The interactions of phenylalanines in β -sheet-like structures from molecular orbital calculations using density functional theory (DFT), MP2, and CCSD(T) methods

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We present density functional theory calculations designed to evaluate the importance of π -stacking interactions to the stability of in-register Phe residues within parallel β -sheets, such as amyloids. We have used a model of a parallel H-bonded tetramer of acetylPheNH₂ as a model and both functionals that were specifically designed to incorporate dispersion effects (DFs), as well as, several traditional functionals which have not been so designed. None of the functionals finds a global minimum for the π -stacked conformation, although two of the DFs find this to be a local minimum. The stacked phenyls taken from the optimized geometries calculated for each functional have been evaluated using MP2 and CCSD(T) calculations for comparison. The results suggest that π -stacking does not make an important contribution to the stability of this system and (by implication) to amyloid formation. © 2013 AIP Publishing LLC. [<http://dx.doi.org/10.1063/1.4811712>]

INTRODUCTION

Amyloid formation has been reported to be a cause or a symptom of several human diseases. Several reports suggest that amino acid residues containing aromatic side chains promote the formation of aggregates such as amyloids.¹ Mutual attraction of the aromatic entities contained in these residues has proven to be a popular hypothesis for this behavior. Also, crystal structures of related molecules indicate the presence of π - π stacking,² but such structures cannot evaluate to what extent such interactions are attractive or simply minimize repulsions. On the other hand, nuclear magnetic resonance (NMR) studies have cast doubt upon the energetic importance of such interactions.³ In this paper, we test the hypothesis that such interactions might be energetically important by evaluating them using a variety of molecular orbital methods. We also consider an alternate (and possibly complementary) hypothesis that the relative insolubility of these aromatic entities in aqueous media shifts the equilibrium from solution to solid phase.

We have chosen a system of four acetyl(Phe)NH₂'s in a parallel β -sheet conformation as our model system for these studies, as Phe provides the simplest model of an amino acid containing an aromatic side chain. The capped ends prevent unwanted interactions that would not be present in a real protein or peptide. This choice preserves the possibility of π - π interactions between the aromatic side chains in a structure that is small enough to allow for the high-level calculations necessary to properly evaluate the dispersion interactions that might contribute to the stacking interactions.

We have used several different methods to calculate optimized geometries for the aggregate, including some that

have been specifically parameterized to describe dispersion interactions. These, as well as MP2 calculation, have been previously shown to overestimate stabilizing interactions in peptides⁴ and in π -stacking interactions.^{4,5} We have specifically chosen them since they do overestimate these interactions, thus providing an estimate of an upper limit to the amount of stabilization that could be expected from π -stacking. Using elements from these optimized geometries, we have calculated the interaction energies at levels as high as MP2 and coupled-cluster single double triple (CCSD(T))/cc-pVTZ.

CALCULATIONAL DETAILS

For the geometrical optimizations, we used several different functionals (B3LYP,⁶ PBE1PBE,⁷ X3LYP,⁸ B97D,⁹ ω B97X-D,¹⁰ and M06-2X¹¹) using the D95(d,p) basis set. The last three of these (DFs) have been specifically parameterized to reproduce dispersion interactions, while the first three are more traditional functionals (TFs). We carried out all optimizations on counterpoise (CP) corrected surfaces¹² to eliminate any possible confusion between basis set superposition error (BSSE) and π -stacking.

Except where noted, all geometries were completely optimized in all (up to 100) internal degrees of freedom. Vibrational calculations confirmed the reported geometries to be true minima on the potential energy surfaces (PESs) as there are no imaginary vibrational frequencies. We used these calculated frequencies to evaluate the enthalpies and free energies of the optimized species. Where structures are not optimized, vibrational calculations have no meaning, so only ΔE 's are reported. All calculations used the standard grids and convergence criteria of the GAUSSIAN 09 program¹³ except for two structures (B and C in Figure 1) which would not

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FIG. 1. The three structural types found from geometry optimizations. The subscripts of the labels refer to the distances (denoted by dashed lines) between the centroids of the rings (R), the O $\cdots$ H distances for the N- and C-terminal H-bonds, respectively (N and C), denoted, respectively, by dotted and full lines.

converge to a true minimum with M06-2X unless we used the “ultrafine” or 99 974 grid.

