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The Binding Orientation of a Norindenoisoquinoline in the Topoisomerase I-DNA Cleavage Complex Is Primarily Governed by π-π Stacking Interactions

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Abstract

High level ab initio quantum chemical studies have shown that the binding orientations of topoisomerase I (Top1) inhibitors such as camptothecins and indenoisoquinolines are primarily governed by π-π stacking. However, a recently discovered norindenoisoquinoline antitumor compound was observed by X-ray crystallography to adopt a "flipped" orientation (relative to indenoisoquinolines), which facilitates the formation of a characteristic hydrogen bond with the Arg364 of Top1 in its binding with the Top1-DNA complex. This observation raises the possibility that hydrogen bonding between the norindenoisoquinoline nitrogen and the Arg364 side chain of Top1 might be responsible for the "flip". It also brings into question whether π-π stacking, as opposed to hydrogen bonding, is primarily responsible for the binding orientations of indenoisoquinolines and norindenoisoquinolines. In this study, the forces responsible for the binding orientation of a norindenoisoquinoline in the DNA cleavage site were systematically investigated using MP2 methods. The theoretical calculation of the preferred binding orientation based solely on π-π stacking was completely consistent with the actual orientation observed by X-ray crystallography, indicating that the binding of the norindenoisoquinoline in the Top1-DNA complex is mainly governed by π-π stacking forces and that the "flip" can occur independently from hydrogen bonding.

Keywords

MP2; interfacial binding; noncovalent interactions; DNA intercalation; anticancer; mechanism of action

Introduction

The binding of small molecules to macromolecular receptors, including proteins, DNA, and especially the recently identified interfaces of macromolecular complexes, is often of pharmacological interest.[1] Interfacial binding is usually governed by a combination of different non-covalent interactions such as hydrogen bonding, electrostatics, van der Waals bonding and hydrophobic interactions. Although the relative contributions of these individual non-covalent interactions to the overall binding energy vary in each case, π-π stacking has been shown to play a crucial role in the interactions of many DNA-intercalating molecules.[2,3] It has been

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Supporting Information Available. Three-dimensional presentation of models **A**-**F** and their Cartesian coordinates, and a complete reference [25]. This material is available free of charge via the internet at http://pubs.acs.org.

demonstrated recently that the binding of some topoisomerase I (top1) inhibitors to DNA-protein interfaces is also governed by π-π stacking,[4-6] although hydrogen bonding of these antitumor agents with these protein target also occurs. Ab initio calculations using the second-order Möller-Plesset perturbation method (MP2) at the conventional 6−31G* level on model intercalation complexes have previously indicated that camptothecin (CPT, **1**, Chart 1),[7] the first identified cytotoxic top1 inhibitor,[8] binds to the top1-DNA interface primarily by π-π stacking interactions with the flanking base pairs.[5] This "π-π stacking hypothesis" was successfully employed to explain the loss of top1 inhibitory activity of 21-lactam-*S*-CPT, *R*-CPT, and 22-hydroxyacuminatine, where hydrogen-bonding explanations fail, and it also correctly predicts CPT binding orientation and binding site selectivity.[4,5,9] Mechanistically, CPT intercalates between DNA base pairs at the DNA cleavage site produced by top1,[10,11] resulting in inhibition of the DNA religation reaction that would otherwise be catalyzed by top1 as well. The inhibition of religation leads to double-stranded DNA damage when the trapped top1-DNA cleavage complex encounters a DNA replication fork, which eventually leads to apoptosis.[12,13]

