<http://www.diva-portal.org>

Postprint

This is the accepted version of a paper published in *Journal of Chemical Physics*. This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Citation for the original published paper (version of record):

Xu, Y., Friedman, R., Wu, W., Su, P. (2021)
Understanding intermolecular interactions of large systems in ground state and excited state by using density functional based tight binding methods
Journal of Chemical Physics, 154(19): 194106
<https://doi.org/10.1063/5.0052060>

Access to the published version may require subscription.

N.B. When citing this work, cite the original published paper.

Permanent link to this version:

<http://urn.kb.se/resolve?urn=urn:nbn:se:lnu:diva-103467>

Understanding intermolecular interactions of large systems in ground state and excited state by using density functional based tight binding methods

Yuan Xu,¹ Ran Friedman,^{2*} Wei Wu,¹ Peifeng Su^{1*}

¹*The State Key Laboratory of Physical Chemistry of Solid Surfaces, Fujian Provincial Key Laboratory of Theoretical and Computational Chemistry, and College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, China*

²*Department of Chemistry and Biomedical Sciences, Linnaeus University, 39182 Kalmar, Sweden*

ABSTRACT:

A novel energy decomposition analysis scheme, named DFTB-EDA, is proposed based on the density functional based tight binding method (DFTB/TD-DFTB), which is a semi-empirical quantum mechanical method based on KS-DFT for large-scale calculations. In DFTB-EDA, the total interaction energy is divided into three terms: frozen density, polarization and dispersion. Owing to the small cost of DFTB/TD-DFTB, DFTB-EDA is capable of analyzing intermolecular interactions in large molecular systems containing several thousand atoms with high computational efficiency. It can be used not only for ground states but also for excited states. Test calculations, involving the S66 and L7 databases, several large molecules and non-covalent bonding complexes in their lowest excited states, demonstrate the efficiency, usefulness and capabilities of DFTB-EDA. Finally, the limits of DFTB-EDA are pointed out.

* To whom correspondence should be addressed.

1. INTRODUCTION

Tight-binding based density functional theory (DFTB),¹⁻⁴ which is a kind of semi-empirical quantum mechanical approach based on a tight-binding treatment of Kohn-Sham density functional theory (KS-DFT),^{5, 6} is designed for large-scale calculations. Since 1990s, various DFTB methods have been proposed.^{1-3, 7} Among them, the most popular formalism is self-consistent charge DFTB (SCC-DFTB).² In SCC-DFTB, a valence minimal basis set and a two-center integral approximation are used. Mulliken atomic charges⁸ representing charge density fluctuations are determined by the self-consistent charge formalism. This self-consistent modification of the DFTB energy with the self-consistent charge formalism is based on a second or third order Taylor expansion of the DFT energy around a reference density (usually the sum of atomic densities), leading to the SCC-DFTB and SCC-DFTB3 methods,^{3, 7} denoted hereafter “DFTB2” and “DFTB3” respectively. In DFTB2/3, thousands of empirical values have to be determined because the Hamiltonian and overlap matrix elements are explicit functions of interatomic distances between atom pairs. By using various parameter sets designed for different purposes, DFTB2/3 makes a good balance in efficiency and accuracy in the description for various noncovalent interaction systems.⁹⁻¹⁴ Lately, the remarkable agreement between DFTB3-D3HX and DLPNO-CCSD(T) results of the data set PLF547 demonstrated the accuracy of DFTB3 for ligand-protein bonding interactions.¹⁵

Using appropriate approximations, SCC-DFTB can be easily extended to excited states based on linear response theory. Thus, the time-dependent DFTB (TD-DFTB) formalism was proposed on the basis of SCC-DFTB.¹⁶⁻²⁰ TD-DFTB directly employs the ground state's parameter sets, no further parameterization is required. It not only allows bypassing the computational bottlenecks of TD-DFT in the calculation of vertical excitations but also enables more efficient excited state geometry optimization and molecular dynamics simulations. As revealed by a benchmark study, the performance of TD-DFTB is similar to TD-DFT, showing the accuracy and efficiency for the description of excitation energies.²¹ Additionally, the recently developed long-range corrected TD-

LC-DFTB method substantially improves the descriptions of HOMO-LUMO gaps and excitation energies.^{22, 23}

Energy decomposition analysis (EDA) is an effective tool for the quantitative analysis of intermolecular interactions based on quantum mechanical calculations.²⁴⁻²⁶ In the recent decades, various EDA methods have been developed and widely used.²⁷⁻³⁸ However, these EDA methods are based on ab initio calculations, which require expensive computational costs. A computationally efficient EDA method, which could be applied to large systems as relevant to biology and material science is highly desired. However, popular EDA methods cannot be directly applied to SCC-DFTB calculations. These EDA methods are based on the variational method or on perturbation theory, and thus conflict with the SCC-DFTB computation strategy, in which Hamiltonian and overlap matrix elements are fixed, while Mulliken atomic charges are varied to compute the DFTB energy. As such, DFTB based EDA method should be redesigned.

Two approaches have been proposed for performing EDA calculations with DFTB. Miriyala and Řezáč discuss mainly two terms, an electrostatic (Coulomb) term and a polarization term.³⁹ They note that there are some difficulties in the treatment, in their words "Our energy decomposition implies that there is a very large error already in the first-order electrostatic term. The description of polarization effects is even worse". Fedorov and Kitaura have applied DFTB within their fragment molecular orbital (FMO) method.⁴⁰ In FMO, a large molecular system is broken down into fragments and the total energy is estimated by considering the electronic states of fragments and their pairs with the effect of the external system approximated through electrostatic embedding.^{41, 42} Fragmentation of a system makes it possible to calculate pair-interaction-energies and thereby energy decomposition analysis is achieved (termed PIEDA, pair-interaction EDA).³² In PIEDA, the terms include electrostatics, a charge transfer and mixing term, and a solvation term (from an implicit solvent treatment). For the water dimer, the authors noted that DFTB treatment was rather accurate for an estimation of total intermolecular interaction value in comparison to DFT, but the contributions from EDA varied, in particular the electrostatic term.⁴⁰

In this paper, encouraged by these earlier efforts to develop an EDA formalism for DFTB, we propose a novel and simple EDA scheme based on DFTB/TD-DFTB calculations, which is called DFTB-EDA. To the best of our knowledge, it is the first EDA scheme that is able to employ the TD-DFTB method. DFTB-EDA can be used to perform analysis for various large molecular systems in ground and excited states with high computational efficiency.

2. THEORY

2.1 The density functional based tight-binding method

In DFTB, the total energy of KS-DFT can be expressed as a Taylor series expansion at reference charge density,^{43, 44}

$$E[\rho] = E^0(\rho_0) + E^1(\rho_0, \delta\rho) + E^2(\rho_0, (\delta\rho)^2) + E^3(\rho_0, (\delta\rho)^3) + \dots \quad (1)$$

where $\rho_0 = \sum_A \rho_A$, ρ_A is the charge density of atom A, and $\rho = \rho_0 + \delta\rho$.

Based on eq 1, the total energy by SCC-DFTB up to the third-order series expansion consists of four terms,³

$$E^{\text{DFTB}} = E^{\text{rep}} + \sum_{\mu \in A} \sum_{\nu \in B} D_{\mu\nu} H_{\mu\nu}^0 + \frac{1}{2} \sum_{A,B} \Delta q_A \Delta q_B \gamma_{AB} + \frac{1}{3} \sum_{A,B} \Delta q_A^2 \Delta q_B \Gamma_{AB} \quad (2)$$

here $D_{\mu\nu}$ is the density matrix, $H_{\mu\nu}^0$ is the fixed Hamiltonian matrix in pre-tabulated Slater-Koster⁴⁵ files from reference atomic pair DFT calculations, and E^{rep} is the two-body repulsion potential, constructed by subtracting the DFTB electronic energy from the DFT total energy with respect to the bond distance for a small set of suitable reference systems.¹ The third and fourth terms account for the second order and third order contributions of charge fluctuations, respectively. DFTB2 covers the expansion up to the third term only while DFTB3 involves all four terms. In eq 2, the atomic charge Δq_A of atom A is calculated as:

$$\Delta q_A = \sum_{\mu \in A} \sum_{\nu} D_{\mu\nu} S_{\mu\nu} - q_A^0 \quad (3)$$

$S_{\mu\nu}$ is the overlap matrix of atomic orbitals μ and ν , and q_A^0 is the reference valence charge of atom A. For example, for the C atom, q_A^0 is 4.0.