We used the geometries of the previously optimized structures to obtain the orientations of the four phenyl rings with the peptide backbone replaced by a hydrogen to calculate interactions between the π -systems using the functionals listed above, MP2 and CCSD(T) all using the cc-pVTZ basis set.

We calculated solvation free energies as single points using the SM5.2¹⁴ and CPCM¹⁵ methods. Using the AMPAC 8.16¹⁶ program, we calculated single point AM1¹⁷ energies and SM5.2 solvation free energies of the peptides in their ONIOM optimized structures as we have done previously.¹⁸ We calculated the CPCM solvation free energies as single points of the relevant previously optimized geometries using the CPCM solvation field in GAUSSIAN 09 with the rad = bondi option, which we very recently determined worked best of the solvation of N-methylacetamide.

RESULTS

We found three kinds of structures (labeled A, B, and C in Figure 1) upon complete optimization of the tetramer of capped phenylalanine on the CP-corrected potential en-

TABLE I. Critical distances (angstroms) for structures A–C (see Figure 1) optimized on a BSSE-corrected surface.

		N _{term} H-bond			C _{term} H-bond			Ring-ring		
		1 _N	2 _N	3 _N	1 _C	2 _C	3 _C	1 _R	2 _R	3 _R
A	B3LYP	1.90	1.93	1.95	1.87	1.84	1.91	6.26	7.56	6.61
	X3LYP	1.89	1.92	1.94	1.86	1.84	1.91	6.11	7.50	6.54
	PBE1PBE	1.87	1.89	1.92	1.85	1.83	1.90	6.04	7.97	6.39
B	B97-D	1.84	1.88	1.91	1.93	1.80	1.91	4.99	6.78	6.52
	ω B97x-D	1.82	1.86	1.90	1.91	1.81	1.90	5.05	6.84	6.53
	M06-2X	1.85	1.89	1.94	1.94	1.85	1.93	4.98	7.54	6.55
C	ω B97x-D	1.81	1.86	1.88	1.84	1.83	1.89	4.71	4.44	4.89
	M06-2X	1.86	1.88	1.94	1.86	1.84	1.94	4.89	4.93	5.37

ergy surface. Table I presents critical distances for these structures. Structure A is the only minimum found by the TFs while structure B is the only structure found by B97-D and the global minimum for the two other DFs. Structure C is a local minimum found for the other two DFs, (ω B97-xD and M06-2X). All of these structures could be characterized as minima from the vibration calculations on the CP-corrected potential energy surfaces (no imaginary frequencies). Structure A does not feature any obviously stabilizing interactions between the rings. Its stability derives from the H-bonds between the backbone amides. Structure B contains one T-shaped interaction between phenyl rings similar to those sometimes found in other calculations^{5,19} and in the crystal structure of benzene.²⁰ In addition, it contains five C–H $\cdots$ O H-bonds. Structure C contains three C–H $\cdots$ O H-bonds in addition to the π -stacking interactions between the rings. As a means of searching for other potential minima, we used the optimized structures found by each functional as starting points for optimizations using each of the other functionals. We found no additional minima on the CP-corrected surfaces. However, when optimized on a normal (not CP-corrected) surface, the B97-D functional found a minimum corresponding to structure C, which reverted to the B-structure when reoptimized from this starting structure on a CP-corrected surface. Table II lists the critical distances for the structure optimized without BSSE, while Table III lists the interaction energies for the aggregation of four monomers to form a parallel sheet of (acetylPheNH₂)₄ on both normal (no CP) and CP-corrected potential surfaces. We include the normal surface optimizations as some of the DFs may be parameterized without correction for BSSE. However, we note that the many data sets used for parameterizations of DFs include calculations made with and without CP correction. We have published an evaluation of the DFs compared to high level calculations for small systems that have dispersion combined with inductive interactions.²¹ This report contains a comprehensive list of the database used for parameterization of the DFs.

