | | -2.381 | -1.694 | -2.421 | -2.107 | -2.316 |
| default     |    |     |     |     |     |       |
CCSD(T)-based NCIs for water clusters as large as (H$_2$O)$_{20}$. Based upon our analysis of all associated error statistics and computation times, we were able to draw the following conclusions:

- PNO-LCCSD(T)-F12b approaches are generally capable of reproducing canonical CCSD(T) results to within ~0.25%. Deviations from the reference values are not systematically positive or negative in sign. This fact prevents using ad-hoc, \textit{a posteriori} corrections such as employing constant scaling factors and the like.

- Basis set convergence patterns, however, are quite erratic. First, using both VnZ-F12 and a'VnZ-F12 families, neither CP corrections nor basis set extrapolations systematically improve results. Second, results of triple-zeta quality are sometimes fortuitously closer to the reference than quadruple-zeta ones – apparently due to different error compensations (e.g., intrinsic basis set insufficiency, F12 and PNO cutoffs, etc.). Third, constant (Ts) scaling of the triples contribution, as suggested in Ref. [55], is somewhat helpful when used with relatively-large basis sets (namely VQZ-F12 and a'VQZ-F12). Finally, unlike for canonical F12 methods alone, augmented basis sets (i.e., a'VnZ-F12) do not necessarily outperform their non-augmented counterparts (VnZ-F12) in PNO-F12 calculations. We tentatively attribute this to PNO domains being too small for using diffuse functions in an effective manner (the latter are designed to “capture” spatial regions found far from the nuclei, and are thus somewhat contradictory to the localized PNO strategy).

- As previously noted,[24,57] PNO-LCCSD(T)-F12b calculations require only a fraction of the computational cost associated with canonical CCSD(T). In our case, a PNO-LCCSD(T)-F12b calculation on the edge-sharing (H$_2$O)$_{20}$ structure took 6 days and 14 hours CPU time, whereas the canonical reference calculation (MP2-F12/CBS + n-body-based HLC) required more than a year (!)

- Based on the error statistics for a’VnZ-F12 (n=T,Q) (H$_2$O)$_{20}$ energetics, employing default PNO domains leads to errors two to six times larger than those obtained using tight domains. Nevertheless, default domains are much more economical computationally, and may therefore be an option for larger systems where tight PNO domains are already impractical. (For instance, for the edge-sharing (H$_2$O)$_{20}$ structure, tight PNO settings required ~7 times as much CPU time as the same calculation with default PNOs.)
The present paper shows that, despite balance issues between a cluster and its separate small monomers due to PNO truncation disproportionately affecting the former, PNO-LCCSD(T)-F12b nevertheless offers a path to reliable NCI energetics for larger water clusters (perhaps as large as (H\textsubscript{2}O\textsubscript{100}). The usefulness of combined PNO-F12 approaches for dimeric noncovalent interactions was shown in detail by Ma and Werner.[58]

In future work, we hope to apply PNO and F12 methodologies to large biochemical systems of interest, such as a 300-atom model of alcohol dehydrogenase.[59] Energy decomposition schemes, such as the recently-proposed LED (local energy decomposition[60]) will be applied for interpretative purposes.

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**Supporting information**

Our best estimates for all total dissociation energies considered in this work are provided in a dedicated spreadsheet, alongside Tables S1-S2. In addition, water cluster geometries used in our calculations are given in .xyz format; example input files for PNO-LCCSD(T)F12b/a’VQZ-F12 calculations, as well as those required for establishing our reference level, are prescribed for the H2O20es structure.

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