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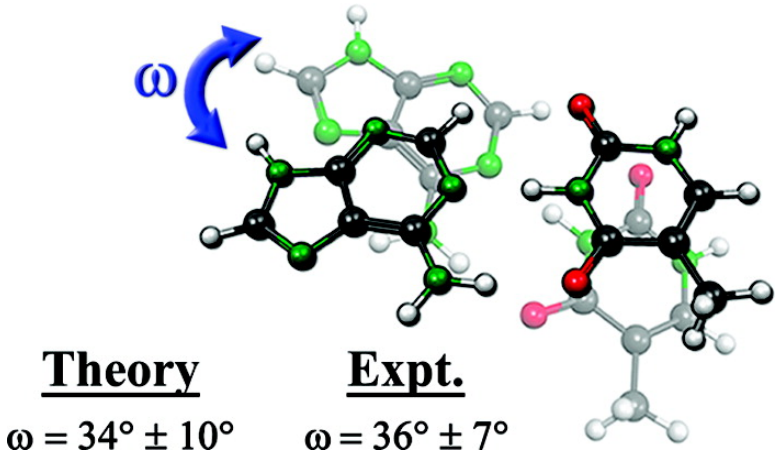

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Stacking Interactions and the Twist of DNA

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Abstract: The importance of stacking interactions for the Twist and stability of DNA is investigated using the fully *ab initio* van der Waals density functional (vdW-DF).[1,2] Our results highlight the role that binary interactions between adjacent sets of base pairs play in defining the sequence-dependent Twists observed in high-resolution experiments. Furthermore, they demonstrate that additional stability gained by the presence of thymine is due to methyl interactions with neighboring bases, thus adding to our understanding of the mechanisms that contribute to the relative stability of DNA and RNA. Our mapping of the energy required to twist each of the 10 unique base pair steps should provide valuable information for future studies of nucleic acid stability and dynamics. The method introduced will enable the nonempirical theoretical study of significantly larger pieces of DNA or DNA/amino acid complexes than previously possible.

Introduction

Experimental data from crystalline DNA have been extensively used to examine how stacking interactions and the orientation of the sugar-phosphate backbone correlate with average DNA structural step parameters such as Twist, Rise, Propeller, Roll, and Slide. This research has revealed that deviations in these structural parameters are sequence-dependent.[3−6] Some studies indicate that variations in the DNA Twist parameter may be attributed to stacking interactions involving steric repulsions between exocyclic groups in DNA's major and minor grooves[5,7] and $\pi-\pi$ interactions between stacked nucleic acid base pairs,[8] while further analysis of DNA X-ray data suggests that the backbone also plays a significant role in determining the helical twist angle of DNA.[9,10] However, empirical models borne from these studies often neglect or inaccurately represent various electrostatic effects and cannot easily isolate the contributions of Twist, Roll, Slide, Propeller, Buckle, Rise, and the conformation of the backbone from each other.

Although it is commonly accepted that base pair stacking interactions as well as hydrogen bonding interactions between base pairs and hydrophobic−hydrophilic interactions with the sugar−phosphate backbone and solvent molecules add to the stability and function of DNA, the relative contributions of each is unclear. One major distinction between DNA and RNA is the replacement of the pyrimidine thymine with the methyl deficient uracil molecule. Calorimetric studies of DNA duplexes and triplexes have shown that the substitution of thymine by uracil weakens the thermodynamic stability of the DNA complex.[11−13] While this decrease in stability of DNA may be attributed to changes in hydrophobic−hydrophilic interactions, hydrogen bonding within a nucleobase, and stacking interactions between nucleobases brought about by this substitution, the effect of the thymine methyl group is also poorly understood.

