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Capping Parallel β-Sheets of Acetyl(Ala)$_6$NH$_2$ with an Acetyl(Ala)$_5$ProNH$_2$ Can Arrest the Growth of the Sheet, Suggesting a Potential for Curtailing Amyloid Growth. An ONIOM and Density Functional Theory Study

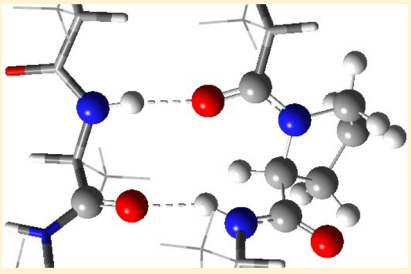
Gabor Pohl,[†] Amparo Asensio,[‡] and J. J. Dannenberg*[,†]

[†]Department of Chemistry, City University of New York, Hunter College and the Graduate School, 695 Park Avenue, New York, New York 10065, United States

[‡]Facultad de Farmacia, Departamento Quimica Organica, Universidad de Valencia, Avda Vicente Andres Estelles, 46100 Burjassot, Valencia, Spain

Supporting Information

ABSTRACT: We present ONIOM calculations using B3LYP/d95(d,p) as the high level and AM1 as the medium level on parallel β-sheets containing four strands of Ac-AAAAAA-NH$_2$ capped with either Ac-AAPAAA-NH$_2$ or Ac-AAAPAA-NH$_2$. Because Pro can form H-bonds from only one side of the peptide linkage (that containing the C═O H-bond acceptor), only one of the two Pro-containing strands can favorably add to the sheet on each side. Surprisingly, when the sheet is capped with AAPAAA-NH$_2$ at one edge, the interaction between the cap and sheet is slightly more stabilizing than that of another all Ala strand. Breaking down the interaction enthalpies into H-bonding and distortion energies shows the favorable interaction to be due to lower distortion energies in both the strand and the four-stranded sheet. Because another strand would be inhibited for attachment to the other side of the capping (Pro-containing) strand, we suggest the possible use of Pro residues in peptides designed to arrest the growth of many amyloids.



Our interest in the relative thermodynamic energetics of competing secondary structures has led us to examine the relative energies and enthalpies of various secondary structures and the relative effects of single-amino acid mutations in models of these secondary structures based upon peptide structures made from all Ala residues. We have already published a study of the effects of such mutations to nonpolar residues in α-helices.[1] We continue to work on a more general paper that will appear elsewhere. In the course of this work, we noticed an unusual effect of mutations of Ala to Pro in parallel β-sheets. Most amyloids, including the amyloid of the protein tau (which is implicated in Alzheimer's disease), form parallel in-register β-sheets,[2−5] although exceptions are known.[4,5] As this mutation might have significant use in arresting parallel β-sheet growth, the potential for control of amyloid formation seems obvious. This result surprised us as all other mutations of Ala to Pro in various β-sheets and α-helices substantially destabilized these structures. This has convinced us to publish this short account. When finished, we intend to report our general studies of the effects of amino acid mutations in different secondary structures elsewhere.

We describe ONIOM and density functional theory (DFT) calculations on the mutations of several specific Ala's to Pro's in β-sheets containing five strands of acetyl(Ala)$_6$NH$_2$. We have included both parallel (P) and antiparallel (AP) structures for comparison.

METHODS

We used the ONIOM[6,7] method as programmed in the Gaussian09[8] suite of computer programs. ONIOM divides the system into up to three segments that can be treated at different levels of calculational complexity. Thus, one can treat the essential part of the system at the high level, while the less critical parts of the system might be calculated at the medium or low level. For this study, we used only two levels (high and medium). We treated the backbones of the peptides (equivalent to a corresponding peptide containing only glycines) at the high level, with only the methyl side chains that distinguish the Ala residues from that of glycine and the acetyl methyl being treated at the medium level. The high level used hybrid DFT methods at the B3LYP/D95(d,p) level. This method combines Becke's three-parameter functional[9] with the nonlocal correlation provided by the correlation functional of Lee, Yang, and Parr.[10] In the ONIOM method, there are unsatisfied valences in the high level at the interface between it and the medium level. These valences were satisfied by using the default method of capping them with a hydrogen atom in the direction of the connecting atom in the medium level with a C−H distance of 0.723886 times the C−C distance. We used