The formulae for γ_{AB} and Γ_{AB} can be found in previous literature.^{2, 3} It is briefly noted that γ_{AB} denotes the Coulomb interaction between atomic partial charges Δq_A and Δq_B . Γ_{AB} introduces the desired chemical behavior for charged systems in DFTB3.³

2.2 DFTB-EDA in ground state

In the DFTB-EDA formalism, a complex (denoted as S) is divided into a given number of monomers (denoted as M). The total interaction energy between any two monomers A and B is divided into a frozen density component (ΔE^{FRZ}), a polarization term (ΔE^{POL}), and a dispersion (ΔE^{DISP}) term:

$$\Delta E^{\text{TOT}} = \Delta E^{\text{FRZ}} + \Delta E^{\text{POL}} + \Delta E^{\text{DISP}} \quad (4)$$

The frozen density interaction term can be expressed as

$$\Delta E^{\text{FRZ}} = E_{\text{S}}^{\text{FRZ}} - \sum_{\text{M}} E_{\text{M}}^{\text{FRZ}} \quad (5)$$

where $E_{\text{P}}^{\text{FRZ}}$ (P = S or M) is written as

$$E_{\text{P}}^{\text{FRZ}} = E_{\text{P}}^{\text{rep}} + \sum_{\mu, \nu \in \text{P}} D_{\mu\nu}^0 H_{\mu\nu}^0 \quad (6)$$

In eq 6, the density matrix $D_{\mu\nu}^0$ is computed by the diagonalization of the Hamiltonian matrix $H_{\mu\nu}^0$.

It is noticed that ΔE^{FRZ} denotes the monomer's interaction without any orbital relaxation, which can be related to the sum of the electrostatic, Pauli repulsion and correlation terms in ab initio EDA schemes.

The polarization term, ΔE^{POL} , is defined as the difference in orbital relaxation energies between the complex and monomers.

$$\Delta E^{\text{POL}} = E_{\text{S}}^{\text{POL}} - \sum_{\text{M}} E_{\text{M}}^{\text{POL}} \quad (7)$$

where $E_{\text{P}}^{\text{POL}}$ (P = S or M) is defined as:

$$E_{\text{P}}^{\text{POL}} = \sum_{\mu, \nu \in \text{P}} (D_{\mu\nu} - D_{\mu\nu}^0) H_{\mu\nu}^0 + \frac{1}{2} \sum_{\text{A}, \text{B} \in \text{P}} \Delta q_{\text{A}} \Delta q_{\text{B}} \gamma_{\text{AB}} + \frac{1}{3} \sum_{\text{A}, \text{B} \in \text{P}} \Delta q_{\text{A}}^2 \Delta q_{\text{B}} \Gamma_{\text{AB}} \quad (8)$$

The density matrix $D_{\mu\nu}$ is computed by the diagonalization of the DFTB2/3 Hamiltonian matrix. As can be seen, the polarization term contains two parts, the first one is the contribution of density matrix variation, while the second one is the contribution of self-consistent charge fluctuations.

Since DFTB2/3 does not include dispersion effects, to achieve good accuracy for non-covalent

interactions, an additional dispersion correction, ΔE^{DISP} , is required.^{15, 46-49} In DFTB-EDA, the dispersion term is defined as

$$\Delta E^{\text{DISP}} = E_{\text{S}}^{\text{DISP}} - \sum_{\text{M}} E_{\text{M}}^{\text{DISP}} \quad (9)$$

Here $E_{\text{p}}^{\text{DISP}}$ (P = S or M) is determined by a dispersion correction scheme. Various dispersion-correction schemes may be applied; in the DFTB+ program for example,^{50, 51} these include Lennard-Jones potentials,⁵² the Slater-Kirkwood polarizable atomic model,⁴⁶ and the DFT-D3/D4 correction.⁵³⁻⁵⁷

2.3 DFTB-EDA in excited state

The total TD-DFTB energy of the I^{th} excited state can be written as the sum of the ground state DFTB energy and the excitation energy ω_I , which can be computed by the approximated Casida's equation.⁵⁸ Once the Kohn-Sham orbitals and energies ε_{ia} are determined, where i and a are occupied and virtual orbitals, respectively, the linear response treatment for the electronic density can be applied directly through an extension with respect to the ground state DFTB, in similarity to TD-DFT.¹⁹

For TD-DFTB calculations, DFTB-EDA includes the same three terms as calculated for ground state DFTB: frozen density $\Delta E^{\text{FRZ}(*)}$, polarization $\Delta E^{\text{POL}(*)}$, and dispersion ΔE^{DISP} :

$$\Delta E^{\text{TOT}(*)} = \Delta E^{\text{FRZ}(*)} + \Delta E^{\text{POL}(*)} + \Delta E^{\text{DISP}} \quad (10)$$

The definition of ΔE^{DISP} is the same as in the ground state, whereas the other two terms differ in comparison to the ground state DFTB. Here we focus on the case where there is only one monomer that is in a certain excited state I .

The frozen term $\Delta E^{\text{FRZ}(*)}$ denotes the frozen density interaction between a monomer in its excited state (X) and another monomer in its ground state (Y), defined as:

$$\Delta E^{\text{FRZ}(*)} = E_{\text{S}}^{\text{FRZ}*} - E_{\text{X}}^{\text{FRZ}*} - E_{\text{Y}}^{\text{FRZ}} \quad (11)$$

E_Y^{FRZ} is defined by eq 6; while $E_X^{\text{FRZ}^*}$ is defined as follows:

$$E_X^{\text{FRZ}^*} = E_X^{\text{rep}} + \sum_{\mu, \nu \in X} D_{\mu\nu}^0 H_{\mu\nu}^0 + \frac{1}{2} \sum_{A, B \in X} \gamma_{AB} \Delta q_A^* \Delta q_B^* \quad (12)$$

Here, the Mulliken atomic transition charge Δq_A^* of atom A in the excited monomer can be expressed as:

$$\Delta q_A^* = \frac{1}{2} \sum_{\mu \in A} \sum_{\nu} (c_{\mu}^i c_{\nu}^a S_{\mu\nu} + c_{\nu}^i c_{\mu}^a S_{\nu\mu}) - q_A^0 \quad (13)$$

$E_S^{\text{FRZ}^*}$ is expressed as:

$$E_S^{\text{FRZ}^*} = E_S^{\text{rep}} + \sum_{\mu, \nu \in S} D_{\mu\nu}^0 H_{\mu\nu}^0 + \frac{1}{2} \sum_{A, B \in S} \gamma_{AB} \Delta q_A^{\text{in}} \Delta q_B^{\text{in}} \quad (14)$$

Δq_A^{in} is the initial Mulliken atomic charge of complex S, which is defined as the sum of the Mulliken atomic transition charge of monomer X and Mulliken atomic charge of monomer Y.

The polarization term in the excited state, ΔE^{POL^*} , can be expressed as:

$$\Delta E^{\text{POL}^*} = (E_S^* - E_S^{\text{FRZ}^*}) - (E_X^* - E_X^{\text{FRZ}^*}) - \sum_{\mu, \nu \in Y} E_Y^{\text{POL}} \quad (15)$$

Here E_S^* and E_X^* are the TD-DFTB energies of complex S and the monomer in excited state X, which can be written as

$$E_S^* = \sum_{\mu, \nu \in S} D_{\mu\nu} H_{\mu\nu}^0 + E^{\text{rep}} + \frac{1}{2} \sum_{A, B \in S} \Delta q_A \Delta q_B \gamma_{AB} + \omega_S \quad (16)$$

and

$$E_X^* = \sum_{\mu, \nu \in X} D_{\mu\nu} H_{\mu\nu}^0 + E^{\text{rep}} + \frac{1}{2} \sum_{A, B \in X} \Delta q_A \Delta q_B \gamma_{AB} + \omega_X \quad (17)$$

3. COMPUTATIONAL DETAILS

3.1 Models

Two databases, the S66 set for small bio-organic molecules⁵⁹ (Figure S1) and the L7 set for medium size dispersion-dominated systems⁶⁰ (Figure S2), were selected to examine the performance of DFTB-EDA for non-covalent interactions. S66 consists of 66 complexes, which can be divided into three groups: the first group includes 23 hydrogen bond dominated systems (HB), the second group involves 23 dispersion (van der Waals, vdW) dominated complexes; while the third one contains the remaining 20 systems (MIX), which mainly belong to $X-H\cdots\pi$ interactions ($X = C, O$ or N atom). The seven dimer interactions in L7 include: a π - π stacked interaction in the parallel coronene dimer (C2C2PD), a π - π stacked interaction in the circumcoronene $\cdots$ adenine dimer (C3A), a π - π stacked interaction between circumcoronene and a guanine-cytosine base pair dimer (C3GC), a stacked interaction between two octadecanes (CBH), a π - π stacked interaction between guanine-cytosine base pair dimers (GCGC), a stacked interaction between a single guanine and a guanine dimer (GGG), and an interaction between a single phenylalanine residue and a phenylalanine dimer (PHE). Two model molecules, a π -stacked aggregate tetramer⁶¹ (Figure 1), and an amyloid-like IYQYGG segment⁶² (PDB code: 6G8C, Figure 2), were employed to examine the capabilities of DFTB-EDA for large systems. A series of complexes in the ground state and the lowest excited states, shown in Figure 3, were used to examine the application of DFTB-EDA in the excited state.