Indenoisoquinolines,[14] represented by compound **2**,[15,16] are a novel class of non-CPT top1 inhibitors that can overcome some of the inherent limitations posed by the CPTs, including lactone instability in blood plasma and cancer cell resistance.[17] Several indenoisoquinolines are undergoing preclinical studies at the National Cancer Institute. X-ray crystallographic analysis of the ternary complex formed by top1, DNA and indenoisoquinoline **3** indicates that indenoisoquinolines have the same mechanism of action as CPT, involving intercalation at the DNA cleavage site and inhibition of the DNA religation step.[10] The orientation of the indenoisoquinolines in the top1-DNA cleavage complex, as in the case of CPT, was also found from quantum chemical investigations using the MP2 method at the conventional 6−31G* level to be primarily governed by π-π stacking interactions.[6] Surprisingly, the X-ray crystal structure of a ternary complex consisting of top1, DNA, and the norindenoisoquinoline compound **4** demonstrated that the orientation of **4** was "flipped" relative to that of compound **3** (Figure 1).[18] This "flipping" facilitates the formation of a characteristic hydrogen bonding interaction between the isoquinoline nitrogen of **4** with the Arg364, which has been shown by X-ray crystallography to be a general phenomenon of several top1 inhibitors in their top1-DNA-inhibitor ternary complexes.[10] This raises the possibility that the "flipping" might result from hydrogen bonding between the Arg364 side chain and the ketone oxygen of **3** or the isoquinoline nitrogen of **4**, which would argue that hydrogen bonding, instead of π-π stacking interactions, might be more important in determining the relative binding orientation of indenoisoquinolines in the top1-DNA cleavage complex. Since compound **4** displays very high cytotoxicity (similar to or higher than CPT) against a variety of different human tumor cell lines including lung, breast, and prostate cancer, it is important to define the key binding forces that are involved in its interaction with the target, since that would be helpful in further quantum mechanics (QM)-guided structural optimization.

As the conventional 6−31G* basis set significantly underestimates polarizability, MP2 calculations at this level will unavoidably underestimate the electron correlation effect and hence also the stabilization energy. Therefore, previous MP2 calculations at the 6−31G* level on CPT and indenoisoquinolines could not describe the dispersion energy very well.[5,6] It should be noted that more appropriate quantum chemical treatment of π-π stacking systems will not challenge but only further support previous conclusions obtained with MP2/6−31G* as it has already verified the importance of π-π stacking. An attractive method to improve the estimation of the π-π stacking in small systems is to use Dunning's correlation-consistent basis sets or the augmented aug-cc-pVXZ basis sets at the MP2 level.[19] This strategy has already been successfully used in both π-π systems and hydrogen-bonding complexes of small molecules. However, it is not practical to use this strategy to study the large system of interests here, which includes 110 atoms. A more feasible choice is to use the modified 6−31G*(0.25)

basis set originally proposed by Hobza et al.,[3] in which the exponent of standard d-polarization functions (0.8) in the 6−31G* basis is replaced by a more diffuse one (0.25) for the second-row elements. It has been shown that the inclusion of more diffuse d-polarization functions describes electron correlation better and thus improves the calculated quality of dispersion. This method has been used as the standard level for decades in a wide range of configurations, including stacked nucleobase dimers,[20] base-intercalator complexes,[3] and other aromatic assemblies of biological or chemical interest.[21] It should still be pointed out that a comparative study indicated that the MP2/6−31G*(0.25) method systematically underestimated the base stacking by ca. 1.0−2.5 kcal/mol per stacked dimer in the systems studied, covering 75−90% of the intermolecular correlation stabilization.[22] As this method provides a good compromise between accuracy and feasibility, and also provides a good estimate of the stacking-stabilization energy, the MP2/6−31G*(0.25) method was used in our quantum chemical investigations. It was also expected to cover the electrostatic, polarization, dispersion energy components, and charge transfer effect properly.

In this study, the practical and more accurate MP2/6−31G*(0.25) method was used to study the π-π stacking of norindenoisoquinoline **4** with DNA base pairs to see whether the π-π stacking, as opposed to hydrogen bonding, primarily determines the orientation of norindenoisoquinoline relative to the neighboring DNA base pairs. In addition, Natural Bonding Orbital (NBO) theory was employed to see whether the charge transfer interaction stabilizes the π-π stacking complex. These quantum chemical investigations will enhance our understanding of how small molecules intercalate between DNA base pairs, which will contribute to the design more potent antitumor agents.

Molecular Modeling

Model Preparation

To construct models that would be useful in investigating π-π stacking interactions, compound **4** and its flanking base pairs were extracted from PDB entry 1TL8[18] and the structures of the deoxyribose rings on the base pairs were replaced with methyl groups (Figure 2).[5] Geometry optimization and frequency calculations were carried out for each substructure including compound **4**, the A-T base pair, and the C-G base pair in the new model at the HF/6−31G** level. The energy-minimized substructures displayed no imaginary frequencies and were thus proved to be real minima in the geometrical optimizations, and were therefore utilized to replace the original units in the model (Figure 2, right) by RMS fitting of all heavy atoms in the monomers to give model **A** (Figure 3). RMS fitting is based on the RMSD (root mean square deviation) calculated according to below equation:[23]

$$RMSD = \sqrt{\frac{1}{N}\sum_{i=1}^{i=N}\delta_i^2} \quad (1)$$

Where, the δ_i is the distance between N pairs of equivalent atoms.

