

Accurate Treatment of Large Supramolecular Complexes by Double-Hybrid Density Functionals Coupled with Nonlocal van der Waals Corrections

Joaquín Calbo,[†] Enrique Ortí,[†] Juan C. Sancho-García,[§] Juan Aragó^{†‡}*

[†]Instituto de Ciencia Molecular, Universidad de Valencia, E-46980, Spain

[§]Departamento de Química Física, Universidad de Alicante, E-03080, Spain

ABSTRACT

In this work, we present a thorough assessment of the performance of some representative double-hybrid density functionals (revPBE0-DH-NL and B2PLYP-NL), as well as their parent hybrid and GGA counterparts, in combination with the most modern version of the nonlocal (NL) van der Waals correction to describe very large weakly-interacting molecular systems dominated by noncovalent interactions. Prior to the assessment, an accurate and homogenous set of reference interaction energies were computed for the supramolecular complexes constituting the L7 and SL12 data sets by using the novel, precise, and efficient DLPNO-CCSD(T) method at the complete basis set limit (CBS). The correction of the basis set superposition error and the inclusion of the deformation energies (especially for the S12L set) have been determining for obtaining precise DLPNO-CCSD(T)/CBS interaction energies. Among the density functionals

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3 evaluated, the double-hybrid revPBE0-DH-NL and B2PLYP-NL with the three-body dispersion
4 correction provide remarkably accurate association energies very close to the chemical accuracy.
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6 Overall, the nonlocal van der Waals approach combined with proper density functionals can be
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8 seen as an accurate and affordable computational tool for the modeling of large weakly-bonded
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10 supramolecular systems.
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3 INTRODUCTION
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6 Noncovalent interactions (NCIs) are considered to be weak but crucial forces governing the
7 tridimensional organization and reactivity of molecular biological systems, such as proteins and
8 nucleic acids, and their understanding is the key for the development of drug design,
9 crystallinity, and design of novel materials by controlling their self-assembly. NCIs can be seen
10 as a combination of electrostatic and dispersion forces; the latter, which mainly arise from long-
11 range electron correlation effects, can be properly captured by highly correlated wave function
12 methods. Coupled-cluster theory with singles, doubles, and perturbatively connected triple
13 excitations [CCSD(T)] in combination with large basis sets has become the “gold-standard”
14 method to accurately deal with these weak but important forces in supramolecular systems.¹⁻³ Its
15 use is, however, restricted to small- or medium-size molecular systems due to its unfavorable
16 computational $O(N^7)$ scaling, where N is related to the molecular size. In this sense, the
17 longstanding quest for efficient highly correlated wave function methods for applications in large
18 (real-life) systems is still an active research field.

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37 Very recently, Neese *et al.* have successfully coupled the domain-based local pair natural
38 orbital (DLPNO) approach with the CCSD(T) method providing a highly correlated near-linear-
39 scaling methodology known as DLPNO-CCSD(T).⁴ The DLPNO-CCSD(T) method has proved
40 to offer promising average errors in relative energies of approximately 0.5 kcal/mol for a
41 challenging test set of medium-size organic molecules, and it is thus increasingly being applied
42 for benchmarking calculations in large systems, where the canonical CCSD(T) approach is
43 unaffordable.⁵ This methodology therefore not only opens the door for rigorous studies in large
44 molecular systems but also offers the opportunity to benchmark and parameterize less-costly
45 quantum chemical methods in the context of NCIs.
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3 On the other hand, Density Functional Theory (DFT) has become the standard tool for a vast
4 array of quantum chemistry applications owing to its more favorable computational cost ranging
5 from $O(N^3)$ to $O(N^5)$. Nevertheless, common density functionals (DFs) are not capable of totally
6 capturing the long-range correlation phenomena required for the adequate description of NCIs.⁶⁻⁸
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8 Over the last years, much effort within the DFT framework has been made to develop
9 approximations that allow the accurate treatment of dispersion forces between molecular
10 entities.⁹⁻¹⁰ Among the most modern approaches, the atom-pairwise dispersion-corrected DFT
11 approach, developed by Grimme *et al.*, known in its current version as DFT-D3, is a manner of
12 dealing with NCIs with a reasonable compromise between computational cost and accuracy.¹¹⁻¹⁴
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14 A less popular but seamless and general approach known as van der Waals Density Functional
15 Theory (vdW-DFT) has recently received a great deal of attention due to its low degree of
16 empiricism.¹⁵⁻¹⁶ The vdW-DFT approach accounts for the long-range electron correlation effects
17 by means of an explicit nonlocal (NL) correlation functional that depends on the electron density
18 at two different points in space (\mathbf{r} and \mathbf{r}') and is added to the general expression of the exchange-
19 correlation energy functional. In the modern and efficient formulation developed by Vydrov and
20 Van Voorhis (VV10),¹⁵ commonly known as DFT-NL, the NL correction can be coupled easily
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43 Compared with the extended DFT-D3 approach, the NL correction has been used with a
44 relatively scarce number of standard DFs. Hujo and Grimme assessed the performance of
45 different Generalized Gradient Approximation (GGA) and hybrid density functionals in
46 combination with the NL correction.¹⁶ More recently, the NL correction was merged with more
47 sophisticated double-hybrid density functionals (DHDFs).¹⁷⁻¹⁸ These studies have proven that
48 DFT-NL can be considered as a robust electronic structure method capable of dealing with the
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3 challenging problems dominated by intermolecular NCIs independently of the functional of
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5 choice. However, despite the great success of the NL approximation combined with standard
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7 DFs for reliable studies in supramolecular chemistry, its performance has been mainly evaluated
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9 in small- and medium-size supramolecular systems where benchmark energies, usually obtained
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11 at CCSD(T) level with extrapolation to infinite basis set, are available. Therefore, investigating
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13 the behavior of the DFT-NL correction in very large systems would provide valuable
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15 information about the reliability of this methodology for treating NCIs in real-life problems.
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20 In this contribution, we first provide an accurate and homogeneous set of reference interaction
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22 energies for large supramolecular complexes by using the novel DLPNO-CCSD(T) approach at
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24 the complete basis set limit (CBS). For that purpose, we have employed the L7¹⁹ and S12L²⁰ data
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26 sets, which are formed by large supramolecular complexes of different nature (*vide infra*).
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28 Second, we use the DLPNO-CCSD(T) interaction energies to assess the performance in large
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30 supramolecular complexes of the NL correction combined with two representative double-hybrid
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32 density functionals (revPBE0-DH-NL and B2PLYP-NL), which behaved remarkably accurate
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34 for the S22 and S66 training sets.¹⁷ A comparison with their corresponding hybrid (revPBE0-NL
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36 and B3LYP-NL) and GGA (revPBE-NL and BLYP-NL) analogues is also performed to assess
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38 the performance across the hierarchy of DFT-based methods.²¹
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47 THEORETICAL MODELS AND COMPUTATIONAL DETAILS