Figures 1-2 are here

3.2 Calculations

SCC-DFTB calculations were performed by DFTB+ program (version 19.1).^{50, 51} DFTB-EDA results were obtained by using the DFTB-EDA code, which is available at www.xmvm.org. The parameter sets MIO² and 3OB⁶³ were used for DFTB2 and DFTB3, respectively. Parameter files were downloaded from www.dftb.org. Two different dispersion correction schemes, D3 and D3H5,

were used.^{49, 53} In this paper, DFTB2/3 with dispersion corrections are denoted as DFTB2-D3/MIO, DFTB3-D3/3OB and DFTB3-D3H5/3OB for brevity.

The geometries of all complexes shown in Figures S1, S2, 1 and 2 were taken directly from the literature.⁵⁹⁻⁶² The complexes in Figure 3 were optimized by DFTB2-D3/MIO and TD-DFTB2-D3/MIO, respectively. The Cartesian coordinates are shown in Table S1. For excited state calculations, only DFTB2 was applied because TD-DFTB in the DFTB+ program currently supports DFTB2 only. For comparison, the GKS-EDA calculations have also been carried out with our in-house GAMESS-US package.⁶⁴ For GKS-EDA, B3LYP-D3 and PBE-D3 were used with the 6-31+G* basis set. The counterpoise (CP) correction by Boys and Bernardi was used for correcting the basis set superposition error (BSSE) in GKS-EDA.⁶⁵

Figure 3 is here

4. RESULTS AND DISCUSSIONS

4.1 Summary of DFTB-EDA calculations for non-covalent interactions in the S66 and L7 datasets

The total interaction energies and their components calculated for the S66 data set at the DFTB3-D3H5 level with the 3OB parameter set are shown in Table 1. Calculations with additional sets and treatments (DFTB2-D3/MIO and DFTB3-D3/3OB), and reference calculations (PBE-D3/6-31+G* and B3LYP-D3/6-31+G*) are shown in Table S2. The errors in total interaction energies calculated by DFTB and KS-DFT, compared to those obtained by CCSD(T)/CBS are shown in Table S3.

Considering the total interaction energies, all the DFTB methods yielded accurate total interaction energies with errors below 1.0 kcal/mol, with the DFTB3-D3H5/3OB calculations having root mean square errors (RMSEs) that are in par with those obtained with more elaborate (and computationally demanding) DFT approaches. The DFTB-EDA results reveal that for hydrogen bond dominated systems, polarization contribution is large while dispersion is small. For example, the polarization terms of the water dimer and methanol dimer were -4.25 and -3.88 kcal/mol, while the

corresponding dispersion terms were -0.21 and -0.87 kcal/mol, respectively. For dispersion dominated complexes and X-H $\cdots\pi$ complexes, the dispersion term was the largest contribution to the interaction energy. For example, for the π - π stacking dominated pyridine $\cdots$ pyridine complex, the dispersion term was -4.07 kcal/mol, covering almost 100% of total interaction energy, whereas the polarization term was only -0.04 kcal/mol. Of note, the difference between dispersion dominated complexes and X-H $\cdots\pi$ complexes is that the polarization interactions in X-H $\cdots\pi$ complexes are larger in absolute value than those in the former. In detail, the average value of polarization term in dispersion dominated complexes was -0.46 kcal/mol, while that in X-H $\cdots\pi$ complexes was -1.0 kcal/mol. Moreover, it can be seen that for the hydrogen bonding complexes, the contributions from the frozen density term were large and negative, while for the other two types of complexes, the frozen density interactions were small and positive.

When comparing the DFTB-EDA results with those from ab initio EDA methods (for example, LMO-EDA³³ and GKS-EDA³⁴), it seems that the DFTB results do not agree with those obtained by ab initio EDA methods, which show that the electrostatic term makes the largest contribution for hydrogen bonding interactions. This discrepancy stems from the difference in the definition of the terms. In LMO-EDA and GKS-EDA, energy decomposition includes additional terms that cannot be calculated from DFTB. The frozen density term in DFTB-EDA corresponds to the sum of electrostatics, Pauli repulsion and correlation terms in ab initio EDA. For typical hydrogen bonding interactions, it is shown that this sum is smaller than polarization term. For example, the sum of the three terms in LMO-EDA at the CCSD(T)/ACCQ level for the water dimer is -1.25 kcal/mol, smaller than the value of polarization term, -2.38 kcal/mol.³³ This is in agreement with the DFTB-EDA result. Given the negative values of the frozen density term for hydrogen bonding complexes, DFTB-EDA does in fact capture the important role of electrostatic interaction in hydrogen bonding interaction.

To further explore the performance of DFTB-EDA, the results of DFTB-EDA at DFTB3-D3H5/3OB level compared to the corresponding GKS-EDA values at the PBE-D3/6-31+G* level, including ΔE^{FRZ} vs. $\Delta E^{\text{ele}} + \Delta E^{\text{Pauli}} + \Delta E^{\text{corr}}$, $\Delta E_{\text{DFTB-EDA}}^{\text{POL}}$ vs. $\Delta E_{\text{GKS-EDA}}^{\text{pol}}$, and $\Delta E_{\text{DFTB-EDA}}^{\text{DISP}}$ vs.

$\Delta E_{\text{GKS-EDA}}^{\text{disp}}$, are shown in Figure 4. For the total interaction energy of the S66 set, the correlation coefficient was 0.973. As can be seen, the correlations between DFTB-EDA and GKS-EDA are also high when it comes to the polarization and dispersion terms. For the polarization term, the coefficient was larger than 0.9, showing that the polarization in DFTB-EDA can be compared to the one calculated by GKS-EDA, that is defined by the orbital relaxations in the SCF procedure. The dispersion term in DFTB-EDA was very close to that in GKS-EDA because that both of them are derived from Grimme's DFT-D scheme. However, it has been found that the correlation coefficient of determination from ΔE^{FRZ} and $\Delta E^{\text{ele}} + \Delta E^{\text{Pauli}} + \Delta E^{\text{corr}}$ was rather low. A possible explanation to this is that the valence minimal basis set in DFTB could not describe the monomers' orbital overlaps properly. Considering the fact that for non-covalent interactions, contributions from the frozen terms are generally smaller (in absolute values) than polarization and dispersion terms, the error could be acceptable.

Figure 4 is here

The results of various EDA methods for L7 set are listed in Table 2. The calculations show that the total DFTB interaction energies are generally in good agreement with those calculated by GKS-EDA. Considering the different terms, the DFTB-EDA results were similar to the GKS-EDA ones, showing that dispersion interaction was dominant with the exception of PHE. For example, with $\Delta E^{\text{FRZ}} = 0.91$, $\Delta E^{\text{POL}} = 0.59$, and $\Delta E^{\text{DISP}} = -21.52$ kcal/mol, the total interaction energy of C2C2PD at the DFTB3-D3H5/3OB level is $\Delta E^{\text{TOT}} = -20.02$ kcal/mol, and the dispersion term was larger (in absolute value) than the frozen and polarization terms.

As for PHE, the DFTB-EDA result was similar to those of GKS-EDA and LMO-EDA, showing that polarization term is the largest. As discussed above, the hydrogen bonding complex is dominated by polarization. The large polarization term suggests there are strong hydrogen bonding interactions in PHE. As can be seen from NCI⁶⁶ and AIM⁶⁷ calculated by Multiwfn program,⁶⁸ shown in Figure S3, there are various interactions in PHE. First, two N-H...O hydrogen bonds, with the peaks located

at -0.016 and -0.029 a.u. in the reduced density gradient (RDG) isosurface, can be considered as strong hydrogen bonds because of the electronegativity of O and N atoms, and the short distances, 1.904 Å and 1.921 Å, between the H and N atoms. Moreover, there are three C-H $\cdots$ O hydrogen bonds with their H $\cdots$ O distances ranging from 2.353 Å to 2.517 Å. It is known that C-H $\cdots$ O hydrogen bond can be considered as an unusual molecular interaction with moderate binding strength. Besides, there are weak π - π stacking interactions between the two benzene rings, which are obviously weaker than the five hydrogen bonds mentioned above. As such, the overwhelming hydrogen bonding interactions leads to a dominant effect of polarization in PHE.

