

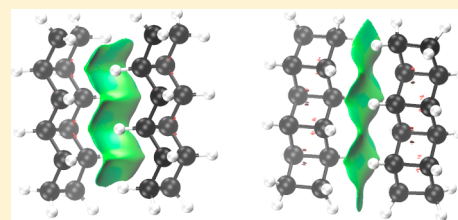
# Nature Utilizes Unusual High London Dispersion Interactions for Compact Membranes Composed of Molecular Ladders

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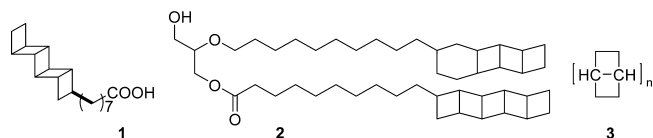
**S** Supporting Information

**ABSTRACT:** London dispersion interactions play a key role in nature, in particular, in membranes that constitute natural barriers. Here we demonstrate that the spatial alignment of “molecular ladders” ( $[n]$ ladderanes), *i.e.*, highly unusual and strained all-*trans*-fused cyclobutane moieties, leads to much larger attractive dispersion interactions as compared to alkyl chains of the same length. This provides a rationale for the occurrence of peculiar ladderane fatty acids in the dense cell walls of anammox bacteria. Despite the energetic penalty paid for the assembly of such strained polycycles, the advantage lies in significantly higher, dispersion-dominated interaction energies as compared to straight-chain hydrocarbon moieties commonly found in fatty acids. We discern the dispersion contributions to the total interaction energies using a variety of computational methods including modern dispersion-corrected density functional theory and high level *ab initio* approaches. Utilizing larger assemblies, we also show that the intermolecular interactions behave additively.



## INTRODUCTION

Pentacycloanammoxic acid (**1**) is a highly unusual lipid with a ladderane core (**3**) structure that was found in the anaerobic microbe *Candidatus Brocadia Anammoxidans* together with several of its derivatives (e.g., **2**, Figure 1).<sup>1</sup> This organism



**Figure 1.** Pentacycloanammoxic acid (**1**), a typical lipid occurring in *Candidatus B. Anammoxidans* **2**, which bears two different ladderane substructures, and the ladderane core (**3**), whereby the corresponding structure would be named  $[n]$ ladderane.

sustains its metabolism by the oxidation of ammonia with nitrite, the so-called anammox-process (anaerobic ammonia oxidation), which chemically resembles a symproportionation reaction. This unusual catabolism<sup>2,3</sup> was discovered only a few years ago and turned out to be an important component of the nitrogen cycle.<sup>4</sup> However, the anammox process is very slow and highly toxic species like hydrazine ( $N_2H_4$ ) and hydroxylamine ( $NH_2OH$ ) form as intermediates. For that reason, the reaction takes place in the anammoxosome, a cellular compartment with a very dense membrane that prevents diffusion into the intracellular space. Ladderane lipids were found to be highly abundant in this cellular compartment.<sup>1</sup>

The high density of the membrane, which has been probed by permeability experiments utilizing some fluorophores, was attributed to the comprising ladderane lipids.<sup>1</sup> These “molecular ladders” stand out on account of their structural rigidity and size,<sup>5</sup> and a molecular mechanics study<sup>1</sup> revealed an