The lack of an unbiased, fully *ab initio* description of these systems has made it difficult to separate stacking interactions from constraints imposed by the sugar-phosphate backbone. Traditionally, first principles calculations of nucleic acids were performed using quantum chemical wave function based techniques.[14,15] These methods have been shown to give accurate and reliable results with regards to the stacking interactions between molecules where long-range dispersion interactions are important. However, due to their computational demands, they can be used only for systems of limited size, therefore making it necessary to resort to more elaborate classical,[8] semiempiri-

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cal,[16] or partitioning[15] methods in order to perform extensive studies on the interactions between nucleic acid base pairs. Density functional theory[17,18] (DFT) calculations, on the other hand, scale extremely well with system size, but until recently standard approximations gave extremely poor results for systems in which dispersion interactions were significant. The vdW-DF[1,2] corrects this error in the previous exchange-correlation functionals used within DFT, thereby making it possible to accurately and feasibly use a first-principles method to study larger vdW complexes. The only input parameters to this nonempirical method, aside from values of the fundamental constants, are the atomic numbers of the constituent nuclei. The vdW-DF method has been extensively tested on many diverse systems, including benzene dimers[19] and monosubstituted benzene dimers,[20] the interaction of methane with aromatic compounds,[21] graphene sheets, molecules adsorbed to the surface of graphite,[22,23] polyethylene crystal,[24] stacked nucleobase dimers,[25] and base pair steps.[26]

Here, we use the vdW-DF to determine the preferred binary base pair stacking configurations for the 10 possible DNA Watson−Crick nucleic acid base pair steps by mapping out the stacking interactions between them as a function of both Twist and Rise. By excluding the sugar−phosphate backbone and by eliminating Roll, Shift, Slide, Buckle, and Propeller, we are able to isolate the contribution of stacking interactions to the Twist and Rise base pair step parameters.[27] The effect of flanking pairs is not included; because of the daunting task of analyzing sufficient high-resolution data, the extent to which such an effect exists is unclear even experimentally, and contradictory analyses[28,29] have appeared. To understand the stabilizing effect of thymine over uracil, we compare our results for adenine−thymine base pair interactions to systems in which thymine nucleobases are replaced by uracil. Similar to high-level quantum chemical methods, the vdW-DF avoids any possible bias through a full, self-consistent solution of the coupled Schrödinger equations (of the Kohn−Sham type[17]) for all the valence electrons of the two base pairs. As such our calculations automatically include direct and induced electrostatic effects, charge-transfer effects and effects due to the non-nuclear centricity of the dispersion interaction, as well as its deviations from the inverse sixth power at smaller than asymptotic separations. Furthermore, steric repulsions between exocyclic groups and $\pi-\pi$ interactions, which were emphasized in previous models,[5,7,8] are implicitly incorporated into our *ab initio* calculations.

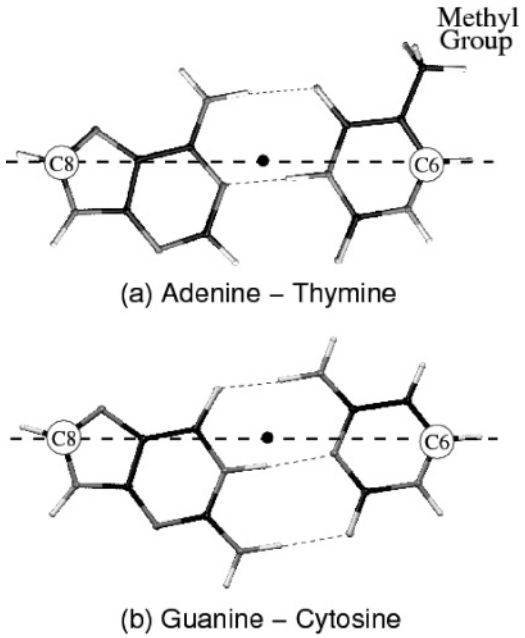

Figure 1. C6−C8 long base-pair axis (dashed line) for the hydrogen-bonded Watson−Crick base pairs (a) adenine:thymine (A:T) and (b) guanine:cytosine (G:C). Here we see that adenine is bonded to thymine by two hydrogen bonds, while guanine makes three hydrogen bonds with cytosine. In RNA, adenine hydrogen bonds with uracil (U), in which the thymine methyl group is replaced by a hydrogen atom. Twists are in-plane counter-clockwise rotations around the center of the C6−C8 axis (denoted by a dot), while Rise is defined as the separation distance between the parallel base pair planes.