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50 Reference interaction energies for the L7¹⁹ and S12L²² training sets were computed with the
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52 DLPNO-CCSD(T) method.⁴ As mentioned above, DLPNO-CCSD(T) can be seen as a highly
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54 correlated wave function method whose accuracy is comparable to the canonical CCSD(T)
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56 counterpart but with a dramatically reduced computational cost. Default values for all internal
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thresholds of the methodology (TCutPairs, TCutPNO and TCutMKN) were used as suggested by the developers.⁵ For further details, the reader is referred to the original literature.^{4,23} The Ahlrich's def2-TZVPP basis set²⁴ was employed for the DLPNO-CCSD(T) calculations. Interaction energies at the DLPNO-CCSD(T)/def2-TZVPP level were extrapolated to the complete basis set limit (CBS) according to the hybrid scheme proposed by Sherrill *et al.*²⁵ and Jurecka *et al.*,²⁶ and further successfully applied by Liakos *et al.* within the LPNO framework (Eq. 1).²⁷⁻²⁸

$$E^{DLPNO-CCSD(T)/CBS} = (E^{HF/CBS} + E_{corr}^{MP2/CBS}) + (E_{corr}^{DLPNO-CCSD(T)/def2-TZVPP} - E_{corr}^{MP2/def2-TZVPP}) = \\ = E^{MP2/CBS} + \Delta E_{corr}^{DLPNO-CCSD(T)} \quad (1)$$

Note that by using this scheme we assume that the residual difference between DLPNO-CCSD(T) and MP2 correlation energies has a less marked dependence on basis set than the MP2 correlation energy itself. The $E^{MP2/CBS}$ term was calculated by a two-point extrapolation scheme using the Dunning's cc-pVDZ and cc-pVTZ basis sets with ordinal numbers $X = 2$ and $Y = 3$, respectively, where the Hartree-Fock ($E^{HF/CBS}$) and the correlation ($E_{corr}^{MP2/CBS}$) terms were computed as

$$E^{HF/CBS} = \frac{E^{HF/(X)}e^{-\alpha\sqrt{Y}} - E^{HF/(Y)}e^{-\alpha\sqrt{X}}}{e^{-\alpha\sqrt{Y}} - e^{-\alpha\sqrt{X}}} \quad (2)$$

and

$$E_{corr}^{MP2/CBS} = \frac{X^\beta E_{corr}^{MP2/(X)} - Y^\beta E_{corr}^{MP2/(Y)}}{X^\beta - Y^\beta} \quad (3)$$

The α and β exponents were set at 4.42 and 2.46 as reported recently in the literature.²⁹

The relevance of the basis set superposition error (BSSE) in medium supramolecular systems has been evidenced, for example, by Janowski *et al.*³⁰ in the case of the coronene dimer. Furthermore, the seminal works on the L7¹⁹ and the S12L²² data sets made use of the BSSE