The structure of compound **4** in model **A** was then rotated by 90°, 180°, and 270° from its original position to give models **B**-**D**. The ligand **4** was also flipped to give model **E**, which is similar to the orientation of indenoisoquinoline **3** in its cleavage complex crystal structure. Its further rotation by 180° produced model **F**. To keep all of the relative orientations of the ligand in the same framework of the DNA base pairs and avoid possible arbitrary errors, an in-house SPL script was coded and used to realize all such operations in the Sybyl 7.2 software package.[24] All such operations were made relative to the centroid of the ligand.

Computational Methods

All the six models **A-F** were subjected to single-point energy calculations using the MP2 method at both the conventional 6−31G* and modified 6−31G*(0.25) levels using the quantum chemical program package Gaussian 03.[25]

The effect of solvation was investigated using the Polarizable Continuum Model (PCM) at the MP2/6−31G*(0.25) level with the default radii scheme.[26,27] The solvation energy $\Delta G_{solvation}$ was expressed as the energetic difference between the solvated complex $E_{PCM-MP2}$ and the in vacuum complex E_{MP2} obtained with the same computational method.

$$\Delta G_{solvation}\,(MP2) = E_{PCM-MP2} - E_{MP2} \quad (2)$$

The solvation energies were also calculated using density functional theory B3LYP/6−31G* with the United Atom Kohn-Sham (UAKS) or the United Atom for Hartree-Fock (UAHF) model to build cavities. Similarly,

$$\Delta G_{solvation}\,(DFT) = E_{PCM-DFT} - E_{DFT} \quad (3)$$

The intermolecular interaction energy was calculated using the supermolecular approach. The energy of interaction between the ligand and the neighboring DNA base pairs is defined as the difference between the energy of the complex $E_{complex}$ and the energies of the monomers E_{ligand} and E_{bp}. The basis set superposition error (BSSE) was also corrected using the Boys and Bernardi counterpoise method because of the use of an incomplete basis set in practical applications of the supermolecular approach.[28] Therefore, the interaction energies of the six orientations were calculated at the MP2/6−31G*(0.25) level through the equation listed below:

$$E_{int} = E_{complex} - E_{ligand} - E_{bp} + BSSE \quad (4)$$

The dispersion energy was defined as the interaction energy difference between the MP2 and HF results at the same basis set, which mainly reflects the contribution of electron correlation.

$$E_{corr} = E_{int(MP2)} - E_{int(HF)} \quad (5)$$

NBO analysis has been shown to be a valuable tool for the investigation of the charge transfer interaction.[29] As it only yields reliable values when the wavefunction is fully defined, NBO analysis performed at the MP2 level could not provide hyperconjugative interaction energy.[30] Therefore, the NBO analysis was performed at the HF/6−31G** level in this study. The interaction between filled orbitals of one subsystem and vacant orbitals of another subsystem can be used as a measure of the intermolecular delocalization as it represents a deviation of the complex from the Lewis structure. The hyperconjugative interaction energy can be deduced from the second-order perturbation approach. This type of interaction is also called charge transfer energy, though the electron density transferred between subsystems is relatively small but chemically significant. It has been estimated that 0.001e of charge transfer roughly corresponds to 1 kcal/mol of the stabilization energy.[30] Here, we use

$$E_{CT} = -\Sigma E(2) \quad (6)$$

where E(2) is all of the individual intermolecular second-order hyperconjugative interactions between the ligand and the neighboring DNA base pairs that exceed a default threshold of 0.05 kcal/mol calculated from NBO analysis at the HF/6−31G** level of theory, reflecting the major contribution of charge transfer to the stabilization of the drug-DNA complex.

Results and Discussion

The model complex (model **A**) was built by replacing the monomers of the crystal structure with QM-optimized monomer structure using RMS fit methodology. Rotation and flipping the ligand relative to the base pairs gave five other representative orientations from models **B** to

F (Figure 3). Geometry optimization of the model complexes using the MP2 method would be ideal. However, it is not computationally feasible. The strategy used in this study is the one that is generally adopted in quantum chemical investigations of DNA intercalators,[3,5,6] which maintains the experimentally verified characteristics of the drug-DNA complex to a great extent. Such a strategy can provide a reliably qualitative conclusion if not a quantitative one.