In order to further probe the local interactions that contribute to overall stabilizations of the stacked structures, we divided each structure into two parts that we considered separately: (1) the peptide backbone, and (2) the aromatic rings. To do this, we eliminated the CH₂–Ph bond in the geometries of the various optimized structures and replaced it with

TABLE II. Critical distances (angstroms) for structures A–C (see Figure 1) optimized on a normal (non-BSSE-corrected) surface.

		N _{term} H-bond			C _{term} H-bond			Ring-ring		
		1 _N	2 _N	3 _N	1 _C	2 _C	3 _C	1 _R	2 _R	3 _R
A	B3LYP	1.83	1.86	1.90	1.84	1.81	1.87	5.95	6.66	6.13
	X3LYP	1.82	1.86	1.89	1.82	1.80	1.89	5.65	6.47	6.06
	PBE1PBE	1.82	1.85	1.87	1.82	1.82	1.86	5.78	7.17	5.98
B	B97-D	1.80	1.83	1.87	1.90	1.80	1.90	4.95	6.51	6.44
	ω B97x-D	1.80	1.82	1.80	1.89	1.80	1.88	5.01	6.75	6.42
	M06-2X	1.83	1.86	1.91	1.92	1.84	1.92	4.98	7.60	6.46
C	B97-D	1.80	1.87	1.87	1.81	1.82	1.86	4.65	4.03	4.58
	ω B97x-D	1.78	1.81	1.85	1.82	1.79	1.85	4.54	4.21	4.49
	m062x	1.82	1.84	1.88	1.83	1.81	1.88	4.76	4.59	4.85

a H-atom on the CH₂ (to get the backbone interactions between what have become alanines), or on the phenyl group (to obtain the interactions between the rings). We kept the geometries fixed at those optimized for the original structures using each of the functionals and made corrections for BSSE *a posteriori*.

As can be seen from Table IV, all three DFs predict stronger interactions for both kinds of interactions than the TFs at their respective optimized geometries. We have recently reported that the DFs overestimate interactions between alanine peptides, which are similar to the backbone interactions.⁴ Furthermore, while the TFs all predict the two interactions to be approximately additive, the DFs predict the combined (i.e., total) interaction to be greater than additive, while the TFs do not. We ascribe this behavior to the fact that the B and C (but not A) structures contain several C–H···O H-bonds, which are broken when the backbone and ring interactions are evaluated separately (only the DFs find the B and C minima).

We also calculated the interactions between the rings using the functionals, MP2 and CCSD(T) with the larger cc-pVTZ basis set (see Table V). These calculations used the fixed geometries of the rings taken from the previously optimized structures obtained using the different functionals. While we could calculate the interaction between all four

TABLE III. Energies (kcal/mol) of aggregation of monomers to parallel sheets of (acetylPheNH₂)₄ obtained using traditional and dispersion functionals with the d95** basis set on both CP corrected and non-CP corrected surfaces. See Figure 1 for structures.

		No CP	CP
A	B3LYP	–44.8	–33.4
	X3LYP	–48.6	–36.6
	PBE1PBE	–48.1	–38.3
B	B97-D	–70.8	–57.6
	ω B97x-D	–73.8	–63.5
	M06-2X	–64.6	–54.3
C	B97-D	–66.1	n/a ^a
	ω B97x-D	–69.6	–58.3
	M06-2X	–60.4	–49.5

^aNot a minimum on the CP corrected surface.TABLE IV. ΔE_{int} (kcal/mol) for aggregation of parallel sheets of [acetyl(Phe)NH₂]₄ from individual strands using several functionals with the d95** basis set including decomposition into backbone (BB) and aromatic ring components as well as ΔH and ΔG for the full aggregate. See Figure 1 for structures A, B, C and text for full explanation.