unusual high degree of compactness. However, the prize that nature pays for such a dense membrane is high: the strain energy<sup>6</sup> of the  $[5]$ ladderane moiety was estimated to be  $101 \text{ kcal mol}^{-1}$  (from a protobranching corrected reaction scheme) and its formation from two molecules of (*E*)-1,3,5-hexatriene is disfavored by about  $20 \text{ kcal mol}^{-1}$ .<sup>5</sup> The laboratory synthesis of ladderanes is rather challenging, whereby one method is the  $[2+2]$ -photocycloaddition of polyunsaturated compounds.<sup>7</sup> However, this process is entropically disfavored as a proper alignment of the double bonds is necessary before the reaction can take place. This has been solved synthetically by the incorporation of the two vinyl moieties into a cyclophane<sup>8</sup> or by preorganization of the reactants in the crystalline state.<sup>9</sup> Corey *et al.* have published a general<sup>5</sup> and an enantioselective<sup>10</sup> synthesis of **1**, whereby especially the latter relies on consecutive photocycloadditions building up the concatenated cyclobutane lipid in a stepwise fashion. The authors state that a biosynthesis utilizing similar chemistry is improbable, because the environment of the microbe is dark and anaerobic. To best of our knowledge, the biosynthesis has not yet been elucidated completely; it is known that a dedicated enzyme apparatus<sup>11</sup> is necessary and that **1** is probably not formed by cyclization of a polyunsaturated fatty acid. It rather seems to be the case that the  $[5]$ ladderane moiety forms separately and then attaches to a lipid that comes from regular type II fatty acid biosynthesis.<sup>12</sup>

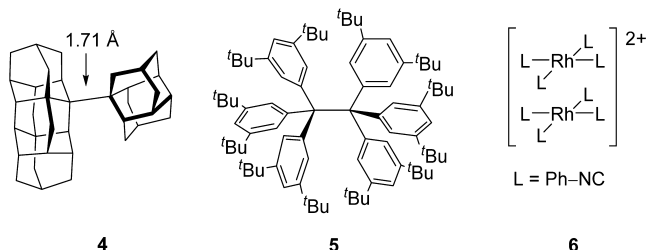
Considering all these obstacles nature overcomes to build these unique membrane materials, we wondered whether, apart from rigidity and shape, there are also stronger than usual intermolecular interactions originating from favorable London dispersion. This situation is nicely visualized by the plot of a

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noncovalent interaction analysis<sup>13</sup> in the table-of-contents figure above. Although the small red spots indicate steric repulsion and can be attributed to the strain present in the molecular ladders, the large green areas in the intermolecular contact surface correspond to favorable London dispersion interactions. To uncover and quantify such interactions is the main motivation for the present work.

Large polarizable groups have been shown to thermodynamically stabilize molecules and henceforth are referred to as dispersion energy donors (DEDs).<sup>14</sup> Upon addition of DEDs to a molecule, unusual binding situations may be realized. Examples include the longest alkane carbon–carbon bonds in diamondoid dimers<sup>15,16</sup> (e.g., 4, Figure 2) or the isolable all-



**Figure 2.** Uncommon bonding situations that are realized by dispersion energy donors.

*meta tert*-butyl substituted hexaphenylethane<sup>17</sup> 5 (note that parent hexaphenylethane has never been reported experimentally). Both systems are held together by very large dispersion interactions leading to their thermodynamic stabilization against central C–C bond dissociation. Even the dimerization of  $\text{Rh}^{1+}$  cations (6) is possible and can be attributed to London dispersion as the driving force for this process.<sup>18</sup>

The importance of London dispersion rapidly grows with the size of the molecule, as shown for the association energies of