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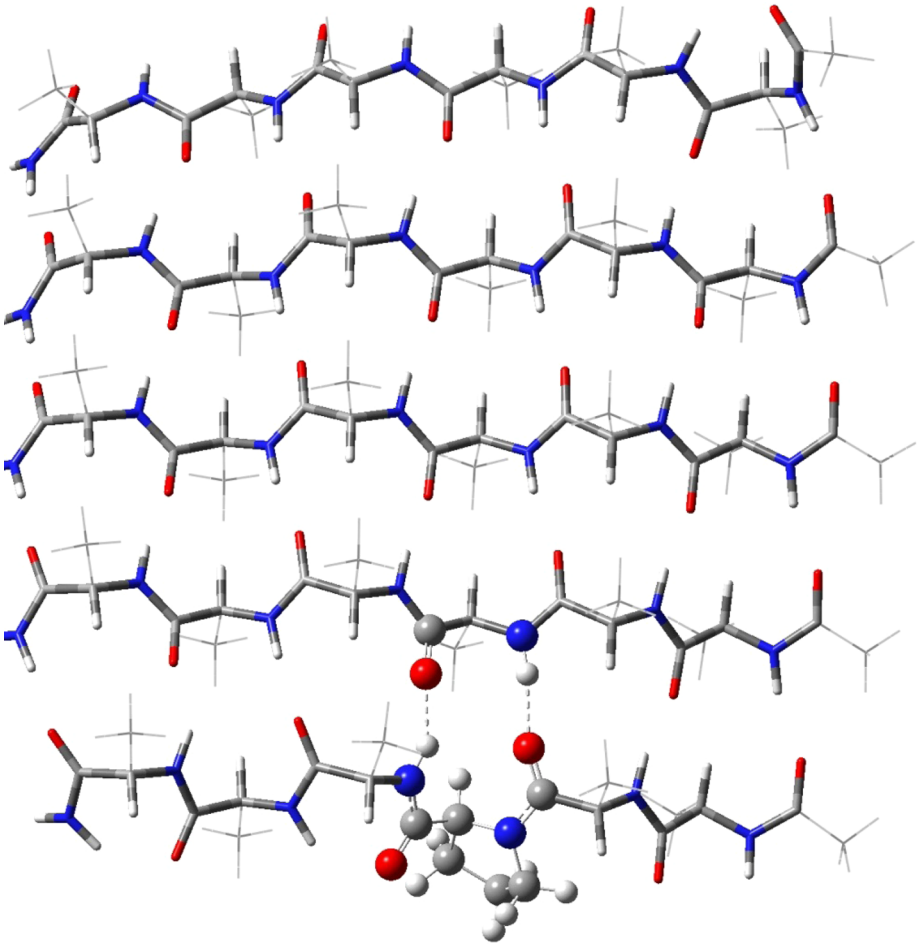

Figure 1. Structure of $(AAAAAA)_5$ capped with AAPAAA. The backbones are shown as tubes and the methyls (calculated at the medium level) as a wire frame, and the Pro and its H-bonding partner are highlighted in ball and stick format. Note that all seven H-bonds between the AAPAAA and the rest of the sheet remain intact.

the AM1[11] semiempirical molecular orbital method for the ONIOM medium level. We have shown B3LYP to be preferable to several functionals specifically parametrized to treat diffusion for calculations on peptides, as the functionals that specifically treat dispersion overestimate the interaction energies in α-helices and predict incorrect geometries in β-sheets.[12] Dispersion interactions weaken in the presence of induction.[13] Also, dispersion interactions do not appear to be important for most H-bonds, as illustrated by the fact that the dispersion-corrected functionals give results similar to those of B3LYP for H-bonds[14−16] but overestimate π-stacking interactions.[15−17]

All geometries were completely optimized in all internal degrees of freedom and vibrational calculations performed to ensure the geometries are true minima on the potential energy surfaces (PESs), as there are no imaginary vibrational frequencies, for both the single extended strands and β-sheets containing four or five strands. We also used the vibrational frequencies to calculate the enthalpies at 298 K.