In order to investigate whether the "π-π stacking hypothesis" still holds in the case of norindenoisoquinoline **4** binding to the top1-DNA cleavage complex, the relative energies of the six models of **4** in Figure 3 were systematically investigated using MP2 calculations performed at both the standard 6−31G* and modified 6−31G*(0.25) levels.

The MP2 calculation results are listed in Table 1. The single-point energies listed are from both MP2/6−31G* calculations without inclusion of BSSE and MP2/6−31G*(0.25) with the inclusion of BSSE using the counterpoise correction method.[28] The relative energy ranking order of the six models resulting from each method is nearly the same, with only the **D** and **E** models ranked differently. The MP2 calculated energies at the 6−31G* level are slightly lower than that from 6−31G*(0.25) calculations, consistent with the previous observation by Hobza et al. that standard MP2 calculations have a tendency to overestimate the dispersion energy.[31] Therefore, only MP2/6−31G*(0.25) was used for further calculations. The change in the relative energy of models **E** and **D** is caused by the basis set superposition error (BSSE), necessitating the inclusion of this effect in the accurate ranking of the binding energies.

The calculated in vacuo energy differences between model **A** and the other five models are listed in Table 1. Based on these energy differences where only the π-π stacking interaction is considered and the protein structure is completely eliminated from the theoretical models, it is clear that the observed X-ray orientation has the lowest energy, indicating that the orientation of **4** in its ternary complex is determined by π-π stacking interactions as opposed to hydrogen bonding interactions with the surrounding protein structure. Therefore, based on the quantum chemical investigation of the simplified drug-DNA intercalation model, we conclude that the "flipped" binding orientation of norindenoisoquinoline **4** relative to indenoisoquinoline **3** is primarily governed by π-π stacking forces instead of hydrogen bond formation. Hydrogen bonding between Arg364 and the isoquinoline nitrogen of **4** only enhances this binding orientation preference further. It is interesting that model **E**, which has the same binding orientation as indenoisoquinoline **3**, is 8.29 kcal/mol higher in energy than model **A**. The binding orientations of **3** and **4** were previously calculated to also result primarily from π-π stacking interactions as opposed to hydrogen bonding interactions with the surrounding protein structure.[6]

The effect of solvation was investigated using the Polarizable Continuum Model (PCM) at the MP2/6−31G*(0.25) level.[26,27] Table 2 lists the calculated solvation energies. It is not surprising that the solvation energies of model **A** and **E** are quite similar considering that compound **4** is somewhat symmetric and strongly hydrophobic. The solvation energy was also calculated using density functional theory B3LYP/6−31G* with both the widely used UAKS and also the UAHF radii scheme. Generally, UAKS performs better than UAHF when used in DFT calculations, since it was optimized to fit density functional methods particularly well and also has been optimized for the PBE/6−31G(d) level of theory. Though a slightly better correlation ($r^2 = 0.98$) was obtained between the MP2 solvation results and the DFT results using the UAKS radii scheme than that obtained ($r^2 = 0.95$) between the MP2 results and the DFT results using the UAHF radii scheme, the DFT method using the UAHF radii scheme provided solvation energies substantially comparable to those resulting from the MP2 method. This indicates that the strategy combining the B3LYP/6−31G* method and the UAHF radii scheme can provide an accurate estimation of the solvation effect at a much cheaper computational cost. Clearly, model **A** is still the most stable one. The second most stable model

E is 8.31 kcal/mol higher in energy, instead of model **C**, which was the second most stable in the in vacuo calculations. It is therefore evident that the solvation effect plays an important contribution in the binding, as the ranking order of the six models varies when it was included.

From the above calculations, π-π stacking plays a very important role in the binding of norindenoisoquinoline **4** to neighboring DNA bases in the cleavage site. Therefore, it is interesting to define the contribution of each of the fundamental forces such as electrostatic, dispersion and charge transfer interactions in the binding of the ligand to its target. Though a reliable and accurate breakdown of the interaction energy could be performed using the symmetry-adapted perturbation theory (SAPT) approach, the size of our drug-DNA intercalation model prevents the use of such a computationally intensive procedure due to the computational resource limitations.[32] From the aspects of drug design, it is much more interesting to identify the critical energy components that contribute to the stabilization because the information will be useful in further rational drug design.