Methods

All calculations were performed using DFT,[17,18] with the vdW-DF[1,2] for the exchange-correlation energy. The vdW-DF was applied as a postprocessing method[30] to a self-consistent PBE[31] charge density obtained using the Abinit DFT package.[32] This postprocessing method has also been successfully applied to a number of vdW complexes.[19−24] For the calculations presented in this study, Troullier−Martins pseudopotentials[33] with a 50 Ry cutoff were used. The planar structures of the nucleic acid base pairs were relaxed using PBE self-consistent calculations, and then the vdW-DF exchange-correlation was used to calculate the stacking energies as a function of Twist. For each angle the base pair separation distance (Rise) was optimized, and only the energy at the optimized distance was reported. Optimization of Twist for a given Rise produces the same results. Initial configurations were constructed such that the planes of the two nucleobase pairs were parallel and that their long base-pair axes were centered and aligned. The long base-pair axis is defined by the C8 of the purine (adenine or guanine) and the C6 of the corresponding pyrimidine (cytosine, thymine, or uracil) (see Figure 1). Twist and Rise follow the coordinates of Olson et al., used in the Nucleic Acid Database,[27,34] where Rise is the separation distance between the stacked base-pair planes and Twist is the in-plane (right-handed) counter-clockwise rotation of the upper base pair around the center of its C6−C8 axis. In this coordinate system, AG:CT refers to a hydrogen-bonded guanine(G)−cytosine(C) base pair stacked on top of a hydrogen bonded adenine(A)−thymine(T) base pair,

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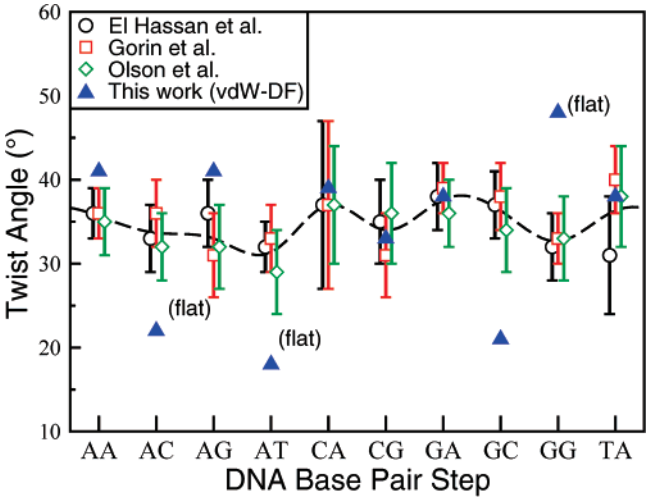

Figure 2. DNA average Twist parameters for DNA dinucleobase steps obtained from X-ray crystallography analysis (El Hassan et al.,[4] Gorin et al.[5] and Olson et al.[6]) and the current computations. The latter omit consideration of the nonplanarity of the base-pair geometry, the conformation of the sugar−phosphate backbone, and the interactions of solvent and other closely bound atoms. For entries marked *flat*, the computed curves (see Figures 3 and 4) were sufficiently shallow in the region surrounding their minima, as in the case of the AT:AT curve in Figure 3, that it was deemed unlikely that the stacking forces play much of a role in determining the Twist. Labels refer to the left strand only; e.g., AG means AG:CT.

letters to the left of the colon represent nucleobases on the 5′−3′ strand, and those to the right are on the 3′−5′ strand. Uracil is denoted with a U.

Results and Discussion

Our results demonstrate that the key DNA parameters of Twist and Rise are strongly linked to the stacking interactions between nucleic acid base pairs. In general, we find that stacked base pairs have a single well-defined minimum with an average Twist of 34° ± 10° (see Figures 2−4). This is consistent with the mean value of 36° ± 7° for a large subset of data for crystalline *B*-DNA[27] taken from the Nucleic Acid Database.[34] Similarly, our average optimized base pair separation distance (Rise) was determined to be 3.5 Å, in reasonable agreement with the value of 3.3 Å from the above data set,[27] especially when vdW-DF's small systematic overestimation of vdW bond lengths of ∼0.2 Å is considered.[2,19−24] In addition, we find that the stacking energies, ranging from 13.5 to 18.2 kcal/mol, are comparable to typical hydrogen-bonding energies between nucleobases (15.0 and 27.5 kcal/mol for A:T and G:C, respectively).[35]