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3 correction, since large basis sets close to the CBS limit remain prohibitive due to the size of the
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6 supramolecular systems. In this work, the basis set convergence was analyzed in detail for the
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9 supramolecular complex **C3GC**, which can be considered as a representative example of the L7
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11 and S12L test sets (Table S1). The interaction energy computed at MP2/CBS(cc-pVDZ/cc-
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13 pVTZ) (-64.69 kcal/mol) provides a small deviation of only 1.9% compared to CBS(cc-
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15 pVTZ/cc-pVQZ) (-63.50 kcal/mol) when the counterpoise (CP)³¹ correction is included. All the
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17 MP2 energies were therefore calculated at the CBS(cc-pVDZ/cc-pVTZ) level and were CP-
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19 corrected to reduce the BSSE. Table S2 clearly shows a notable BSSE effect on the systems
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21 considered in L7 and S12L data sets at the MP2/CBS level.
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25 Deformation energies (*vide infra*) were computed at the spin-scaled MP2 method (SCS-
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27 MP2).³² This method has proven to attenuate the overbinding tendency of MP2 in π - π
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29 supramolecular complexes similar in nature but smaller in size than those considered herein.³³
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31 All MP2 and SCS-MP2 calculations made use of the ‘resolution of the identity’ (RI) and the
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33 ‘chain-of-spheres’ (COSX) techniques, for Coulomb and exchange integrals, respectively, to
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35 alleviate the computational cost. The corresponding matching auxiliary basis sets (cc-pVDZ/C
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37 and cc-pVTZ/C, and cc-pVDZ/JK and cc-pVTZ/JK) were employed throughout.³⁴ Grids for the
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39 COSX approximation were increased from defaults to Gridx6.³⁵
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44 Two families of DFs have been employed in this work: the Becke-Lee-Yang-Parr (BLYP) and
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46 the revised Perdew-Burke-Ernzerhof (revPBE). For each family, the Generalized-Gradient
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48 Approximation (GGA), the hybrid (H), and the double-hybrid (DH) DFs were used. Note that the
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50 GGA is considered as the baseline for further improvements (rungs) within each family. A
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52 general expression for the exchange-correlation (x_c) density functionals utilized in this work and
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54 coupled to the nonlocal approach can be expressed as:
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$$E_{xc}[\rho] = w_{\text{HF}} E_x^{\text{HF}} + (1 - w_{\text{HF}}) E_x[\rho] + (1 - w_{\text{PT2}}) E_c[\rho] + w_{\text{PT2}} E_c^{\text{PT2}} + E_c^{\text{NL}}[\rho], \quad (4)$$

where $E_x[\rho]$ and $E_c[\rho]$ correspond to the GGA exchange and correlation energy terms, respectively, weighted by the scaling parameter w_i . The E_x^{HF} and E_c^{PT2} terms are, respectively, the exact exchange HF-like energy and the correlation energy obtained at the Møller–Plesset perturbation theory up to second order.³⁶ Note that the E_x^{HF} , E_c^{PT2} , and E_c^{NL} terms are evaluated with the orbitals arising from the solution of the Kohn–Sham one-electron equations but discarding the last two terms of Eq. 4. Table 1 presents a detailed description for the composition of all the exchange-correlation functionals used in this work.

Table 1. Composition of the Exchange-Correlation Functionals Used along This Work

Functional	Type	$E_x[\rho]$	$E_c[\rho]$	w_{HF}^a	w_{PT2}^b	b^c	Ref.
revPBE0-DH-NL	Double-Hybrid GGA	revPBE	PBE	0.50	0.125	5.7	17
revPBE0-NL	Hybrid GGA	revPBE	PBE	0.25	0	4.2	37
revPBE-NL	GGA	revPBE	PBE	0	0	3.6	38-39
B2PLYP-NL	Double-Hybrid GGA	B88	LYP, VWN	0.53	0.270	7.8	36
B3LYP-NL	Hybrid GGA	B88	LYP, VWN	0.20	0	4.6	40-41
BLYP-NL	GGA	B88	LYP	0	0	4.0	42-43

^a Weight of the HF-like exchange. ^b Weight of the perturbative term. ^c Values used for the adjustable parameter b in the E_c^{NL} term.