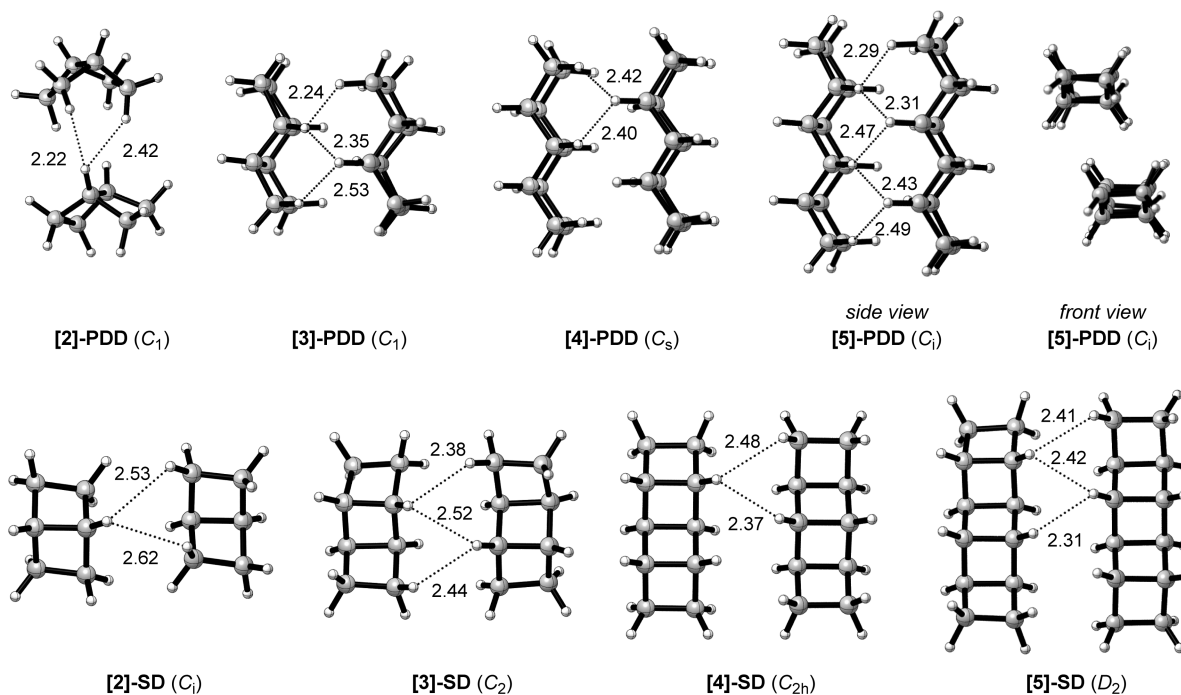
graphanes.<sup>19</sup> The corresponding binding energies increase linearly with the number of carbon atoms ( $\sim 1.2 \text{ kcal mol}^{-1}$ ) and exceed the strength of a C–C covalent bond already for [97]graphane. London dispersion can not only be tuned through the size of the interacting fragments but also by their structure. Polyhedranes exhibit remarkably high melting points, which were attributed to their structural properties depending on their degree of substitution and the pyramidity of the interacting C–H units.<sup>20</sup>

Encouraged by these recent findings, we aimed at probing our hypothesis of enhanced London dispersion interactions between ladderanes, as compared to simple linear alkanes. We computed the interaction energies of [2] to [5]ladderane with state-of-the-art computational methods for such large dispersion-driven systems.

## COMPUTATIONAL METHODS

We employed both high-level wave function theory as benchmarks for the performance of DFT approaches including *a posteriori* dispersion corrections through Grimme's D3-correction<sup>21</sup> or medium-range correlation as parametrized into modern functionals such as Truhlar's M06-2X functional.<sup>22</sup> As DFT approaches such as the highly popular B3LYP<sup>23,24</sup> functional combination lack the inclusion of van-der-Waals interactions,<sup>25–27</sup> this allows a clear-cut analysis of the dispersion contribution to molecular aggregation.

We initially employed second order Møller–Plesset perturbation theory (MP2), which was found to account very well for the interactions of saturated systems and which performs much better for these than does the more modern *spin-component scaled* version (SCS-MP2).<sup>28</sup> The energies of alkane dimers can be computed very accurately utilizing MP2 and CCSD(T) corrections consequently turned out to be small.<sup>29,30</sup>



**Figure 3.** Optimized structures of the parallel displaced (PDD) and side-on dimers (SD) at the MP2/aug-cc-pVDZ level of theory. Selected H...H distances are given in Å; note that these continuously decrease as the length of the SD structures increases.

As computations of dimerization energies are typically corrupted by basis set superposition errors, the application of the counterpoise correction (CP) of Boys and Bernardi<sup>31</sup> is a standard tool to overcome this bias. However, this method is quite laborious and Antony *et al.* found that when using basis set extrapolation, the CP-corrected and uncorrected energies virtually approach the same value. This is also true for the use of extended diffuse functions. At the complete basis set limit (CBS), the interaction energies are about the same.<sup>28</sup> Therefore, we decided to use Dunning's systematically converging correlation-consistent cc-pVXZ basis sets<sup>32</sup> (X = D, T, Q, 5) without CP-correction to compute the interaction energies.