Figure 5 shows the relationship between the polarization term of DFTB-EDA and the difference in monomers' Mulliken charges when comparing the charges of the monomers to those of the complexes, calculated for S66 and L7 datasets. This analysis shows that the polarization term was positively correlated with the monomers' charge variation. In other words, a large variation in the monomer's charge (between the monomer and the complex) leads to a larger polarization term in absolute value. The five complexes shown in red, including AcOH $\cdots$ AcOH, AcNH₂ $\cdots$ AcNH₂, AcOH $\cdots$ uracil, AcNH₂ $\cdots$ uracil, and uracil $\cdots$ uracil (BP), have the extra-dominant polarization terms ranging from -18.04 kcal/mol to -20.36 kcal/mol. In these complexes, there exist conjugated double and single bonds between polar functional groups, which can be defined as resonance assisted hydrogen bonds (RAHB).^{69, 70} In RAHB, orbital delocalization is known to be highly important, leading to a large binding strength.³⁷ The dominant polarization term calculated for these complexes betrays that DFTB-EDA is capable of revealing the characteristics of RAHB.

Figure 5 is here

4.2 DFTB-EDA results for large molecules

Large interacting systems containing more than 300 atoms are challenging for ab initio or DFT-based EDA due to the large number of basis set functions. A prohibitive computational cost prevents

the use of EDA for calculations that involve such complexes. An advantage of DFTB-EDA, besides being faster to compute, is the ability to perform EDA calculations for large systems. Here, we considered two cases of large systems. The first is a π -stacked aggregate tetramer composed of an ortho-ethynylene-bridged PDI dyad (PEP) and the slightly longer orthobutadiyne-bridged PDI dyad (PBP),⁶¹ denoted as PBP-PEP-PEP-PBP. This tetramer contains 324 atoms. As shown in Figure 1, there are two kinds of stacking interactions in the complex. The first, (denoted here as 1v3) is an interaction between PBP and PEP-PEP-PBP. The second (denoted as 2v2), is an interaction between PBP-PEP and PEP-PBP. According to the DFTB-EDA results (Figure 6), both interactions are dominated by the dispersion term. For the 1v3 interaction, the total binding energy was -84.6 kcal/mol which was -27.7 kcal/mol lower than that of 2v2. This shows that a stronger binding is achieved by 1v3 stacking. The EDA analysis revealed that this was mainly attributed to dispersion, because, compared to 2v2 stacking, there were additional vdW interactions in 1v3 (between PBP and the most adjacent PEP).

Figure 6 is here

The model of two amyloid-like IYQYGG fibril-like structures, which consists of 1710 atoms (Figure 2) was also studied with DFTB-EDA. Each fibril-like structure was made of nine identical fragments, each containing 190 atoms. We considered two different peptides capping for the fragments, neutral ($\text{H}_2\text{N-IYQYGG-COOH}$) and zwitterionic ($\text{H}_3\text{N}^+-\text{IYQYGG-COO}^-$).

The DFTB-EDA results for the interactions in (1) a dimer of two fragments and (2) the whole amyloid fibril-like complex are listed in Table 3. For the neutral fragment dimer, the total interaction energies calculated with DFTB were -10.59, -9.97 and -11.45 kcal/mol as calculated by DFTB3-D3/3OB, DFTB3-D3H5/3OB and DFTB2-D3/MIO, respectively. These values can be compared to the value calculated with B3LYP-D3/6-31G, -14.22 kcal/mol. The DFTB-EDA and GKS-EDA results both reveal that the dispersion term dominates the interaction.

For the zwitterionic fragment dimer, the interaction energies were -28.29, -27.59 and -25.27

kcal/mol as calculated by DFTB3-D3/3OB, DFTB3-D3H5/3OB and DFTB2-D3/MIO, respectively. The interaction energies were thus somewhat smaller than the value obtained with B3LYP-D3/6-31G, -36.99 kcal/mol. It is interesting to note that while the dispersion contribution of the zwitterionic complex was almost unchanged compared to that calculated for the neutral one, the total interaction energies greatly increased (in absolute value), which can be attributed to the polarization term. For the whole complex, the tendency was the same, i.e., polarization contributed most to binding energy in the zwitterionic model. While the charge-charge interactions were offset by repulsion and exchange giving rise to a rather small frozen term, the highly charged system induces polarization which then becomes the dominant term in DFTB-EDA (while GKS-EDA calculations show that the contribution from electrostatic term is the most dominant).

4.3 DFTB-EDA for intermolecular interactions in excited states

Intermolecular interactions in electronic excited states are important for the structure and properties of molecular systems in various photophysical and photochemical processes. Upon electronic excitation, the charge density of molecular systems could be redistributed significantly compared to that in ground state. The intermolecular interactions in ($n \rightarrow \pi^*$) excitations have been studied extensively.^{71, 72} Han et al. demonstrated that the intermolecular hydrogen bond in the electronic excited state is greatly strengthened for coumarin chromophores and weakened for thiocarbonyl chromophores.⁷³ With the extension of ALMOEDA for excited state interactions, Head-Gordon et al. performed interaction analysis for several hydrogen-bonding complexes (formamide-water, pyridine/pyrimidine-water) in excited states.⁷⁴ Reimers et al. studied the interactions between water and heterocyclic compounds (pyridine, pyridazine, pyrimidine, and pyrazine) in their (n, π^*) excited states.⁷¹ Their analysis showed that in some circumstances, the interactions become weakened in the excited state, whereas in other cases the interactions become stronger because the enhanced electron density after excitation can result in a new type of binding mode.

To understand the origin of the excited state intermolecular interactions, a series of complexes,

shown in Figure 3, including three hydrogen bonding complexes (water-pyridine, water-pyrimidine and fluorenone-methanol) and two $\text{OH}\cdots\pi$ complexes (water-pyridine and water-pyrimidine) were investigated by DFTB-EDA. In these complexes, the excitations were locally excited in pyridine, pyrimidine and fluorenone, while H_2O and CH_3OH remained in their ground states.

First, as can be seen from Figure 7 and Table S4, the two $\text{O-H}\cdots\pi$ interactions in the excited states became stronger compared to those in ground states. During the excitation, dispersion terms remained almost unchanged due to the fact that the dispersion correction is irrespective of the variation of electronic density. The increase of the total interaction energy was due to the polarization term. For instance, in pyridine- H_2O ($\text{O-H}\cdots\pi$), the polarization term in the excited state was -2.54 kcal/mol, i.e., more favorable than the value in the ground state, -1.42 kcal/mol. In the lowest excited state, the LUMO of the heterocyclic compound had a large orbital mixing with the frontier molecular orbital of H_2O , which led to the large orbital delocalization; this might explain why an increase in the overall contribution from polarization could be expected. Furthermore, the $n\rightarrow\pi^*$ excitation weakened the electronic attraction of the lone pair to the H atom of H_2O , resulting in a decrease of electrostatic interactions. As such, from the ground to the excited state, the frozen density term became positive or less negative.

In the hydrogen-bonded systems, in similarity to those that involve $\text{O-H}\cdots\pi$ interactions, the variation of the total interactions from the ground to the excited state could be attributed to the competition between the polarization and frozen density terms. In agreement with the conclusion of Han et al.,⁷³ the strength of the hydrogen bond in the fluorenone- CH_3OH system was greatly enhanced by the excitation. DFTB-EDA revealed that the contributing factor to this was an increase (in absolute value) in the polarization term from -4.57 kcal/mol to -18.53 kcal/mol. At the same time, the frozen density term became repulsive as it increased from -0.97 kcal/mol to 4.83 kcal/mol. Similarly, the hydrogen bond of pyrimidine- H_2O in the excited state became stronger. However, it should be noted that hydrogen bond of pyridine- H_2O in the excited state was weaker than that in ground state. This was due to the fact that the increase of polarization term could not compensate for the repulsive frozen

term.