The DFs under study were merged with the NL approximation (DFT-NL), such as it was proposed by Vydrov and Van Voorhis.¹⁵ The NL energy functional is added to the exchange-correlation energy functional non-self-consistently.¹⁶⁻¹⁷ In the DFT-NL approach, the NL energy functional depends on the electron density and the short-range (b) and long-range (C) adjustable parameters (the reader is referred to the original work for further details, Ref. 15). The short-range attenuation parameter b used here for the density functionals was carefully fitted using the

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3 S22⁴⁴⁻⁴⁵ and S66⁴⁶⁻⁴⁷ data sets,¹⁷ whereas the long-range parameter C is fixed to its original value
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5 $C = 0.0093$ (its optimization leads to only minor improvements).¹⁶⁻¹⁷ To assess the errors of the
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7 different DFT-NL functionals, the mean signed error (ME), the mean absolute error (MAE), and
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9 the maximum absolute error (MAX) are employed. A negative ME indicates an overbinding
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11 trend, while positive ME values signify an underestimation in the interaction energy.
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15 The DFT-NL calculations were performed with the def2-TZVP basis set.^{24,48} Although the
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17 combination of DFT calculations (with dispersion corrections) and a basis set of triple-zeta
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19 quality (cc-pVTZ) has been shown to provide interaction energies with a small BSSE,⁴⁹ this error
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21 can be large enough for the supramolecular systems investigated herein. Consequently, all the
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23 interaction energies calculated were counterpoise corrected (see Eq. S1 in the Supporting
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25 Information). The computational effort for the DFT calculations was significantly reduced in all
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27 cases by making use of the ‘resolution of the identity’ (RI)⁵⁰ and the ‘chain-of-spheres’
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29 (COSX)⁵¹ techniques, for Coulomb and exchange integrals, respectively. The COSX
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31 approximation was extensively applied by using the overlap fitting procedure described in Ref.
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33 52. Large grids (Gridx6), especially required for the treatment of noncovalent interactions, have
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35 been employed in the COSX procedure. The corresponding matching auxiliary basis sets def2-
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37 TZVP/C and def2-TZVP/JK were employed throughout.³⁴ The quadrature grids needed for
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39 numerical integration of DFs were also increased (Grid6) with respect to defaults, as it is
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41 strongly recommended for intermolecular interaction energies, as well as the corresponding
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43 thresholds for converging energies in the self-consistent field procedure (TightSCF). A larger
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45 grid for the NL approximation was also used (Vdwwgrid4). For comparison, double-hybrid
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47 B2PLYP-D3 calculations were carried out by means of the Grimme’s dispersion correction (D3)
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49 using the Becke-Johnson damping function.^{11-12,53-55} The three-body dispersion correction
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3 (E_{ABC})¹¹ has been evaluated in all cases. All the calculations were carried out by using the ORCA
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5 3.0 program package.³⁵
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10 RESULTS AND DISCUSSION

11 12 13 14 1.1. Benchmark energies for large supramolecular complexes.

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17 Two sets of very large supramolecular complexes (known as L7 and S12L) have been
18 specially designed to evaluate the performance of accurate quantum-chemical methods with low
19 computational cost for “real-life” applications (see Figure S1 and S2 for the structure of the
20 supramolecular complexes of L7 and S12L, respectively). The L7 set proposed by Sedlak *et al.*¹⁹
21 contains seven supramolecular complexes intentionally selected to be mostly dispersion-
22 dominated (aliphatic-aliphatic and π - π interactions) and their size ranges from 48 to 112 atoms.
23 The reference association energies reported before for L7 were computed at the QCISD(T)/CBS
24 level.¹⁹ The S12L data set includes twelve supramolecular complexes (involving both neutral and
25 charged species) dominated by non-polar, π -stacking, H-bonding, and electrostatic cation-dipolar
26 interactions. In contrast to the L7 set, the reference interaction energies in the S12L set, proposed
27 in the seminal work of Grimme *et al.*, were estimated from (back-corrected) experimental
28 binding affinities.²⁰ Nevertheless, the authors admitted some uncertainty about the validity of
29 these gas-phase interaction energies for benchmarking purposes. In a further step, Ambrosetti *et*
30 *al.* provided accurate values for the interaction energy of six host-guest complexes of the S12L
31 set at the diffusion quantum Monte Carlo (DQMC) level.⁵⁶ More recently, Hesselmann *et al.*
32 calculated the interaction energies for the complexes of S12L by using intermolecular symmetry-
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3 adapted perturbation theory combined with a density-functional theory description of the
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5 interacting molecules.⁵⁷
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9 Due to the difference in the methods employed to estimate the reference binding energies in L7
10 and S12L (theoretical and experimental data), a homogeneous set of benchmark interaction
11 energies computed at the same level of theory is a clear demand for these data sets. Hence,
12 interaction energies at the DLPNO-CCSD(T)/CBS level of theory have been consistently
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14 computed for L7 and S12L (Table 2). Hesselmann *et al.*⁵⁷ showed that the deformation energies
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16 can be important for compounds of S12L and they should be taken into account to provide
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18 accurate interaction energy values. Additionally, it was proven that the deformation energies can
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20 be overestimated by MP2 due to its overbinding tendency in π - π supramolecular complexes
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22 (especially in compounds **3a** and **3b**). The authors corrected the deformation energies for S12L
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24 using the SCS-MP2 method since it provides a better description for π - π interactions than MP2
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26 does.³³ Deformation energies (see the Supporting Information for further details) were therefore
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28 corrected at SCS-MP2/CBS for S12L (Table S3). Deformation energies for complexes of L7
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30 were supposed to be small and were not corrected.¹⁹ Table S4 collects the different interaction
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32 energy terms of the total interaction energy computed for L7 and S12L supramolecular systems.
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Table 2. Interaction Energies (in kcal/mol) Computed for the L7 and S12L Data Sets at the DLNPO-CCSD(T)/CBS level