We adopted a procedure that has been described by Riley and Hobza in a recent review<sup>33</sup> that provides an estimate for the CCSD(T) energy (coupled cluster theory with iteratively included single and double and perturbatively included triple excitations)<sup>34–36</sup> at the CBS limit. Herein, the energy is partitioned into the self-consistent field (SCF) energy, the MP2 correlation energy and the contributions of higher order correlation effects. We decided to compute the SCF energy within the almost saturated cc-pV5Z basis set to avoid extrapolation errors.<sup>37</sup> The MP2 correlation energy was estimated with a standard Helgaker-type two-point-extrapolation<sup>38</sup> from triple- and quadruple- $\zeta$  basis sets:

$$E_X^{\text{corr}} = E_{\text{CBS}}^{\text{corr}} + BX^{-3}$$

where X is the cardinal number of the basis set.

As MP2 and CCSD(T) correlation energies converge at a similar rate, it is possible to account for higher order correlation effects utilizing only moderately sized basis sets to estimate the CCSD(T)/CBS energy. The  $\Delta\text{CCSD(T)}$  correction is the difference in association energy at the CCSD(T) and MP2 levels, respectively:

$$\Delta\text{CCSD(T)} = (\Delta E^{\text{CCSD(T)}} - \Delta E^{\text{MP2}})_{\text{small basis}}$$

In this case, we used the 6-31G(d,p) basis to evaluate the  $\Delta\text{CCSD(T)}$  correction. The entire procedure is summarized in the following equation:

$$\Delta E_{\text{est}}^{\text{CCSD(T)}} = \Delta E^{\text{HF}} + \Delta E_{\text{CBS}}^{\text{MP2}} + \Delta\text{CCSD(T)}$$

Utilizing the methane dimer as a benchmark system for our computations, we found that the MP2/aug-cc-pVDZ level of theory without CP correction leads to an equilibrium C–C distance of 3.57 Å, in excellent agreement with the CCSD(T)/CBS result that gives 3.60 Å.<sup>30</sup> The complete benchmark procedure is given in the Supporting Information. Henceforth, we fully optimized all geometries at the MP2/aug-cc-pVDZ level of theory, utilizing the highest available point group symmetry (Figure 3). The monomers were characterized as minima on the potential energy hypersurface by vibrational frequency computations, which was, however, computationally not viable for all of the dimers. We computed zero-point vibrational energy (ZPVE) differences at the M06-2X/6-31G(d,p) level of theory; the ZPVE corrections to the dimerization energies vary between 0.6 and 1.0 kcal mol<sup>−1</sup> (cf. Supporting Information, Table S7). Alternatively, we evaluated the Hessian matrix within the smaller 6-31G(d,p) basis set to ensure that it contained no negative eigenvalues. All geometries were subjected to reoptimization at the M06-2X, B3LYP, and B3LYP-D3 (with a Becke–Johnson damping function<sup>39</sup>) levels of theory with a 6-311+G(d,p) basis set to

further elucidate the role of dispersion. The computationally less demanding density functional theory (DFT) computations were also employed to investigate the molecular association to trimers to discern whether dispersion between ladderanes behaves additively or cooperatively. We utilized the *Gaussian09*<sup>40</sup> program package for all computations.

## RESULTS AND DISCUSSION

Although a large number of ladderane dimers may be envisioned, we focused on two types that resemble the situation most likely found in natural membranes. The first dimer under consideration is the parallel-displaced dimer (PDD), in which the two ladderanes' faces are staggered. The other one relates to that typically found for the most stable antiparallel alkane dimers<sup>41</sup> that we call the side-on dimer (SD). The optimized structures are shown in Figure 3.