Figure 7 is here

5. CONCLUSIONS

We presented a DFTB/TD-DFTB based EDA method, called DFTB-EDA. DFTB-EDA can perform interaction analysis at a fraction of the computational cost associated with ab initio EDA schemes and can thus be applied for large systems. Furthermore, DFTB-EDA can be used to study systems that involve molecules in their excited states. Limitations of DFTB-EDA, which are inherent to the semi-empirical nature and approximations used in DFTB, are that the frozen density term cannot be further separated, and that the use of a minimal basis set cannot be expected to capture minute details of the interaction energies. Moreover, DFTB-EDA currently supports single excitation only because TD-DFTB can be regarded as the approximation of TD-DFT. It is hopeful that DFTB-EDA will be capable of describing excited states of single, double, and mixed excitation character when spin-flip TD-DFTB is employed.⁷⁵ With further development of DFTB, improvements in the accuracy of DFTB-EDA can also be expected.

In summary, the following are highlighted:

- (1) With few exceptions, DFTB interaction energies were shown to be similar to those obtained by more elaborate methods. In such cases, DFTB-EDA calculations qualitatively capture the dominant term in the interaction energies.
- (2) The frozen density term (which correspond to the sum of electrostatics, exchange and repulsion) was not the dominant contribution in the ground-state complexes studied here.
- (3) For hydrogen bonding interactions, the polarization term was the most dominant; while for vdW interactions, dispersion was the most dominant term.
- (4) The variation of intermolecular interaction in excited states compared to the ground state can be explained as an interplay between the polarization and frozen density terms.

Overall, DFTB-EDA provides a useful, semi-quantitative analysis of intermolecular interactions in large systems, and might capture the intricate nature of such interactions. The method can thus be

used to analyze and design molecular systems and can be applied in particular to biological systems and material science.

SUPPLEMENTARY MATERIAL

See the supplementary material associated with this article. It includes the geometries of S66 and L7; AIM and NCI plots of interactions in PHE; Cartesian coordinates of the complexes in Figure 3, and additional GKS-EDA, DFTB-EDA results.

ACKNOWLEDGEMENTS

This project is supported by the National Natural Science Foundation of China (Nos. 21733008 and 21973077), New Century Excellent Talents in Fujian Province University and the Fundamental Research Funds for the Central Universities (No. 20720190046).

DATA AVAILABILITY

The data that supports the findings of this study are available within the article and its supplementary material.

Reference

1. D. Porezag, T. Frauenheim, T. Köhler, G. Seifert, and R. Kaschner, "Construction of tight-binding-like potentials on the basis of density-functional theory: Application to carbon," *Phys. Rev. B* **51**, 12947-12957 (1995).
2. M. Elstner, D. Porezag, G. Jungnickel, J. Elsner, M. Haugk, T. Frauenheim, S. Suhai, and G. Seifert, "Self-consistent-charge density-functional tight-binding method for simulations of complex materials properties," *Phys. Rev. B* **58**, 7260-7268 (1998).
3. M. Gaus, Q. Cui, and M. Elstner, "DFTB3: Extension of the Self-Consistent-Charge Density-Functional Tight-Binding Method (SCC-DFTB)," *J. Chem. Theory Comput.* **7**, 931-948 (2011).
4. A. S. Christensen, T. Kubař, Q. Cui, and M. Elstner, "Semiempirical Quantum Mechanical Methods for Noncovalent Interactions for Chemical and Biochemical Applications," *Chem. Rev.* **116**, 5301-5337 (2016).
5. W. Kohn and L. J. Sham, "Self-Consistent Equations Including Exchange and Correlation Effects," *Phys. Rev.* **140**, A1133-A1138 (1965).
6. R. G. Parr and W. Yang, *Density Functional Theory of Atoms and Molecules* (Oxford University Press, New York, 1989).
7. Y. Yang, H. Yu, D. York, Q. Cui, and M. Elstner, "Extension of the Self-Consistent-Charge Density-Functional Tight-Binding Method: Third-Order Expansion of the Density Functional Theory Total Energy and Introduction of a Modified Effective Coulomb Interaction," *J. Phys. Chem. A* **111**, 10861-10873 (2007).
8. R. S. Mulliken, "Electronic Population Analysis on LCAO-MO Molecular Wave Functions. I," *J. Chem. Phys.* **23**, 1833-1840 (1955).
9. Q. Cui and M. Elstner, "Density functional tight binding: values of semi-empirical methods in an ab initio era," *Phys. Chem. Chem. Phys.* **16**, 14368-14377 (2014).
10. M. Elstner and G. Seifert, "Density functional tight binding," *Phil. Trans. R. Soc. A* **372**, 20120483 (2014).
11. M. Gaus, Q. Cui, and M. Elstner, "Density functional tight binding: application to organic and biological molecules," *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **4**, 49-61 (2014).
12. A. F. Oliveira, G. Seifert, T. Heine, and H. A. Duarte, "Density-functional based tight-binding: an approximate DFT method," *J. Braz. Chem. Soc.* **20**, 1193-1205 (2009).
13. G. Seifert and J.-O. Joswig, "Density-functional tight binding—an approximate density-functional theory method," *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2**, 456-465 (2012).
14. F. Spiegelman, N. Tarrat, J. Cuny, L. Dontot, E. Posenitskiy, C. Martí, A. Simon, and M. Rapacioli, "Density-functional tight-binding: basic concepts and applications to molecules and clusters," *Adv. Phys. X* **5**, 1710252 (2020).
15. K. Kříž and J. Řezáč, "Benchmarking of Semiempirical Quantum-Mechanical Methods on Systems Relevant to Computer-Aided Drug Design," *Journal of Chemical Information and Modeling* **60**, 1453-1460 (2020).
16. F. Trani, G. Scalmani, G. Zheng, I. Carnimeo, M. J. Frisch, and V. Barone, "Time-Dependent Density Functional Tight Binding: New Formulation and Benchmark of Excited States," *J. Chem. Theory Comput.* **7**, 3304-3313 (2011).
17. T. A. Niehaus, "Approximate time-dependent density functional theory," *J. Mol. Struct.: THEOCHEM* **914**, 38-49 (2009).
18. D. Heringer, T. A. Niehaus, M. Wanko, and T. H. Frauenheim, "Analytical excited state forces for the time-dependent density-functional tight-binding method," *J. Comput. Chem.* **28**, 2589-2601 (2007).
19. T. A. Niehaus, S. Suhai, F. Della Sala, P. Lugli, M. Elstner, G. Seifert, and T. Frauenheim, "Tight-binding approach to time-dependent density-functional response theory," *Phys. Rev. B* **63**, 085108 (2001).
20. Y. Nishimoto, "Time-dependent density-functional tight-binding method with the third-order expansion of electron density," *J. Chem. Phys.* **143**, 094108 (2015).