In a previous study of five 17-amino acid peptides,[18] we found little difference in relative energies between this procedure and another in which the side chains (in this case, the methyls) were subsequently optimized using DFT, with the (previously optimized) peptide chain held fixed. The current procedure also gave relative energies that agreed well with complete DFT optimizations for a series of five small 3_{10}-helical peptides.[19] We have used this procedure with success for several previous studies of peptide structures[1,19−25] and have shown it to compare favorably with other functional/basis set combinations for calculations in the gas phase water dimer.[14]

The counterpoise correction (CP) for the basis set superposition error (BSSE) has been applied to all interaction energies and enthalpies using the single-point a posteriori procedure,[26−29] as optimization of such large structures on a CP-corrected surface[30] would have been too computationally intensive and the ONIOM and CP optimization cannot be performed simultaneously using the Gaussian09 program. Balabin has recently emphasized the importance of BSSE correction for biochemical and other calculations.[31,32]

Because the model for these calculations is solid state (the amyloids are not soluble), no solvation energies have been calculated.

RESULTS

Proline is the only naturally occurring amino acid that lacks an N−H bond. This restricts Pro residues to forming H-bonds only using their C═O groups as H-bond acceptors, which contributes (along with the lack of conformational mobility caused by the five-membered ring) to the disruptive influence of Pro residues on α-helical and β-sheet secondary structures. However, we have determined that one type of parallel β-sheet structure in which the Pro residue is not disruptive exists. In

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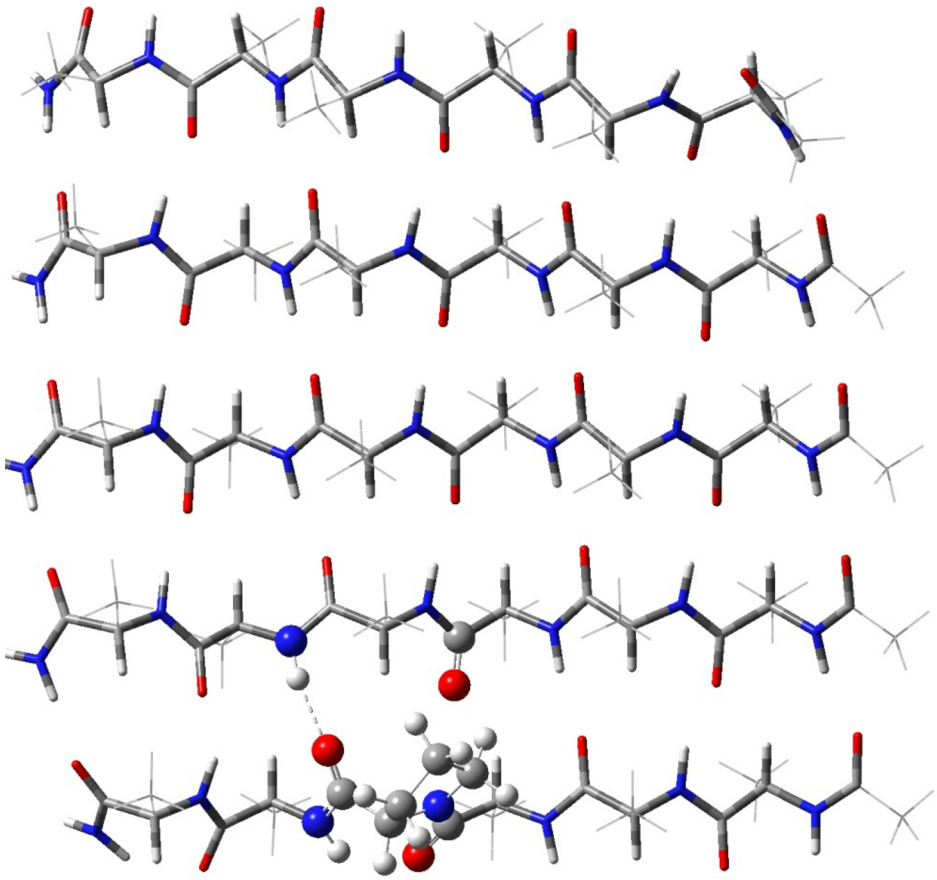