The monomers were optimized in  $C_2$  symmetry, except for [2]ladderane, which belongs to the  $C_1$  point-group because of the puckering of the cyclobutyl moieties; [2]-PDD and [3]-PDD were optimized without symmetry constraints. Although the latter retained the spoon-like orientation during optimization, [2]-PDD distorted and the molecules slightly shifted to maximize the dispersion interaction. Structures [4]-PDD and [5]-PDD display  $C_s$  and  $C_i$  symmetry, respectively. The [2]-, [3]-, [4]-, [5]-SD structures were optimized in  $C_i$ ,  $C_2$ ,  $C_{2h}$  and  $D_2$  symmetry, respectively.

Although the results of Hartree–Fock theory imply repulsive interactions of two ladderanes, MP2 yields strongly bound complexes (Table 1). This result clearly indicates that dimer

**Table 1.** HF and MP2 Interaction Energies of the Ladderane Dimers Employing Dunning-Type Basis Sets

species	HF/				MP2/		
	cc-pVDZ	cc-pVTZ	cc-pVQZ	cc-pV5Z	cc-pVDZ	cc-pVTZ	cc-pVQZ
[2]-PDD	3.6	3.9	4.0	4.0	−2.6	−3.0	−3.0
[3]-PDD	4.8	5.2	5.3	5.3	−3.4	−4.0	−4.3
[4]-PDD	6.3	6.8	7.0	7.0	−4.8	−5.5	−5.8
[5]-PDD	8.2	8.9	9.1	9.2	−6.4	−7.2	−7.4
[2]-SD	3.3	3.7	3.8	3.8	−3.2	−3.6	−3.6
[3]-SD	4.3	4.9	5.0	5.1	−4.3	−5.1	−5.0
[4]-SD	4.9	5.6	5.8	5.9	−5.7	−6.7	−6.8
[5]-SD	6.6	7.5	7.8	7.9	−7.3	−8.5	−8.4

formation is an electron correlation effect that must be attributed to London dispersion. For both levels of theory, the change in interaction energy from triple- to quadruple- $\zeta$  (and 5- $\zeta$ ) basis set is quite small and a triple- $\zeta$  basis set seems to be sufficient to describe the interaction properly.

Table 2 lists the MP2 interaction energies at the CBS-limit estimated from the two-point extrapolation scheme and the SCF energies with the cc-pV5Z basis set. In most cases, the values are very close to those obtained at MP2/cc-pVQZ. The higher order correlation contributions ( $\Delta\text{CCSD(T)}$ , Table 2) are positive in all cases, as MP2 usually tends to overbind complexes, and is on the order of some tenth of a kcal mol<sup>−1</sup>. This underlines the good performance of the MP2 method and is in agreement with previous observations investigating alkane dimers.<sup>29</sup>

Table 2. Extrapolated MP2/CBS Energies of Dimer Formation, Higher Order Correlation Effects Correction and Estimated CCSD(T)/CBS Energies in kcal mol<sup>-1</sup>

	[2]-PDD	[3]-PDD	[4]-PDD	[5]-PDD	[2]-SD	[3]-SD	[4]-SD	[5]-SD
$\Delta E_{\text{CBS}}^{\text{MP2}}$	-3.0	-4.5	-6.0	-7.5	-3.7	-5.0	-6.9	-8.4
$\Delta \text{CCSD(T)}$	+0.4	+0.3	+0.5	+0.9	+0.3	+0.4	+0.4	+0.8
$\Delta E_{\text{est}}^{\text{CCSD(T)}}$	-2.7	-4.2	-5.5	-6.6	-3.3	-4.1	-6.5	-7.5

As expected, the dimerization energies increase with system size. The reason is that London dispersion forces, the attractive part of van der Waals interactions, are cumulative in nature as the number of pairwise C–H...H–C and C–H...C interactions rises. The dimer stabilities of [4]ladderane already exceeds the binding energy of the water dimer (about 5 kcal mol<sup>-1</sup>),<sup>42</sup> which is a prototypical hydrogen-bonded system and is often considered stronger than dispersion interactions. As straight-chain aliphatic fatty acids are very common in Nature, a comparison of the dimerization energies of alkanes of the same length to the ladderanes is instructive. A plot of the chain length vs. the MP2/CBS interaction energies of alkanes ranging from propane to hexane taken from ref 29 and those of the ladderanes at the MP2/CBS level of theory is given in Figure 4.