Data set	Complex	DLPNO-CCSD(T)/CBS ^a	QCISD(T)/CBS ^b	“Experimental” ^c	DQMC ^d
L7	C2C2PD	-24.81	-24.36		
	C3A	-17.98	-18.19		
	C3GC	-29.86	-31.25		
	CBH	-11.64	-11.06		
	GCGC	-13.21	-14.37		
	GGG	-1.68	-2.40		
	PHE	-22.81	-25.76		
S12L	2a	-30.65		-29.9	-27.2
	2b	-23.04		-20.5	-17.2
	3a	-23.68		-24.3	
	3b	-23.08		-20.4	
	4a	- ^e		-27.5	-25.8
	4b	- ^e		-28.7	
	5a	-33.40		-34.8	-33.4
	5b	-22.98		-21.3	
	6a	-79.79		-77.4	-81.0
	6b	-77.82		-77.0	
7a	-123.89 ^f		-131.5		
7b	-22.74		-22.6	-24.1	

^a This work. ^b Reference interaction energies computed at the QCISD(T) level and extrapolated to the complete basis set limit (CBS) by means of a hybrid scheme as explained in Ref. 19. For the correlated component of the energy, a relatively small 6-31G*(0.25) basis set was employed. ^c Gas-phase interaction energies were obtained back-correcting experimental values for binding affinities in solution according to Ref. 20. ^d The stochastic DQMC electronic structure method using Slater-Jastrow trial wave functions was employed to compute the reference interaction energies as explained in Ref. 56. ^e Calculations for these complexes at the DLPNO-CCSD(T)/def2-TZVPP did not converge due to the high number of interacting electron pairs between the two moieties originated by the huge amount of close carbon-carbon contacts. ^f The $E^{MP2/CBS}$ term was computed according to Eq. 2 and 3 by using Ahlrichs basis sets with double and triple- ζ quality (def2-SVP and def2-TZVPP, respectively) due to the inexistent definition of the auxiliary cc-pVDZ/C basis set for Fe. The exponential α and β values were set to 10.39 and 2.40, respectively.²⁹

The combination of the two sets of systems provides a wide range of interaction energies for very large supramolecular complexes ranging from -1.68 kcal/mol in the stacked guanine trimer GGG of the L7 set (Figure S1) to -123.89 kcal/mol in the cucurbit[7]uril@ferrocene-based

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3 complex of S12L (Figure S2). Broadly speaking, the DLPNO-CCSD(T) association energies
4 present small differences with respect to the previous values available in the literature, especially
5 for the L7 set, which were obtained from a purely theoretical treatment.¹⁹ The largest
6 discrepancy obtained for the L7 set is found for the PHE complex (an amyloid fragment
7 consisting in three phenylalanine residues in mixed H-bonded-stacked conformation, Figure S1),
8 for which a value of -22.81 kcal/mol is calculated at DLPNO-CCSD(T) and of -25.76 kcal/mol
9 at QCISD(T)/CBS. The mean absolute error (MAE) between the reported interaction energies
10 and our suggested DLPNO-CCSD(T) values is of only 1.07 kcal/mol. The experimental back-
11 corrected values provided for S12L²⁰ differ from our suggested DLPNO-CCSD(T) energies with
12 a MAE of around 2 kcal/mol. The largest (absolute) deviation is found for the doubly positive
13 charged ferrocene/adamantane derivative **7a**, for which a difference of 7.61 kcal/mol (6 %) is
14 obtained. This may stem from the important role of the counterions in the stabilization of the
15 doubly charged **7a** complex, which would increase the experimental free interaction energy used
16 in obtaining the values presented in the fifth column of Table 2. For the rest of supramolecular
17 complexes, the proposed DLPNO-CCSD(T) interaction energies remain close to the previously
18 reported values. We therefore consider that the interaction energies computed at DLPNO-
19 CCSD(T)/CBS can be used as reference values for benchmark studies and they are employed in
20 the following discussion if not otherwise indicated.
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46 1.2. Performance of NL-corrected BLYP and revPBE functional families

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48 Recently, several double-hybrid functionals merged with the NL approach were tested in the
49 small S22 and S66 data sets and they were shown to provide a very good performance to deal
50 with NCIs of different nature.¹⁷ However, their behavior when increasing the molecular size has
51 not been analyzed so far. We have evaluated the performance of the B2PLYP-NL and revPBE0-
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DH-NL functionals as well as their hybrid (B3LYP-NL and revPBE0-NL) and GGA (BLYP-NL and revPBE-NL) analogues in the large L7 and S12L test sets. The B2PLYP-NL and revPBE0-NL DH-NL functionals have been selected because they exhibited the best performance in the S22 and S66 data sets.¹⁷