Figure 2. Structure of $(AAAAAA)_5$ capped with AAAPAA. The backbones are shown as tubes and the methyls (calculated at the medium level) as a wire frame, and the Pro and its actual and putative H-bonding partners are highlighted in ball and stick format. Note that one H-bond between AAAPAA and the remainder of the sheet is lost.

this structure, illustrated by a sheet containing four acetyl-$(Ala)_6NH_2$ strands capped at the edge with a similar strand with one Ala mutated to Pro, where the latter uses its C═O acceptor to H-bond (see Figure 1), its N faces away from the rest of the sheet that does not disrupt the H-bonding of this strand to the rest of the sheet. However, the lack of a donor N−H group on this (terminal strand) will inhibit further sheet growth by another acetyl$(Ala)_6NH_2$ strand. To illustrate this, we have capped the $[acetyl(Ala)_6NH_2]_4$ sheet with either acetyl$(Ala)_2Pro(Ala)_3NH_2$ (AAPAAA), which can form seven H-bonds, or acetyl$(Ala)_3Pro(Ala)_2NH_2$ (AAAPAA), which can form only six H-bonds (see Figures 1 and 2).

We have calculated the isomeric structures that have the Pro on the other position on the edge strand (where it forms no H-bond) and another with the Pro-containing strand in the middle of the sheet (see Figure 3). The last structure is equivalent to that obtained by moving two all Ala strands from one edge and adding them to the edge with the Pro-containing strand. This costs ∼9 kcal/mol, which would be much more than enough to prevent additional all Ala strands from attaching to the edge containing a Pro.

DISCUSSION

Because peptides containing a Pro can bind to parallel polyalanine β-sheets as well as (or slightly better than) an Ala, placing one or more Pro's might be useful as a design feature for peptides to be used as anti-amyloid medications. While the computed preference for binding of the strand containing Pro might be slight, the impediment to further binding by other strands is quite large. If more than one Pro is to be used, they must be spaced so that each one can form a H-bond to the sheet, requiring that all the Pro's used be on the even- or odd-numbered positions of that region of the peptide meant to cap the amyloid. While this study does not represent a useful capping agent in itself, we have demonstrated a principle that could be combined in peptides with other residues that enhance selective binding to the amyloid in question. For example, because Gln (Q) has been shown to be important to the formation of many amyloids, Pro might be used in conjunction with Q as part of such designs. We also note that Eisenberg has identified other peptide-based inhibitors of amyloid fibrils[33,34] and that we are evaluating other possibilities that will be described elsewhere. The data in Table 1 indicate the slight binding preference of the AAPAAA strand to be due to the lower distortion energies of both the strand and the four-stranded sheet. In fact, the ΔE_{HB}'s show that the AAAAA strand binds with a slightly more favorable interaction. Thus, we attribute the added stabilization to the relative rigidity of the Pro-containing strand that keeps it in a conformation energetically closer to that it attains when in the sheet.

We should also note that a parallel β-sheet of acetyl-$(Ala)_6NH_2$ can be considered as a linear crystal with a repeating unit of acetyl$(Ala)_6NH_2$ (in contrast to antiparallel β-sheets that have a repeat unit of two strands).[23] As such, another peptide strand can bind to either edge to increase the crystal length. In this paper, we have considered the binding at only