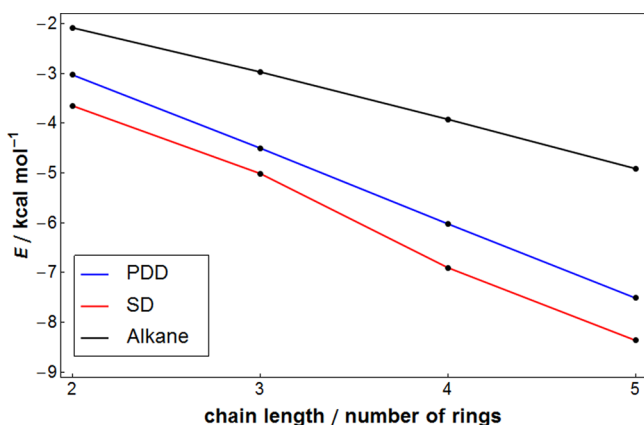


Figure 4. Interaction energies of [2]- to [5]ladderanes in the SD and PDD structures at the MP2/CBS level of theory compared to those of the alkanes from propane to hexane (MP2/CBS taken from ref 29). Note that the values of the abscissa correspond to the number of C–C bonds for the alkanes and the number of rings for the ladderanes, respectively.

The level of theory has been chosen for the sake of comparability; the plot of the estimated CCSD(T)/CBS interaction energies is given in the Supporting Information. For [2]ladderane, the interaction in the SD (PDD) structure is about 1.6 kcal mol<sup>-1</sup> (0.9 kcal mol<sup>-1</sup>) higher than that for propane. This difference increases for [5]ladderane up to 3.4 kcal mol<sup>-1</sup> (2.6 kcal mol<sup>-1</sup>) for SD (PDD). That is, not only is the interaction energy higher but the increment ( $1.49 \pm 0.02$  kcal mol<sup>-1</sup> for PDDs,  $1.57 \pm 0.23$  kcal mol<sup>-1</sup> for SDs and 0.92 kcal mol<sup>-1</sup> for the alkanes<sup>29</sup>) to the next higher homologue is

larger. This is remarkable considering that the juxtaposed surfaces in alkanes and SDs are structurally extremely similar. These results confirm our prediction that there are substantial dispersion interactions between the ladderanes, which further makes their occurrence in membranes comprehensible. To achieve the same interaction energy by elongation of the alkyl chain of a fatty acid, one would have to prolong it from hexyl (instead of [5]ladderane) to nonyl or even decyl.<sup>29</sup> At the same time, ladderanes enable membranes to be more compact and dense.

The unusual high dispersion interactions between ladderanes are in accord with the work of Echeverría *et al.* on polyhedranes<sup>20</sup> who found that the magnitude of interaction depends on the degree of substitution of the interacting C–H carbon atom, whereby higher substitution with longer chains increases the interaction's strength. This is also the case for the ladderanes as they consist of numerous internal tertiary and terminal secondary carbons. Furthermore, the magnitude of dispersion depends on the pyramidity of the interacting C–H unit: the smaller the C–C–H angle the stronger the attraction. Although the C–C–H angles in the ladderanes (typically 115° to 119°) are larger than the tetrahedral angle, they lie between those of dodecahedrane<sup>43</sup> and cubane,<sup>44</sup> two of the most strongly interacting polyhedranes. This angular dependence has been rationalized in terms of a reduced Pauli repulsion between the monomers.<sup>45</sup>

As we had generated a good set of high-level reference data, we next examined the performance of some DFT approaches for this class of compounds. As expected, the “highly repulsive” B3LYP functional cannot account for dimer formation of the molecular ladders. Upon geometry optimization, the monomers drift apart and the structures obtained are essentially unbound within the error limit. With the addition of the D3(BJ) correction, tightly bound dimers can be identified as minima, again emphasizing that London dispersion is largely responsible for the dimerization. The relative energies of the dimers agree very well with the CCSD(T)/CBS values and the error is less than 1 kcal mol<sup>-1</sup> in all cases. The performance of Truhlar's M06-2X functional is also satisfactory having a similar error (Table 3).