A comparison with experimental data compiled by El Hassan et al.,[4] Gorin et al.,[5] and Olson et al.[6] shows that our results generally follow the trend variations in those databases (Figure 2), though with larger fluctuations. Several special cases will be discussed later. More importantly, we find that, while changes in Rise account for the majority of the base pair stacking stability (8−13 kcal/mol), Twists further enhance these interactions by 2−5 kcal/mol (Figures 3 and 4). This clearly illustrates that these interactions contribute significantly to defining the sequence-dependent Twists observed in *B*-DNA.[36] These results also suggest that the large variances observed in experiment may be a consequence of the fact that the minima of interaction energy versus Twist angle are relatively wide and as such energy contributions as small as 0.3 kcal/mol could result in changes of ±5° (Figures 3 and 4).

Possible exceptions to the angular stability can be seen for AT:AT and AC:GT, where the respective curves are rather flat and kinky (see Figure 3 for AT:AT curve), and, as we shall see, strongly affected by interactions with the methyl group of thymine. Further deviations from the average are observed in the abnormally small Twist for the GC:GC step and the relatively flat region near the minimum of the GG:CC step. In these cases, we expect that the final magnitude of the Twist will be more influenced by the sugar−phosphate backbone and interactions with adjacent nucleic acid base pairs and solvent molecules, not to mention the fact that these base pair steps all have significant Roll and Propeller[5] which have been shown to be correlated with the Twist parameter.[4,37]

Šponer et al.[15] have also evaluated the stacking energy of isolated DNA steps for Twists of 30°, 36°, and 42° using a modification of the force field of Cornell and co-workers.[38] These semiempirical calculations give results that are consistent with our much more complete nonempirical results.[39] In particular, the two methods agree on which dimers have Twists greater than 42° or less than 30°. Our results are consistent with the notion that stacking interactions stabilize DNA for a reasonable range of Rise and Twist and that there is some flexibility in the sugar−phosphate backbone.

We shall now turn to the discussion of the effect of thymine on the base pair stacking energies, after a brief mention of hydrogen bonding in the Watson−Crick pair A:T and its RNA analogue A:U. Using the vdW-DF, we computed hydrogen bond energies (15.3 kcal/mol for A:T and 15.2 kcal/mol for A:U) and dipole moments (1.5 and 1.3 D for A:T and A:U, respectively). Our results are in good agreement with MP2 calculations for A:T[35] and show little change on methyl substitution. This suggests that discrepancies in the stability of DNA and RNA are most likely related to interactions of the methyl group with adjacent nucleobases, the sugar−phosphate backbone, and/or solvent molecules. For the purpose of this study we neglect the latter effects and focus on the influence of thymine's methyl group on the stacking interactions between base pair steps.

Figure 3 depicts the stacking energies for three thymine-containing nucleobases and the corresponding uracil base pair steps. Each of these plots is representative of the three types of interactions that may occur between stacked nucleobase pairs. Figure 3a indicates that for AT:AT base pair stacks there is an enhancement of up to 2 kcal/mol (nearly 15% of the total stacking energy), which decreases significantly for larger Twist

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(36) A complete table of vdW-DF interaction energies and preferred Twist and Rise parameters for the nucleobases studied can be found in Supporting Information Table 1.
(37) An early calculation[9,10] employing a simple parameterized method gave very little influence on Twist from stacking interactions in the absence of the backbone. We have tested this parameterization on the CO_2 dimer where vdW-DF agrees well with high level quantum chemical calculations.[2] It gives a substantially weaker dependence of energy on geometry, notably in the repulsive regime that is a substantial contributor to the Twist in our DNA calculations, thus indicating a possible reason for the discrepancy. The use of methyl terminations of the backbone connections is another difference between ref 10 and this work, where hydrogen terminations are used.
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(39) Complete comparison of vdW-DF results, X-ray crystallography analyses, and QC data can be found in Supporting Information Table 2.