21. A. Fihey and D. Jacquemin, "Performances of Density Functional Tight-Binding Methods for Describing Ground and Excited State Geometries of Organic Molecules," *J. Chem. Theory Comput.* **15**, 6267-6276 (2019).
22. J. J. Kranz, M. Elstner, B. Aradi, T. Frauenheim, V. Lutsker, A. D. Garcia, and T. A. Niehaus, "Time-Dependent Extension of the Long-Range Corrected Density Functional Based Tight-Binding Method," *J. Chem. Theory Comput.* **13**, 1737-1747 (2017).
23. V. Q. Vuong, J. Akkarapattiakal Kuriappan, M. Kubillus, J. J. Kranz, T. Mast, T. A. Niehaus, S. Irle, and M. Elstner, "Parametrization and Benchmark of Long-Range Corrected DFTB2 for Organic Molecules," *J. Chem. Theory Comput.* **14**, 115-125 (2018).
24. M. J. S. Phipps, T. Fox, C. S. Tautermann, and C.-K. Skylaris, "Energy decomposition analysis approaches and their evaluation on prototypical protein–drug interaction patterns," *Chem. Soc. Rev.* **44**, 3177-3211 (2015).
25. M. v. Hopffgarten and G. Frenking, "Energy decomposition analysis," *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2**, 43-62 (2012).
26. P. Su, Z. Tang, and W. Wu, "Generalized Kohn-Sham energy decomposition analysis and its applications," *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **10**, e1460 (2020).
27. K. Morokuma, "Molecular Orbital Studies of Hydrogen Bonds. III. C=O···H–O Hydrogen Bond in H₂CO···H₂O and H₂CO···2H₂O," *J. Chem. Phys.* **55**, 1236-1244 (1971).
28. T. Ziegler and A. Rauk, "On the calculation of bonding energies by the Hartree Fock Slater method," *Theoret. Chim. Acta (Berl.)* **46**, 1-10 (1977).
29. Y. Mo, J. Gao, and S. D. Peyerimhoff, "Energy decomposition analysis of intermolecular interactions using a block-localized wave function approach," *J. Chem. Phys.* **112**, 5530-5538 (2000).
30. S. a. Rybak, B. Jeziorski, and K. Szalewicz, "Many-body symmetry-adapted perturbation theory of intermolecular interactions. H₂O and HF dimers," *J. Chem. Phys.* **95**, 6576-6601 (1991).
31. R. Z. Khaliullin, E. A. Cobar, R. C. Lochan, A. T. Bell, and M. Head-Gordon, "Unravelling the Origin of Intermolecular Interactions Using Absolutely Localized Molecular Orbitals," *J. Phys. Chem. A* **111**, 8753-8765 (2007).
32. D. G. Fedorov and K. Kitaura, "Pair interaction energy decomposition analysis," *J. Comput. Chem.* **28**, 222-237 (2007).
33. P. Su and H. Li, "Energy decomposition analysis of covalent bonds and intermolecular interactions," *J. Chem. Phys.* **131**, 014102 (2009).
34. P. Su, Z. Jiang, Z. Chen, and W. Wu, "Energy Decomposition Scheme Based on the Generalized Kohn–Sham Scheme," *J. Phys. Chem. A* **118**, 2531-2542 (2014).
35. W. B. Schneider, G. Bistoni, M. Sparta, M. Saitow, C. Riplinger, A. A. Auer, and F. Neese, "Decomposition of Intermolecular Interaction Energies within the Local Pair Natural Orbital Coupled Cluster Framework," *J. Chem. Theory Comput.* **12**, 4778-4792 (2016).
36. P. Su, H. Liu, and W. Wu, "Free energy decomposition analysis of bonding and nonbonding interactions in solution," *J. Chem. Phys.* **137**, 034111 (2012).
37. P. Su, Z. Chen, and W. Wu, "An energy decomposition analysis study for intramolecular non-covalent interaction," *Chem. Phys. Lett.* **635**, 250-256 (2015).
38. A. J. Misquitta, R. Podeszwa, B. Jeziorski, and K. Szalewicz, "Intermolecular potentials based on symmetry-adapted perturbation theory with dispersion energies from time-dependent density-functional calculations," *J. Chem. Phys.* **123**, 214103 (2005).
39. V. M. Miriyala and J. Řezáč, "Description of non-covalent interactions in SCC-DFTB methods," *J. Comput. Chem.* **38**, 688-697 (2017).
40. D. G. Fedorov and K. Kitaura, "Pair Interaction Energy Decomposition Analysis for Density Functional Theory and Density-Functional Tight-Binding with an Evaluation of Energy Fluctuations in Molecular Dynamics," *J. Phys. Chem. A* **122**, 1781-1795 (2018).
41. K. Kitaura, E. Ikeo, T. Asada, T. Nakano, and M. Uebayasi, "Fragment molecular orbital method: an approximate computational method for large molecules," *Chem. Phys. Lett.* **313**, 701-706 (1999).
42. T. Ishikawa, T. Ishikura, and K. Kuwata, "Theoretical study of the prion protein based on the fragment molecular orbital method," *J. Comput. Chem.* **30**, 2594-2601 (2009).

43. M. Elstner, "SCC-DFTB: What Is the Proper Degree of Self-Consistency?," J. Phys. Chem. A **111**, 5614-5621 (2007).
44. C. Bannwarth, E. Caldeweyher, S. Ehlert, A. Hansen, P. Pracht, J. Seibert, S. Spicher, and S. Grimme, "Extended tight-binding quantum chemistry methods," Wiley Interdiscip. Rev.: Comput. Mol. Sci. **11**, e1493 (2021).
45. J. C. Slater and G. F. Koster, "Simplified LCAO Method for the Periodic Potential Problem," Phys. Rev. **94**, 1498-1524 (1954).
46. M. Elstner, P. Hobza, T. Frauenheim, S. Suhai, and E. Kaxiras, "Hydrogen bonding and stacking interactions of nucleic acid base pairs: A density-functional-theory based treatment," J. Chem. Phys. **114**, 5149-5155 (2001).
47. L. Zhechkov, T. Heine, S. Patchkovskii, G. Seifert, and H. A. Duarte, "An Efficient a Posteriori Treatment for Dispersion Interaction in Density-Functional-Based Tight Binding," J. Chem. Theory Comput. **1**, 841-847 (2005).
48. J. Řezáč and P. Hobza, "Advanced Corrections of Hydrogen Bonding and Dispersion for Semiempirical Quantum Mechanical Methods," J. Chem. Theory Comput. **8**, 141-151 (2012).
49. J. Řezáč, "Empirical Self-Consistent Correction for the Description of Hydrogen Bonds in DFTB3," J. Chem. Theory Comput. **13**, 4804-4817 (2017).
50. B. Aradi, B. Hourahine, and T. Frauenheim, "DFTB+, a Sparse Matrix-Based Implementation of the DFTB Method," J. Phys. Chem. A **111**, 5678-5684 (2007).
51. B. Hourahine, B. Aradi, V. Blum, F. Bonafé, A. Buccheri, C. Camacho, C. Cevallos, M. Y. Deshayé, T. Dumitrică, A. Dominguez, S. Ehlert, M. Elstner, T. van der Heide, J. Hermann, S. Irle, J. J. Kranz, C. Köhler, T. Kowalczyk, T. Kubař, I. S. Lee, V. Lutsker, R. J. Maurer, S. K. Min, I. Mitchell, C. Negre, T. A. Niehaus, A. M. N. Niklasson, A. J. Page, A. Pecchia, G. Penazzi, M. P. Persson, J. Řezáč, C. G. Sánchez, M. Sternberg, M. Stöhr, F. Stuckenberg, A. Tkatchenko, V. W. z. Yu, and T. Frauenheim, "DFTB+, a software package for efficient approximate density functional theory based atomistic simulations," J. Chem. Phys. **152**, 124101 (2020).
52. A. K. Rappe, C. J. Casewit, K. S. Colwell, W. A. Goddard, and W. M. Skiff, "UFF, a full periodic table force field for molecular mechanics and molecular dynamics simulations," J. Am. Chem. Soc. **114**, 10024-10035 (1992).
53. S. Grimme, J. Antony, S. Ehrlich, and H. Krieg, "A consistent and accurate ab initio parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu," J. Chem. Phys. **132**, 154104 (2010).
54. S. Grimme, S. Ehrlich, and L. Goerigk, "Effect of the damping function in dispersion corrected density functional theory," J. Comput. Chem. **32**, 1456-1465 (2011).
55. D. G. A. Smith, L. A. Burns, K. Patkowski, and C. D. Sherrill, "Revised Damping Parameters for the D3 Dispersion Correction to Density Functional Theory," J. Phys. Chem. Lett. **7**, 2197-2203 (2016).
56. E. Caldeweyher, C. Bannwarth, and S. Grimme, "Extension of the D3 dispersion coefficient model," J. Chem. Phys. **147**, 034112 (2017).
57. E. Caldeweyher, S. Ehlert, A. Hansen, H. Neugebauer, S. Spicher, C. Bannwarth, and S. Grimme, "A generally applicable atomic-charge dependent London dispersion correction," J. Chem. Phys. **150**, 154122 (2019).
58. M. E. Casida, *Time-Dependent Density Functional Response Theory for Molecules* (World Scientific, Singapore, 1995).
59. J. Řezáč, K. E. Riley, and P. Hobza, "S66: A Well-balanced Database of Benchmark Interaction Energies Relevant to Biomolecular Structures," J. Chem. Theory Comput. **7**, 2427-2438 (2011).
60. R. Sedlak, T. Janowski, M. Pitoňák, J. Řezáč, P. Pulay, and P. Hobza, "Accuracy of Quantum Chemical Methods for Large Noncovalent Complexes," J. Chem. Theory Comput. **9**, 3364-3374 (2013).
61. F. Su, G. Chen, P. A. Korevaar, F. Pan, H. Liu, Z. Guo, A. P. H. J. Schenning, H.-J. Zhang, J. Lin, and Y.-B. Jiang, "Discrete π -Stacks from Self-Assembled Perylenediimide Analogues," Angew. Chem.

Int. Ed. **58**, 15273-15277 (2019).

62. S. Perov, O. Lidor, N. Salinas, N. Golan, E. Tayeb- Fligelman, M. Deshmukh, D. Willbold, and M. Landau, "Structural Insights into Curli CsgA Cross- β Fibril Architecture Inspire Repurposing of Anti-amyloid Compounds as Anti-biofilm Agents," *PLoS Pathog.* **15**, e1007978 (2019).