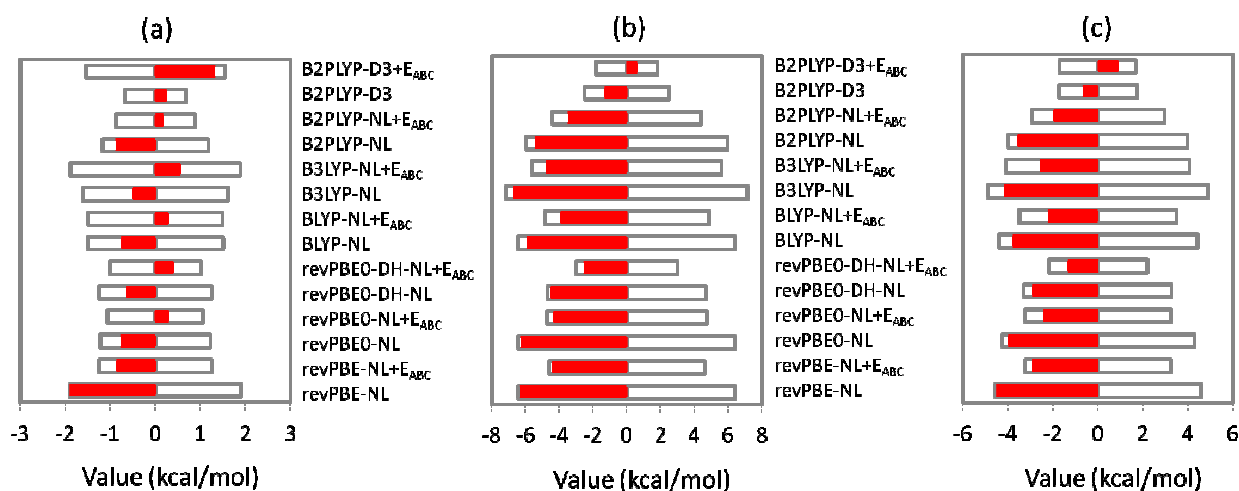


Figure 1. ME (red bar) and MAE (grey-border bar) computed for the different DFs coupled to the NL approach (the B2PLYP-D3 method is included for comparison purposes) for L7 (a), S12L (b), and considering both sets as one (c). The DLPNO-CCSD(T)/CBS interaction energies given in Table 2 are used as a reference. Note that the MAE (grey-border bar) has been mirrored.

Figure 1 summarizes the ME and MAE errors for the association energies of the L7 and S12L data sets obtained for the different DFs coupled to the NL approach with respect to the reference DLPNO-CCSD(T)/CBS values given in Table 2. The values of the errors (ME, MAE, and MAX) and of the interaction energies are given in the Supporting Information (Tables S5–S7). ME, MAE, and MAX deviations with respect to reference values reported in Ref. 19 and 22 for L7 and S12L, respectively, have also been included for comparison purposes (Tables S8–S10 and Figure S3). Similar to the DLPNO-CCSD(T)/CBS interaction energies, deformation energies for

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3 complexes of S12L have been included for all the density functionals. Despite their different
4 flavor according to the Jacob's ladder (GGA, hybrid, and double-hybrid character), the two
5 families of DFT-NL functionals perform strikingly well for the L7 set with MAE errors below
6 2.00 kcal/mol (Figure 1a and Table S5). Note that it is being admitted now that the standard
7 "chemical accuracy" (1 kcal/mol) is too stringent when interaction energies of very large
8 supramolecular complexes are computed and deviations around 2–3 kcal/mol can be perfectly
9 accepted.⁵⁸ A closer inspection of Figure 1a clearly reveals that the double-hybrid B2PLYP-NL
10 and revPBE0-DH-NL functionals exhibit a very good performance within their corresponding
11 family of DFs providing small MAE errors of less than 1.25 kcal/mol. For example, in the BLYP
12 family, the MAE noticeably decreases from 1.51 kcal/mol (BLYP-NL) and 1.62 kcal/mol
13 (B3LYP-NL) to 1.17 kcal/mol (B2PLYP-NL). A similar behavior is also found for the revPBE
14 family with MAE values of 1.91, 1.22, and 1.25 kcal/mol for revPBE-NL, revPBE0-NL, and
15 revPBE0-DH-NL, respectively. Both double-hybrid functionals show a systematic
16 overestimation of the dispersion forces governing the supramolecular associates with negative
17 ME errors of –0.88 and –0.65 kcal/mol for B2PLYP-NL and revPBE0-DH-NL, respectively.
18 The overestimation can be easily understood since many-body dispersion effects are not included
19 in the DFT-NL functionals. It should be mentioned that in both double-hybrid functionals the
20 MAX error is found for complex **C3GC** with values below 2.60 kcal/mol (Table S5).