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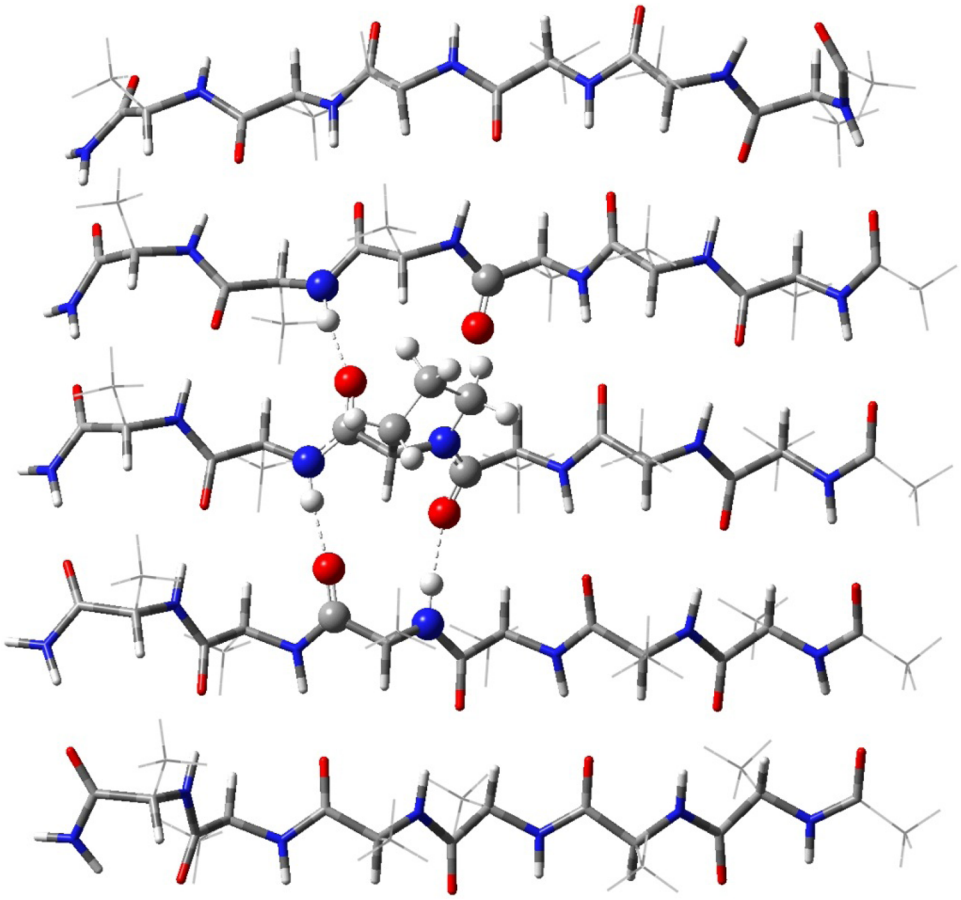

Figure 3. Structure of $(AAAAAA)_4$ with AAAPAA inserted in the middle. The backbones are shown as tubes and the methyls (calculated at the medium level) as a wire frame, and the Pro and its actual and putative H-bonding partners are highlighted in ball and stick format. Note that a H-bond is lost on one side of the AAAPAA.

Table 1. Comparison of the Energetics for Adding an AAPAAA or AAAPAA Cap versus an AAAAA Cap to a Four-Stranded Parallel β-Sheet of AAAAA[a]

cap	ΔH_{int}	relative ΔH_{int}	ΔE_{HB}	E_{dist}(total)	E_{dist}(cap)	E_{dist}(sheet)
			Residue 3 at the High Level			
AAPAAA	−26.5	−1.4	−43.5	13.0	6.7	6.3
			Residue 4 at the High Level			
AAAPAA	−21.9	3.0	−38.8	13.2	7.1	6.1
			Residue 3 or 4 at the High Level			
AAAAAA	−25.1	0	−45.0	15.5	9.0	6.5

[a]The ΔH_{int} is decomposed into ΔE_{HB}, the energy of the H-bonds calculated by breaking those between the cap and the four-stranded sheet keeping both in their optimized capped (five-stranded) sheet geometry, and E_{dist}(total), which is the sum of E_{dist}(cap) and E_{dist}(sheet), which represent the energies required to distort the relaxed strand and four-stranded sheet, respectively, to the geometry taken in the capped sheet. As noted in the text, the Pro and the specific Ala it replaces (in position 3 or 4) have been calculated at the high (DFT) level.

one of the edges. AAPAAA (but not AAAPAA) binds favorably to that edge. However, we note that AAAPAA (and not AAPAAA) would bind favorably with an (almost) equivalent interaction had we considered the other edge as the binding site.

The attachment of a strand to a growing amyloid β-sheet involves a phase change for the strand, as it is in solution before and in the solid state after attachment. This presents a problem as solvation should be considered for the strand in solution, but not the amyloid solid. A useful peptide inhibitor would need to be modified to adjust its solubility. For example, the solubility of a poly Q peptide can be adjusted by substituting H's for Q's, thereby controlling the peptide's ability to form aggregates.[35]

From the foregoing, we can see that if a longer Pro-containing peptide were to interact with a β-sheet of a hexapeptide, it could bind favorably to either side by shifting the Pro interaction by an odd number of residues when binding to the different edges of the growing sheet.