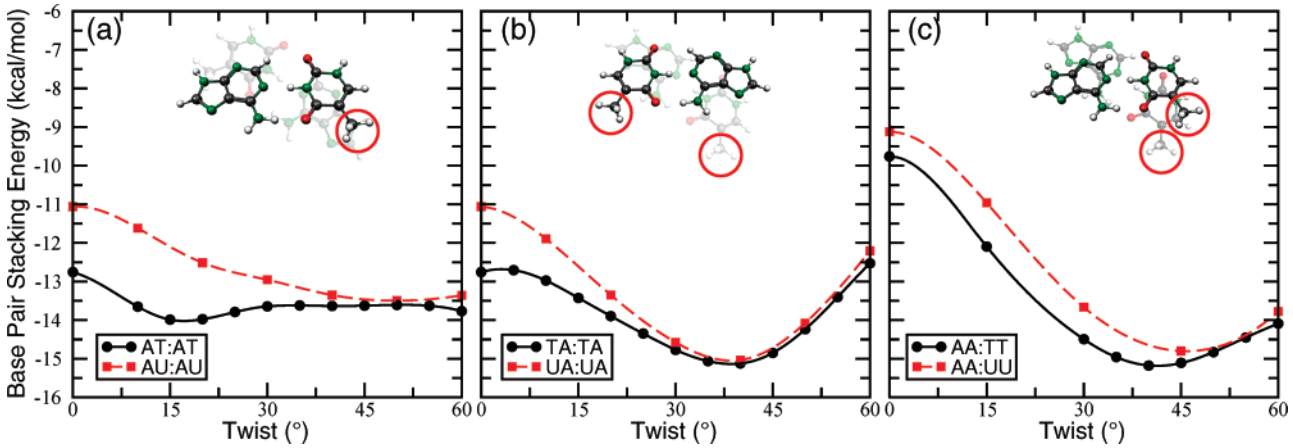

Figure 3. Stacking energy as a function of Twist for the AT:AT (a), TA:TA (b), and AA:TT (c) base pair sequences and their uracil containing counterparts. Insets show top views of the stacking configuration at 36°.[41] Both AA:TT and AT:AT show enhancement through methyl group interactions.

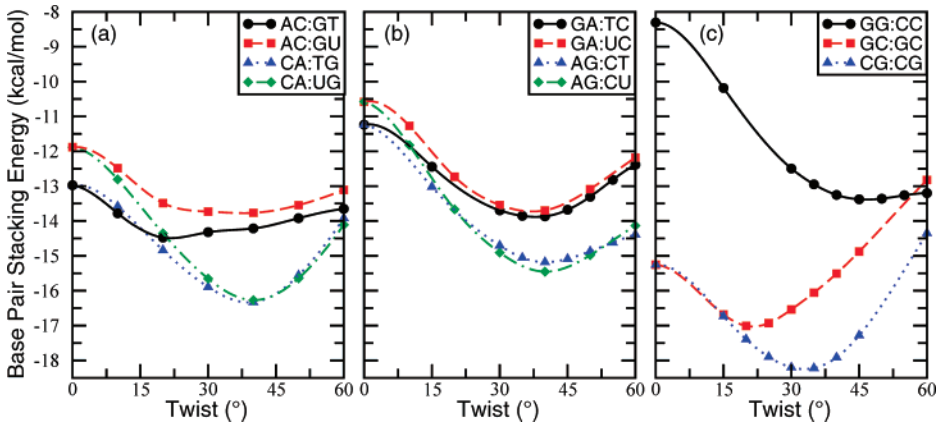

Figure 4. Base pair stacking energies as a function of Twist angle for the remaining seven DNA nucleic acid base pair steps and their uracil containing counterparts computed using the vdW-DF. For each angle the energy reported is for the optimized separation distance.

angles. Perhaps more importantly, the methyl interaction removes a torque that would result in an overtwisted step in its absence. A consideration of the methyl group position shows that the enhancement is strongest when the thymine methyl group is in close contact with the adjacent thymine (Figure 3a inset). Previous quantum chemical and vdW-DF studies of the methane−indole dimer[21,40] show that the interactions of methane with a nitrogen-containing π system could be as large as ∼2 kcal/mol. This suggests that, here, the dominant effect is due to strong methyl interactions with the π system of the adjacent nucleic acid. Interestingly, the minimum of the AT:AT curve occurs when a methyl hydrogen is closest to the N7 atom of the adjacent adenine, suggesting an incipient H-bond; on the other hand, a Twist of 36° reduces this interaction, resulting in smaller differences in stacking energy relative to UA:UA. Similar interactions, albeit smaller, were observed for the AC:GT system (see Figures 3 and 4). Conversely, neither TA:TA nor CA:TG exhibit any appreciable enhancement due to the presence of thymine (Figures 3b and 4a). In these cases the Twists result in movement of thymine away from the adjacent nucleobase, thereby eliminating any possible methyl−π stabilization.