63. M. Gaus, A. Goez, and M. Elstner, "Parametrization and Benchmark of DFTB3 for Organic Molecules," *J. Chem. Theory Comput.* **9**, 338-354 (2013).

64. G. M. J. Barca, C. Bertoni, L. Carrington, D. Datta, N. De Silva, J. E. Deustua, D. G. Fedorov, J. R. Gour, A. O. Gunina, E. Guidez, T. Harville, S. Irle, J. Ivanic, K. Kowalski, S. S. Leang, H. Li, W. Li, J. J. Lutz, I. Magoulas, J. Mato, V. Mironov, H. Nakata, B. Q. Pham, P. Piecuch, D. Poole, S. R. Pruitt, A. P. Rendell, L. B. Roskop, K. Ruedenberg, T. Sattasathuchana, M. W. Schmidt, J. Shen, L. Slipchenko, M. Sosonkina, V. Sundriyal, A. Tiwari, J. L. Galvez Vallejo, B. Westheimer, M. Włoch, P. Xu, F. Zahariev, and M. S. Gordon, "Recent developments in the general atomic and molecular electronic structure system," *J. Chem. Phys.* **152**, 154102 (2020).

65. S. F. Boys and F. Bernardi, "The calculation of small molecular interactions by the differences of separate total energies. Some procedures with reduced errors," *Mol. Phys.* **19**, 553-566 (1970).

66. E. R. Johnson, S. Keinan, P. Mori-Sánchez, J. Contreras-García, A. J. Cohen, and W. Yang, "Revealing Noncovalent Interactions," *J. Am. Chem. Soc.* **132**, 6498-6506 (2010).

67. R. F. W. Bader, *Atoms in Molecules: A Quantum Theory* (Oxford University Press, New York, 1996).

68. T. Lu and F. Chen, "Multiwfn: A multifunctional wavefunction analyzer," *J. Comput. Chem.* **33**, 580-592 (2012).

69. G. Gilli, F. Bellucci, V. Ferretti, and V. Bertolasi, "Evidence for resonance-assisted hydrogen bonding from crystal-structure correlations on the enol form of the .beta.-diketone fragment," *J. Am. Chem. Soc.* **111**, 1023-1028 (1989).

70. P. Gilli, V. Bertolasi, V. Ferretti, and G. Gilli, "Evidence for resonance-assisted hydrogen bonding. 4. Covalent nature of the strong homonuclear hydrogen bond. Study of the O-H--O system by crystal structure correlation methods," *J. Am. Chem. Soc.* **116**, 909-915 (1994).

71. J. R. Reimers and Z.-L. Cai, "Hydrogen bonding and reactivity of water to azines in their S1 (n,π^*) electronic excited states in the gas phase and in solution," *Phys. Chem. Chem. Phys.* **14**, 8791-8802 (2012).

72. R. W. Newberry and R. T. Raines, "The $n\rightarrow\pi^*$ Interaction," *Acc. Chem. Res.* **50**, 1838-1846 (2017).

73. G.-J. Zhao and K.-L. Han, "Hydrogen Bonding in the Electronic Excited State," *Acc. Chem. Res.* **45**, 404-413 (2012).

74. Q. Ge, Y. Mao, and M. Head-Gordon, "Energy decomposition analysis for exciplexes using absolutely localized molecular orbitals," *J. Chem. Phys.* **148**, 064105 (2018).

75. M. Inamori, T. Yoshikawa, Y. Ikabata, Y. Nishimura, and H. Nakai, "Spin-flip approach within time-dependent density functional tight-binding method: Theory and applications," *J. Comput. Chem.* **41**, 1538-1548 (2020).

Table 1. DFTB-EDA interaction energies (in kcal/mol) calculated for intermolecular interactions in the S66 data set at DFTB3-D3H5/3OB level.

#	Hydrogen bond	ΔE^{FRZ}	ΔE^{POL}	ΔE^{DISP}	ΔE^{TOT}
1	H ₂ O...H ₂ O	-0.90	-4.25	-0.21	-5.36
2	H ₂ O...MeOH	-0.72	-4.21	-0.58	-5.51
3	H ₂ O...MeNH ₂	-1.82	-6.00	-0.54	-8.35
4	H ₂ O...NMe-acetamide	-0.50	-7.24	-0.89	-8.64
5	MeOH...MeOH	-0.79	-3.88	-0.87	-5.53
6	MeOH...MeNH ₂	-1.91	-5.68	-1.21	-8.80
7	MeOH...NMe-acetamide	-0.63	-6.47	-1.39	-8.49
8	MeOH...H ₂ O	-0.93	-3.90	-0.37	-5.21
9	MeNH ₂ ...MeOH	-0.11	-1.46	-1.21	-2.78
10	MeNH ₂ ...MeNH ₂	0.12	-2.49	-1.15	-3.51
11	MeNH ₂ ...NMe-acetamide	0.32	-2.90	-1.92	-4.50
12	MeNH ₂ ...H ₂ O	-1.29	-6.17	-0.63	-8.10
13	NMe-acetamide...MeOH	0.54	-4.63	-1.60	-5.69
14	NMe-acetamide...MeNH ₂	-0.04	-5.82	-1.79	-7.65
15	NMe-acetamide...NMe-acetamide	0.64	-7.02	-2.43	-8.81
16	NMe-acetamide...H ₂ O	0.16	-4.35	-0.77	-4.97
17	Uracil...Uracil (BP)	4.27	-19.01	-2.16	-16.90
18	H ₂ O...Pyridine	-1.71	-4.33	-0.85	-6.89
19	MeOH...Pyridine	-1.76	-4.12	-1.30	-7.19
20	AcOH...AcOH	-0.27	-18.26	-1.46	-19.99
21	AcNH ₂ ...AcNH ₂	2.65	-18.04	-1.59	-16.99
22	AcOH...Uracil	2.35	-20.36	-1.79	-19.80
23	AcNH ₂ ...Uracil	4.05	-21.24	-1.87	-19.06
#	Dispersion	ΔE^{FRZ}	ΔE^{POL}	ΔE^{DISP}	ΔE^{TOT}
24	Benzene...Benzene (π - π)	0.14	0.29	-3.85	-3.42
25	Pyridine...Pyridine (π - π)	0.15	-0.04	-4.07	-3.96
26	Uracil...Uracil (π - π)	0.67	-3.74	-6.29	-9.36
27	Benzene...Pyridine (π - π)	0.16	0.12	-3.97	-3.70
28	Benzene...Uracil (π - π)	0.31	-1.15	-5.23	-6.07
29	Pyridine...Uracil (π - π)	0.30	-2.33	-5.21	-7.25
30	Benzene...Ethene	0.03	0.30	-2.28	-1.95
31	Uracil...Ethene	0.09	-0.84	-2.84	-3.58
32	Uracil...Ethyne	0.17	-1.53	-2.25	-3.61
33	Pyridine...Ethene	0.00	0.26	-2.37	-2.11
34	Pentane...Pentane	-0.14	0.03	-3.88	-3.99
35	Neopentane...Pentane	-0.23	-0.03	-2.69	-2.95
36	Neopentane...Neopentane	-0.36	-0.03	-2.12	-2.50
37	Cyclopentane...Neopentane	-0.28	-0.04	-2.61	-2.92
38	Cyclopentane...Cyclopentane	-0.25	0.05	-2.83	-3.02
39	Benzene...Cyclopentane	0.04	0.09	-3.76	-3.63
40	Benzene...Neopentane	-0.05	-0.05	-3.14	-3.24
41	Uracil...Pentane	0.16	-0.67	-5.00	-5.52
42	Uracil...Cyclopentane	0.06	-0.40	-4.46	-4.79
43	Uracil...Neopentane	0.16	-0.31	-3.69	-3.84
44	Ethene...Pentane	-0.03	-0.03	-1.84	-1.90