At the request of a reviewer, we add a detailed discussion of the possible errors that theoretical studies such as this might encounter and the steps that we have taken to minimize these possible errors. If the method used to calculate the optimized structures be faulty, the results would not be credible. For this reason, we have used the results from our extensive experience in conducting similar calculations on peptides of various types.[1,16,19,21−25,36−45] We have also tested some more recent

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methods that use functionals that have been parametrized to include "dispersion" interactions. Pure dispersion (as in rare gas dimers) is poorly estimated by some of the more traditional functionals (such as B3LYP). In our tests, we observed several important results. Perhaps most important is that these new dispersion-corrected functionals systematically overestimate the interaction enthalpies of folding per residue for all alanine α-helices by a factor of ~4[12] as compared to several experimental studies,[46−49] while the methods that we use here remain in reasonable agreement with those experiments. For example, our calculated values of the enthalpy of folding per residue for folding of acetyl$(Ala)_{17}NHCH_3$ into the helix are −0.7, −0.8, and −1.2 kcal/mol using ONIOM/B3LYP, B3LYP, and X3LYP, respectively, compared to experimental values that range from −0.9 to −1.1 kcal/mol,[47−49] and experimental estimates for polylysine[50] and polyglutamic acid[51] give similar values (−1.1 and −1.2 kcal/mol, respectively). Also, the structures of the β-sheets (as judged by the Ramachandran dihedral angles) formed by all alanine hexapeptides fall outside the accepted range of experimental databases,[12,52,53] while the structures calculated using the methods used here remain within the acceptable limits of these databases. Thus, in performing these tests of the methodology, we have demonstrated that different methods will give different results and that some methods give results that do not agree with experimental data. Clearly, we chose methods that appear to work best, although we cannot know that they work perfectly as we do not always have experimental data that are sufficiently precise and reliable.

We have shown that the methods that we use have successfully calculated the amide I vibrational modes of α-helices[42] and β-sheets,[43] as well as the trans-H-bond J couplings in peptides.[40,54]

Errors in differences calculated by the same method (be that method accurate or not) will always be more reliable (within the limits of the method) as one would expect many systematic errors to cancel. The foregoing will be particularly true when one compares isomeric structures (as we do in this study) as each structure has the same number of atoms. Our experience with DFT and MO calculations on geometrically optimized structures suggests that energy differences between isomers can be reliably calculated with a precision of ~0.1 kcal/mol for small systems and a slightly higher value for larger ones. These errors tend to be due to the acceptable error in energy for convergence to an optimized geometry (one never reaches the absolute minimum on the potential energy surface). Thus, the 1.4 kcal/mol preference for the structure for the first structure of Table 1 falls well withing the error of the precision of the calculation. The foregoing does not mean that this preference might not change or disappear when it is evaluated by another method or by experiment. That is why we stated that our observation is not sufficient for the design of a therapeutic agent. Rather, it could be used as one factor (a design principle) that could be combined with others to design such an agent.

In principle, theoretical calculations using MO or DFT methods treat the isolated system. Although some methods allow for periodic calculations (as in crystal structures), these are often termed gas phase calculations, as the average distance between molecules in the gas phase is large. Clearly, the results of such calculations will change somewhat if the environment changes (for example, putting the system in a solvent). However, the foregoing will also be true for the experimental system. Using theory to simulate dissolved molecule(s) requires some method for evaluating the effects of the solvent in addition to the structure and energy of the molecule(s) in question.

CONCLUSION

Peptides containing Pro can bind to parallel β-sheets as illustrated by the interaction of AAPAAA with one edge of $[acetyl(Ala)_6NH_2]_4$. This suggests that Pro can be used as one factor (presumably accompanied by others) in the design of peptides that might be used as medications to arrest the growth of amyloids, some of which cause debilitating diseases.

ASSOCIATED CONTENT

Supporting Information

Cartesian coordinates for all optimized structures. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: jdannenberg@gc.cuny.edu. Phone: (212) 772-5343.

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Notes

The authors declare no competing financial interest.

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