Figure 3c shows that for AA:TT there are thymine-induced stabilization energies of ∼1 kcal/mol (∼7% of the total stacking energy) for angles less than ∼30° but which become negligible for angles greater than 50°. For the AA:TT stack both thymine molecules are on the same strand (see inset of Figure 3c), and for smaller angles the methyl−methyl distances are ∼4 Å. These interaction energies and methyl−methyl distances are consistent with previous studies of methane dimers,[42] suggesting that, here, methyl−methyl interactions are most likely the mechanism for thymine stabilization. This is further supported by the lack of stabilization observed in analogous steps where a thymine is replaced with a methyl deficient pyrimidine. In other words, we find nearly identical energy vs angle interactions for AG:CT and AG:CU and for GA:TC and GA:TU (see Figure 4), indicating the absence of thymine-induced stabilization. Note, here structural considerations eliminate the possibility of any methyl−π stabilization.

Conclusion

In conclusion we have shown from first principles, in the absence of a sugar-phosphate backbone and any solvent medium, that stacking interactions between nucleic acid base pairs are important for defining the Twist angle and base pair separation distance (Rise) of DNA. Our results indicate that these parameters are a consequence of the interplay between long-

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range electrostatic and vdW interactions and short-range Pauli repulsions and that the magnitude of stacking interactions is indeed comparable to hydrogen bonding interactions between nucleobase pairs. Furthermore, we apply this concept of strong stacking interactions to show that methyl−nucleobase and methyl−methyl interactions can stabilize DNA over its uracil counterpart, RNA, by up to 15% of the total stacking energy. In short, these results emphasize the importance of stacking interactions for the structural stability of DNA.

Unlike other nonempirical methods, vdW-DF can promise applications to substantially larger systems in the near future. We expect that further simulations that extend these studies to include the interactions of additional DNA base pairs, flanking sequences, a sugar−phosphate backbone, and/or an aqueous medium can elucidate the relative importance of each of these interactions on the structure and function of DNA in vitro. Another issue that could be studied is the sequence-dependent variability of bending and curvature of *B*-DNA.[43] In particular, our work on the effects of the thymine methyl interactions lays the foundation for investigating more general effects such as understanding the role that sequences of repeated A:T pairs [A-tracts] play in this regard.[44] In addition the results may be useful in parametrizing empirical potentials for large scale simulations of DNA, while offering suitable limits on these model-potential approaches. Many important applications should follow.

In summary, this work has pinpointed the role that stacking interactions play in defining the Twist and Rise of base pair steps. It has also identified and quantified the role that the methyl group of thymine plays in providing additional stabilization. Perhaps more importantly, the relative success of the method is likely to unleash the nonempirical study of significantly larger segments of DNA or DNA/amino acid complexes. Its use should be especially important where self-consistent charge distributions are required, as these are not available from force field methods. An application of this type to sequence-dependent protein−DNA binding via charged amino acid residues has already begun. Also begun are vdW-DF applications to molecules that intercalate between base pairs, which are important in drug design and drug action.[45] As such the current results are a first step in the development of a complete *ab initio* understanding of DNA structure and function.

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Supporting Information Available: Complete table of dinucleobase interaction energies, Twist and Rise parameters, complete table of DNA Twist parameters from this work, previous theoretical calculations and X-ray crystallography analyses, and representative plots of comparisons between vdW-DF and MP2 for the adenine dimer and comparisons between vdW-DF and partitioned CCSD(T) calculations for stacked nucleobase pair steps at 36°. Also complete refs 27 and 32. This material is available free of charge via the Internet at http://pubs.acs.org.

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