45	Ethyne...Pentane	0.00	0.03	-1.96	-1.93
46	NMe-acetamide...Pentane	0.15	-0.52	-3.83	-4.20
#	MIX	ΔE^{FRZ}	ΔE^{POL}	ΔE^{DISP}	ΔE^{TOT}
47	Benzene...Benzene (TS)	0.13	-0.17	-2.47	-2.52
48	Pyridine...Pyridine (TS)	0.11	-0.50	-2.39	-2.79
49	Benzene...Pyridine (TS)	0.17	-0.30	-2.48	-2.61
50	Benzene...Ethyne (CH... π)	-0.03	-0.62	-1.48	-2.13
51	Ethyne...Ethyne (TS)	-0.16	-0.36	-0.59	-1.11
52	Benzene...AcOH (OH... π)	-0.24	-1.64	-2.43	-4.31
53	Benzene...AcNH ₂ (NH... π)	0.13	-1.58	-2.09	-3.54
54	Benzene...H ₂ O (OH... π)	-0.32	-0.93	-1.67	-2.92
55	Benzene...MeOH (OH... π)	-0.26	-0.71	-2.58	-3.56
56	Benzene...MeNH ₂ (NH... π)	0.02	-0.22	-2.65	-2.85
57	Benzene...NMe-acetamide (NH... π)	0.13	-1.13	-3.66	-4.66
58	Pyridine...Pyridine (CH...N)	0.24	-1.22	-1.23	-2.21
59	Ethyne...H ₂ O (CH...O)	-0.30	-2.25	-0.37	-2.93
60	Ethyne...AcOH (OH... π)	-0.22	-2.35	-0.97	-3.54
61	Pentane...AcOH	-0.01	-0.35	-3.05	-3.41
62	Pentane...AcNH ₂	0.00	-0.65	-3.25	-3.91
63	Benzene...AcOH	0.21	-0.84	-3.01	-3.64
64	NMe-acetamide...Ethene	0.06	-0.79	-2.10	-2.83
65	Pyridine...Ethyne (CH...N)	-0.73	-2.11	-0.79	-3.62
66	MeNH ₂ ...Pyridine	0.19	-1.25	-2.15	-3.22

- * Notations: “H₂O”, water; “Me”, methyl; “OH”, hydroxyl; “NH₂”, amidogen; “Ac”, Acetyl; “BP” in parentheses, base pair and “TS” in parentheses, T-shape geometry. Other values in parentheses stand for the interaction types.

Table 2. DFTB-EDA and GKS-EDA interaction energies (in kcal/mol) calculated for the systems in the L7 data set.

System	EDA method	Level of theory	ΔE^{FRZ}	ΔE^{POL}	ΔE^{DISP}	ΔE^{TOT}
C2C2PD	DFTB-EDA	DFTB2-D3/MIO	0.11	0.75	-22.58	-21.73
		DFTB3-D3/3OB	0.91	0.58	-22.40	-20.92
		DFTB3-D3H5/3OB	0.91	0.59	-21.52	-20.02
	GKS-EDA	PBE-D3/6-31G*	9.51	-3.46	-21.83	-15.78
		B3LYP-D3/6-31G*	17.42	-3.16	-30.64	-16.38
C3A	DFTB-EDA	DFTB2-D3/MIO	0.09	-0.47	-15.95	-16.33
		DFTB3-D3/3OB	0.91	-0.51	-15.95	-15.55
		DFTB3-D3H5/3OB	0.91	-0.46	-16.18	-15.73
	GKS-EDA	PBE-D3/6-31G*	5.16	-2.55	-16.19	-13.58
		B3LYP-D3/6-31G*	10.82	-2.80	-22.56	-14.54
C3GC	DFTB-EDA	DFTB2-D3/MIO	0.16	-0.42	-27.53	-27.79
		DFTB3-D3/3OB	1.65	-0.74	-28.00	-27.09
		DFTB3-D3H5/3OB	1.65	-0.65	-28.72	-27.73
	GKS-EDA	PBE-D3/6-31G*	10.95	-5.39	-28.43	-22.87
		B3LYP-D3/6-31G*	20.76	-5.46	-39.71	-24.41
CBH	DFTB-EDA	DFTB2-D3/MIO	-1.56	0.00	-13.74	-15.30
		DFTB3-D3/3OB	-1.22	-0.05	-12.88	-14.15
		DFTB3-D3H5/3OB	-1.22	0.15	-12.84	-13.91
	GKS-EDA	PBE-D3/6-31G*	-1.07	1.14	-14.23	-14.16
		B3LYP-D3/6-31G*	4.35	0.06	-18.42	-14.01
GCGC	DFTB-EDA	DFTB2-D3/MIO	0.12	-1.22	-14.80	-15.90
		DFTB3-D3/3OB	1.08	-0.25	-15.63	-14.81
		DFTB3-D3H5/3OB	1.08	-0.25	-16.70	-15.87
	GKS-EDA	PBE-D3/6-31G*	5.49	-0.99	-16.25	-11.75
		B3LYP-D3/6-31G*	12.42	-2.00	-22.58	-12.16
GGG	DFTB-EDA	DFTB2-D3/MIO	0.00	4.49	-5.61	-1.12
		DFTB3-D3/3OB	0.17	5.11	-5.65	-0.36
		DFTB3-D3H5/3OB	0.17	5.27	-6.21	-0.76
	GKS-EDA	PBE-D3/6-31G*	4.53	0.06	-5.98	-1.39
		B3LYP-D3/6-31G*	7.20	-0.42	-8.09	-1.31
PHE	DFTB-EDA	DFTB2-D3/MIO	0.49	-16.74	-8.09	-24.34
		DFTB3-D3/3OB	2.63	-19.89	-7.67	-24.93
		DFTB3-D3H5/3OB	2.63	-21.80	-7.98	-27.14
	GKS-EDA	PBE-D3/6-31G*	-2.77	-14.05	-8.18	-25.00
		B3LYP-D3/6-31G*	-1.44	-13.65	-11.24	-26.33

System	EDA method	Level of theory	ΔE^{FRZ}	ΔE^{POL}	ΔE^{DISP}	ΔE^{TOT}
190-atom neutral	DFTB-EDA	DFTB3-D3/3OB	0.78	-3.05	-8.32	-10.59
		DFTB3-D3H5/3OB	0.78	-2.88	-7.87	-9.97
		DFTB2-D3/MIO	-0.55	-2.59	-8.32	-11.45
	GKS-EDA	B3LYP-D3/6-31G	4.40	-7.74	-10.88	-14.22
1710-atom neutral	DFTB-EDA	DFTB3-D3/3OB	13.08	-68.41	-152.45	-207.78
		DFTB3-D3H5/3OB	13.08	-64.99	-143.06	-194.97
		DFTB2-D3/MIO	-9.42	-59.65	-152.45	-221.52
190-atom zwitterionic	DFTB-EDA	DFTB3-D3/3OB	0.74	-20.70	-8.33	-28.29
		DFTB3-D3H5/3OB	0.74	-20.68	-7.64	-27.59
		DFTB2-D3/MIO	-0.33	-16.61	-8.33	-25.27
	GKS-EDA	B3LYP-D3/6-31G	-2.98	-26.14	-10.85	-36.99
1710-atom zwitterionic	DFTB-EDA	DFTB3-D3/3OB	7.04	-290.86	-150.32	-434.14
		DFTB3-D3H5/3OB	7.04	-283.74	-141.10	-417.81
		DFTB2-D3/MIO	-9.02	-253.01	-150.32	-412.35

The captions of Figures

Figure 1. The geometry of the π -stacked aggregate tetramer.

Figure 2. Side and front views of amyloid-like IYQYGG segment (PDB code: 6G8C).

Figure 3. A series of complexes in ground and excited states (a) pyridine-H₂O (OH $\cdots\pi$), (b) pyridine-H₂O (hydrogen bond), (c) pyrimidine-H₂O (OH $\cdots\pi$), (d) pyrimidine-H₂O (hydrogen bond), (e) fluorenone-CH₃OH (hydrogen bond).

Figure 4. A comparison of DFTB-EDA results at the DFTB3-D3H5/3OB level with those of GKS-EDA at the PBE-D3/6-31+G* level, (a) total interaction, (b) frozen term, (c) polarization term and (d) dispersion term, calculated for the S66 dataset.

Figure 5. The relationship between the polarization term in DFTB-EDA and the variation of monomers' Mulliken charges (shown as ΔQ , the charges in the monomer state are compared with those of in the complex), calculated for the S66 and L7 datasets.

Figure 6. DFTB-EDA results of the π -stacked aggregate tetramer.

Figure 7. DFTB-EDA analysis of complexes that are dominated by hydrogen bonding (HB) and OH $\cdots\pi$ interactions in the ground state (S0) and lowest excited state (S1). (a) pyridine-H₂O (OH $\cdots\pi$), (b) pyrimidine-H₂O (OH $\cdots\pi$), (c) pyridine-H₂O (HB), pyrimidine-H₂O (HB), (e) fluorenone-CH₃OH (HB).

side view

monomer A

monomer B

front view

(a)

(b)

(c)

(d)

(e)

(a)

(b)

(c)

(d)

(a)

(b)

(c)

(d)

(e)