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46 Recently, the repulsive three-body approximation (E_{ABC}), usually employed with the pairwise
47 dispersion correction developed by Grimme *et al.*, has been successfully combined with the NL
48 approximation to correct the interaction energies in large supramolecular complexes and the
49 cohesive energies calculated for the anthracene crystal.^{22,59} The inclusion of the E_{ABC} term has a
50 significant effect in both double-hybrid functionals. For revPBE0-DH-NL, the E_{ABC} term gives
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3 rise to a decrease of the MAE error (1.25 vs. 1.01 kcal/mol) and a change of sign in the ME
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6 (−0.65 vs. 0.40 kcal/mol) indicating a small underestimation with respect to the reference
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8 interaction energies. For B2PLYP-NL, the MAE decreases from 1.17 to 0.88 kcal/mol upon
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10 addition of the E_{ABC} term, and the ME moves from −0.88 to 0.18 kcal/mol, which is the lowest
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12 ME value computed along the series. It should be also noted that the performance of B2PLYP-
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14 NL is similar to that found for its B2PLYP-D3 homologous, which can be thus judged also as a
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16 high-quality method, presenting a slightly smaller MAE of 0.69 kcal/mol. Nevertheless,
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18 B2PLYP-D3 does not benefit from the additional E_{ABC} correction with the corresponding
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20 increase of the MAE error up to 1.54 kcal/mol (Figure 1a). It should be also mentioned that the
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22 MAX error, once the E_{ABC} correction is introduced in both double-hybrid density functionals, is
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24 found for complex **C2C2PD** (Table S5).

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30 Regarding the hybrid and GGA density functionals, it is necessary to stress the good
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32 performance of the hybrid revPBE0-NL functional with a MAE of 1.22 kcal/mol, which is even
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34 slightly smaller than that found for its double-hybrid analogue. In general, the incorporation of
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36 the three-body dispersion correction in the GGA and hybrid functionals has also an improvement
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38 in terms of MAE (Figure 1a), with the sole exception of the hybrid B3LYP-NL functional, which
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40 slightly worsens upon addition of the E_{ABC} dispersion term (from 1.62 to 1.88 kcal/mol). In terms
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42 of performance, the revPBE family incorporating the E_{ABC} term gives in overall interaction
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44 energies for the L7 set slightly closer to the reference energy values than the BLYP family with
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46 MAEs in the 1.01–1.26 kcal/mol range. Nevertheless, the double-hybrid B2PLYP-NL functional
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48 provides the most accurate interaction energies among the two families with ME and MAE going
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50 beyond the chemical accuracy (0.18 and 0.88 kcal/mol, respectively).
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3 Moving to the S12L set of complexes, a general overestimation in the association energy is
4 computed for all DFs under study with negative ME values (Figure 1b and Table S6). Due to this
5 overbinding, the inclusion of the three-body E_{ABC} correction improves the results in terms of
6 MAE errors in all cases. Similarly to the L7 data set, the double-hybrid density functionals (and
7 their variants with the three-body dispersion correction, revPBE0-DH-NL+ E_{ABC} and B2PLYP-
8 NL+ E_{ABC}) exhibit the best performance with the smallest MAE along the two density functional
9 families. For instance, the MAE (ME) values are found to be 4.71 (−4.47) and 3.01 (−2.53)
10 kcal/mol for revPBE0-DH-NL and revPBE0-DH-NL+ E_{ABC} , respectively. A similar behavior is
11 predicted for B2PLYP-NL and B2PLYP-NL+ E_{ABC} in terms of MAE errors (5.95 and 4.39,
12 respectively). The general overestimation and the improvement with the E_{ABC} correction is in
13 concordance with previous results where the overbinding and the role of the three-body E_{ABC}
14 correction in large supramolecular complexes were also discussed.²² It is necessary to mention
15 that we neglect at this stage the many-body corrections higher than E_{ABC} terms, which might still
16 contribute in systems with large and permanent multipole moments, but are, however, beyond
17 the scope of the present study. Note that B2PLYP-D3 with the addition of the E_{ABC} term behaves
18 slightly better than their analogues, revPBE0-DH-NL+ E_{ABC} and B2PLYP-NL+ E_{ABC} (Figure 1b).
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41 Among the GGA and hybrid density functionals, the best performance is found for the
42 revPBE-NL+ E_{ABC} with ME and MAE errors of −4.38 and 4.62 kcal/mol, respectively.
43 Nevertheless, the rest of GGA and hybrid functionals upon inclusion of the E_{ABC} correction show
44 MAEs below 5.61 kcal/mol (Table S6). Figure S4 displays the absolute errors for each
45 compound of S12L according to the nature of the interaction. Compounds **7a** and **7b** dominated
46 by cation-dipolar and H-bonding interactions, respectively, present the maximum errors for all
47 density functionals whereas compounds mainly dominated by non-polar and π - π interactions
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3 (compounds **2a**, **2b**, **3a** and **3b**) are better described (Figure S4). For further comparison,
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5 interaction energies reported by Risthaus *et al.*²² for S12L using the GGA PBE functional with
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7 the def2-TZVP basis set were extracted and compared to the DLPNO-CCSD(T)/CBS reference
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9 values proposed in this work (Table S14). The PBE-NL+ E_{ABC} functional outperforms the
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11 accuracy of the revPBE-NL+ E_{ABC} with MAE and ME values of 3.76 and -2.52 kcal/mol,
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13 respectively.²² Furthermore, the PBE functional coupled to the D3 approximation and the three-
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15 body dispersion term behaves remarkably accurate with a MAE value of only 1.87 kcal/mol for
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17 the S12L data set, corroborating the accuracy of the D3 approach.
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22 By combining the L7 and S12L test sets (Figure 1c), the relative deviations resemble the
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24 picture obtained for S12L due to the larger MAE and ME values computed for this set. Again,
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26 the inclusion of the three-body dispersion correction improves the results in all GGA, hybrid, and
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28 double-hybrid DFs due to the general overbinding of the interaction energies computed along the
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30 different DFs merged with the NL approach. Interestingly, the revPBE0-DH-NL and B2PLYP-
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32 NL functionals with the E_{ABC} correction show promising results with MAEs of 2.19 and 2.95
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34 kcal/mol, respectively, for the joint L7+S12L data set containing very large supramolecular
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36 complexes of diverse interacting nature. Likewise, the ME values are computed to be as small as
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38 -1.32 kcal/mol for revPBE0-DH-NL+ E_{ABC} and -1.96 kcal/mol for B2PLYP-NL+ E_{ABC} . It is
39
40 worth noting that the conclusions drawn by using the DLPNO-CCSD(T)/CBS interaction
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42 energies presented here or by using the previously reported reference data (Ref. 19 and 20) are in
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44 good accord (compare Figure 1 with Figure S3). Again, both double-hybrid revPBE0-DH-
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46 NL+ E_{ABC} and B2PLYP-NL+ E_{ABC} provide the smallest MAEs (3.08 and 2.51 kcal/mol,
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48 respectively) along the series for the joint L7+S12L data set. Therefore, the rung of double-
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50 hybrid density functionals (revPBE0-DH and B2PLYP-NL) coupled to the NL approach, which
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3 have demonstrated a great performance in the smaller S22 and S66 test sets,¹⁷ is now
4 consolidated as accurate functionals for challenging and “real-life” supramolecular systems,
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6 standing close to the chemical accuracy.
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10 11 12 CONCLUSIONS