		ΔE				ΔH	ΔG
		Ring	BB	Sum	Full aggregate		
A	B3LYP	–0.2	–34.1	–34.2	–33.4	–17.1	16.0
	X3LYP	–0.4	–36.8	–37.2	–36.6	–19.8	13.6
	PBE1PBE	–0.6	–38.2	–38.8	–38.3	–23.7	10.3
B	B97-D	–4.4	–45.6	–50.0	–57.6	–38.5	3.1
	ω B97x-D	–4.0	–50.6	–54.6	–63.5	–46.9	–4.8
	M06-2X	–2.4	–43.5	–48.9	–54.2	–39.5	5.0
C	ω B97x-D	–7.0	–46.0	–53.0	–58.2	–41.8	–6.9
	M06-2X	–3.7	–42.2	–45.9	–49.6	–34.2	4.9

rings using the functionals and MP2, the CCSD(T) calculations proved too costly to run on these systems. To do the CCSD(T) calculations, we calculated the interactions between adjacent pairs of rings fixed in the geometries of the optimized tetramers found for each functional. For comparison, we compared the sum of these pairwise ring-ring interactions with that of the four ring systems calculated using density functional theory (DFT) and MP2 calculations. These confirm approximate pairwise additivity for these methods. The results indicate that the TFs underestimate while both the DFs (with the exception of M06-2X) and MP2 significantly overestimate the interaction compared to CCSD(T), consistent with other reports.^{5,19} In particular, MP2 overestimates the stabilities of structure A by 0.3 kcal/mol. Structure B by 1.1–1.2 kcal/mol and structure C by 2.7–3.5 kcal/mol when compared to CCSD(T). The behavior of M06-2x for this interaction contrasts with previous results that showed M06-2X to overestimate the π -stacking interaction in the dimer of π -benzoquinone and pyrimidine.¹⁹ Our CCSD(T) results are consistent with those reported by Sherrill,^{5,22} who used aug-cc-pVXZ (X = D, T, and Q) and estimated the extrapolated complete basis set, CBS, limit (sometimes referred to as focal point calculations). Extrapolated calculations of this type generally give slightly greater dispersion bonding interactions. We have used this procedure on small systems.²¹ However,

TABLE V. ΔE 's (kcal/mol) for aggregation of parallel sheets and sums of pairwise interactions using DFT, MP2, and CCSD(T) with the cc-pVTZ basis set for structures of Figure 1.

		DFT		MP2		CCSD(T)
		Pairwise	Full aggregate	Pairwise	Full aggregate	Pairwise
A	B3LYP	–0.2	–0.1	–1.9	–1.8	–1.5
	X3LYP	–0.5	–0.4	–2.1	–2.0	–1.7
	PBE1PBE	–0.8	–0.7	–2.2	–2.1	–1.8
B	B97-D	–4.4	–4.4	–4.7	–4.7	–3.5
	ω B97x-D	–4.1	–4.2	–4.1	–4.2	–3.1
	M06-2X	–2.6	–2.7	–4.0	–4.1	–3.0
C	ω B97x-D	–7.4	–7.6	–8.0	–8.2	–4.7
	M06-2X	–3.7	–3.9	–6.6	–6.8	–4.1

TABLE VI. Solvation free energies (kcal/mol) of parallel sheets of [acetyl(Phe)NH₂]₄ calculated using CPCM and SM5.2 for structures of Figure 1.

Structure	Functional	$\Delta G_{\text{Solvation}}$	
		CPCM	SM5.2
A	B3LYP	− 43.1	− 51.6
	X3LYP	− 43.0	− 51.0
	PBE1PBE	− 43.6	− 50.0
B	B97-D	− 40.4	− 47.1
	ω B97x-D	− 43.0	− 46.4
	M06-2X	− 44.2	− 45.7
C	ω B97x-D	− 42.8	− 44.8
	M06-2X	− 43.8	− 44.7

the small changes expected would not bring the CCSD(T) values close to the interaction energies predicted by the DFs.

Table VI collects the results of the calculations of aqueous solvation. The CPCM results do not indicate that aqueous media preferentially stabilizes one of the conformation, while the SM5.2 method preferentially stabilizes the A structure.