To extend our model toward the situation in a real membrane, we optimized two trimers of [4]ladderane at M06-2X/6-311+G(d,p), whereby one is an extension of [4]-SD and the other of [4]-PDD (Figure 5). As the aggregation energies of the trimers are twice that of the dimers, the London dispersion interactions behave additively. We must conclude

Table 3. Dimerization Energies in kcal mol<sup>-1</sup> Obtained by Density Functionals with a 6-311+G(d,p) Basis Set

	[2]-PDD	[3]-PDD	[4]-PDD	[5]-PDD	[2]-SD	[3]-SD	[4]-SD	[5]-SD
B3LYP	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
B3LYP-D3(BJ)	-3.2	-4.1	-5.3	-6.5	-3.1	-4.4	-5.7	-7.0
M06-2X	-3.2	-4.4	-5.7	-7.1	-3.8	-5.1	-6.4	-7.7
$\Delta E_{\text{est}}^{\text{CCSD(T)}}$	-2.7	-4.2	-5.5	-6.6	-3.3	-4.1	-6.5	-7.5



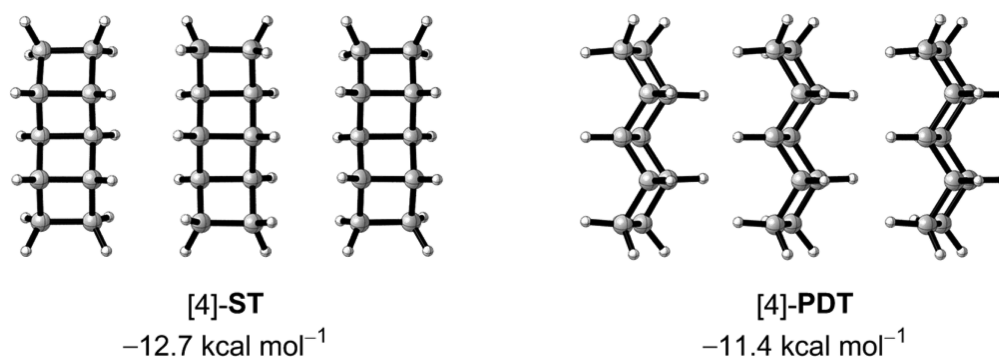


Figure 5. The trimers [4]-ST and [4]-PDT and their complexation energies at the M06-2X/6-311+G(d,p) level of theory.

that these computed strong interactions have a profound effect on membrane stability.

## CONCLUSIONS

Employing high level wave function theory, we demonstrate that unusually strong London dispersion forces are at work between molecular ladders, the  $[n]$ ladderanes. The dimerization energies are significantly larger than those of alkyl chains of the same length. Thus, it may be rationalized that *Candidatus B. Anammoxidans* incorporates ladderane-type fatty acids in very dense and additionally stabilized membranes, despite the high formal energetic penalty paid for assembling the highly strained ladderane moieties. The driving force for their association can be attributed to London dispersion based on our findings that HF fails to yield bound dimers and that only correlated wave function methods are capable of describing the interaction properly. This finding is underscored with DFT approaches for which dispersion corrections have been included: although B3LYP does not give tightly bound dimers, adding the D3(BJ) dispersion correction accurately reproduces the estimated CCSD(T)/CBS interaction energies; M06-2X performs similarly well. By employing the latter functional, we show that dispersion interactions between ladderanes are additive in character.

Our work provides further evidence that not only the size of the molecular system but also its structure is an important factor determining the strength of noncovalent interactions. Further investigations will be needed to fully understand the factors that influence London dispersion forces that might allow the purposeful design of novel motives that may be applicable in fields such as molecular recognition and catalysis.<sup>46</sup>

## ASSOCIATED CONTENT

### Supporting Information

A summary of the complete benchmarking procedure, Cartesian coordinates of all optimized structures and a plot of the estimated CCSD(T)/CBS interaction energies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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