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15 In this contribution, we provide an accurate and homogenous set of reference interaction
16 energies for the L7 and S12L sets calculated by using the DLPNO-CCSD(T) method
17 extrapolated to the complete basis set limit. The correction of the basis set superposition error
18 and the incorporation of the deformation energies (especially for the S12L set) have been crucial
19 for obtaining accurate interaction energies. These interaction energy values are taken as a
20 reference to assess the performance of the double-hybrid density functionals, revPBE0-DH-NL
21 and B2PLYP-NL, as well as their hybrid and GGA counterparts, which include the nonlocal van
22 der Waals correction formulated by Vydrov and Voorhis to describe noncovalent interactions.
23
24 Among the density functionals evaluated, the double-hybrid revPBE0-DH-NL and B2PLYP-NL
25 with the three-body dispersion correction behave remarkably accurate with mean absolute errors
26 in the range of the chemical accuracy for the large weakly-bound molecular systems of the L7
27 and S12L sets. The performance of the double hybrid density functionals is irrespective of the
28 reference interaction energies employed. These results therefore confirm that the nonlocal van
29 der Waals approach combined with modern density functionals can be seen as an accurate and
30 affordable computational tool for the modeling of “real-life” supramolecular assemblies
31 governed by noncovalent interactions.
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52 53 54 ASSOCIATED CONTENT

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3 **Supporting Information.** Chemical structures of the supramolecular complexes and interaction
4 energies computed at DLPNO-CCSD(T)/CBS and with the different DFT-NL functionals for the
5 weakly-bonded molecular complexes of the L7 and S12L sets. Absolute errors according to the
6 nature of the interaction computed for S12L. This material is available free of charge via the
7 Internet at <http://pubs.acs.org>.
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15 AUTHOR INFORMATION

16 **Corresponding Author**

17
18
19 *E-mail: juan.arago@uv.es (J.A)
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24 **Notes**

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27 The authors declare no competing financial interest.
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30 **Present Addresses**

31
32
33 J.A.: ‡ Department of Chemistry and Centre for Scientific Computing, University of Warwick,
34 Coventry CV4 7AL, UK.
35
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37

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Accurate Treatment of Large Supramolecular
Complexes by Double-Hybrid Density Functionals
Coupled with Nonlocal van der Waals Corrections

Joaquín Calbo,[†] Enrique Ortí,[†] Juan C. Sancho-García,[§] Juan Aragó^{†‡}*