DISCUSSION

None of the functionals used, even those specifically designed to include dispersion interactions (and which have been shown to exaggerate the importance of these interactions^{4,19,21}), predict the stacked structure, C, to be the most stable. The results strongly suggest that π -stacking of phenylalanine residues does not provide a substantial energetic contribution to the formation of β -sheet type structures. The present results are in accord with earlier studies that suggest π -stacking of aryls provides only a weak stabilization,⁵ less than that expected from normal N–H $\cdots$ O = C H-bonds.¹⁹ While, most DFs adequately describe H-bonds,²² they tend to overestimate dispersion interactions.^{4,18,19} Thus, the DF results should be considered limiting: If they do not find π -stacking to be important in parallel sheets of capped Phe's, then the likelihood that such an interaction provides any significant contribution to the stability of these sheets must be quite small.

If not π -stacking, what might be the cause of the observed propensity of Phe-containing peptides to form amyloids? Amyloids are aggregates of proteins that precipitate out of the biological solution environment, thus disturbing or destroying the natural function of these proteins, at least in humans. Thus, by definition, they possess decreased solubility. Studies of poly Gln fragments thought to be active in the formation of amyloids related to Huntington's disease have been shown to decrease this propensity upon incorporation of His residues which increase the solubility of these peptides.²³ The aqueous solubility of Phe (0.17 molal at 298 K) is less than 1/10 that of Ala and 1/20th that of Gly, while those of Tyr and Trp (two other aromatic amino acids thought to promote amyloids) are even lower.²⁴ Thus, the solubility of the amino acid residues may play an important role in amyloid formation.

Solubility reflects the equilibrium between the solute in solution and in the solid phase. Changes in equilibria can re-

sult from changes in the forces between the molecules in the solid phase or between the solvent and solute as compared to solvent-solvent interactions. Thus, the equilibrium can change because of changes of the stability of the solute in solution and/or in the solid phase. Since our calculations cast considerable doubt upon the stabilizing effect of stacking the phenyls, which would stabilize the solid, we must look elsewhere (i.e., the solution phase) for a cause.

The calculated solvation free energies (Table V) only apply to the liquid state, so they do not directly reflect the solubility. We note that the methods used do not reflect the importance of the pressure within the solvent due to the hydrophobic effect upon solvation. The hydrophobic effect results from increased pressure within the solvent²⁵ consistent with the observed result of alkanes preferring conformations that minimize their volumes in aqueous media.²⁶ Solvation models do not generally include this effect.

The stability afforded by the C–H $\cdots$ O H-bonds that appear in structure B might be another possible factor that makes the solid more favorable. However, these should also be obtained from the TFs, but are not, suggesting that exaggerated dispersion might be coupled with this interaction when calculated using the DFs.

Clearly, aggregation of capped Phe (which is not even an oligopeptide, let alone a protein), should not be confused with amyloid formation. Nevertheless, studies have shown that Phe does form fibrils that precipitate from aqueous solution and have some amyloid characteristics.²⁷ Although crystalline filaments form, their structure has not been determined. Thus, they could be ordered or disordered and could contain parallel and antiparallel β -sheet-like interactions or both. Only the parallel interactions would benefit from π -stacking. On the other hand, antiparallel interactions (at least of alanine and glycine peptides) have been shown to be more stable than their parallel counterparts²⁸ so they may provide more stabilizing interactions in the solid phase than do the parallel (stacked) conformations.

Complete Cartesian coordinates for all optimized structures are included in the supplementary material.²⁹

CONCLUSIONS

Since the present calculations find no appreciable stabilizing factors associated with the π -stacking of the Phe's, even when we used methods that probably overestimate the importance of this interaction, we conclude that whatever interactions that favor the presence of Phe's next to each other in adjacent strands of peptides must be due to other causes. The relative insolubility of Phe in water, C–H $\cdots$ O H-bonds involving the phenyls and the formation of antiparallel interactions figure among the possibilities.

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- ²⁹See supplementary material at <http://dx.doi.org/10.1063/1.4811712> for complete Cartesian coordinates for all optimized structures.