As π-π stacking mainly originates from dispersion and charge transfer interactions, we calculated the dispersion and charge transfer contributions to make a direct quantitative comparison of their roles in the binding of norindenoisoquinoline **4** to the top1-DNA complex. The dispersion energy was defined as the interaction energy difference between the MP2 and HF results at the same basis set, which mainly reflects the contribution of electron correlation. From Table 3, models A, C, E and F share comparable dispersion energies, indicating this kind of interaction is isotropic and proportional to the geometrical overlap of the stacked systems. The MP2 binding energy of the ligand to the simplified DNA base pairs in model **A** was −31.56 kcal/mol. This result is reasonable considering that the stacking energies vary from −9.5 kcal/mol (GG) to −13.2 kcal/mol (GC) in the standard B-DNA steps calculated by Sponer et al. at the same theoretical level.[33]

The charge transfer energy was calculated from Natural Bond Orbital (NBO) analysis using the HF/6−31G** method. From Table 3, charge transfer interaction makes a comparable contribution with dispersion in the stabilization of the norindenoisoquinoline **4**-DNA complex in model **A**. However, charge transfer was previously calculated to play a minor role for indenoisoquinolines when compared with dispersion.[6] This may be an important difference that confers superior top1 inhibitory activity to norindenoisoquinoline **4** relative to the corresponding indenoisoquinolines **2** and **3**, and it might prove to be useful for future rational structural modification of norindenoisoquinolines.[15,16,18]

Conclusions

The forces responsible for the binding orientation of norindenoisoquinoline **4** in the top1-DNA cleavage site were systematically investigated with high level ab initio quantum chemical calculations. The calculations are consistent with the observed results of X-ray crystallography structure determination, thus indicating that the binding of the norindenoisoquinoline in the top1-DNA complex is primarily governed by π-π stacking. Further calculations of the relative contributions of dispersion and charge transfer demonstrate that the charge transfer interaction plays a much more important role in the stabilization of the ternary norindenoisoquinoline **4**-top1-DNA complex than the indenoisoquinoline **2**-top1-DNA complex, which might help to explain the superior biological activity of norindenoisoquinoline **4** versus the corresponding indenoisoquinoline **2**.[15,16,18] To date, ab initio calculations performed at the MP2 level involving models similar to those displayed in Figure 2 have been consistent with the binding behavior of indenoisoquinolines and CPTs in addition to the presently described norindenoisoquinoline case.[4-6] This theoretical approach to understanding the binding of top1 inhibitors therefore appears to be quite general. The method used here is applicable to future

structural optimization of norindenoisoquinolines to discover better antitumor drugs acting on DNA topoisomerase I.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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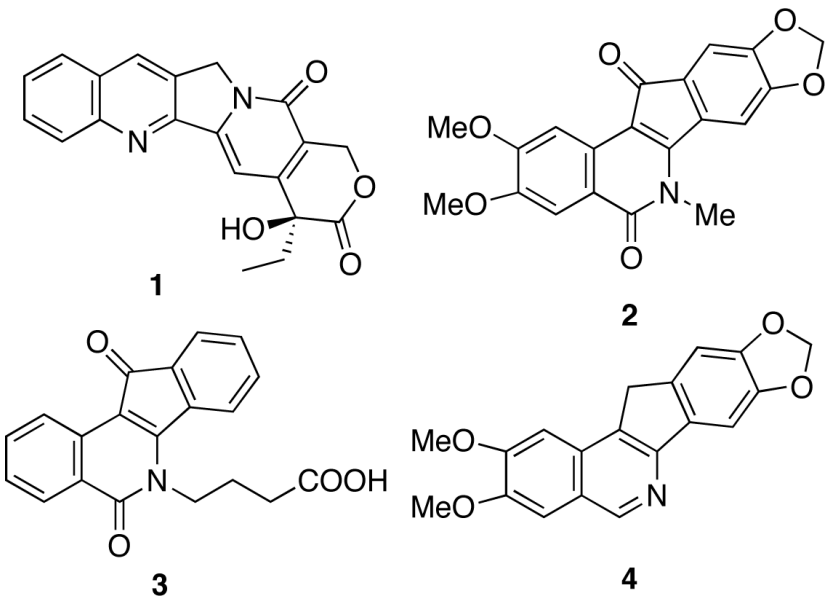

Chart 1.
Chemical structures of CPT **(1)** and indenoisoquinolines

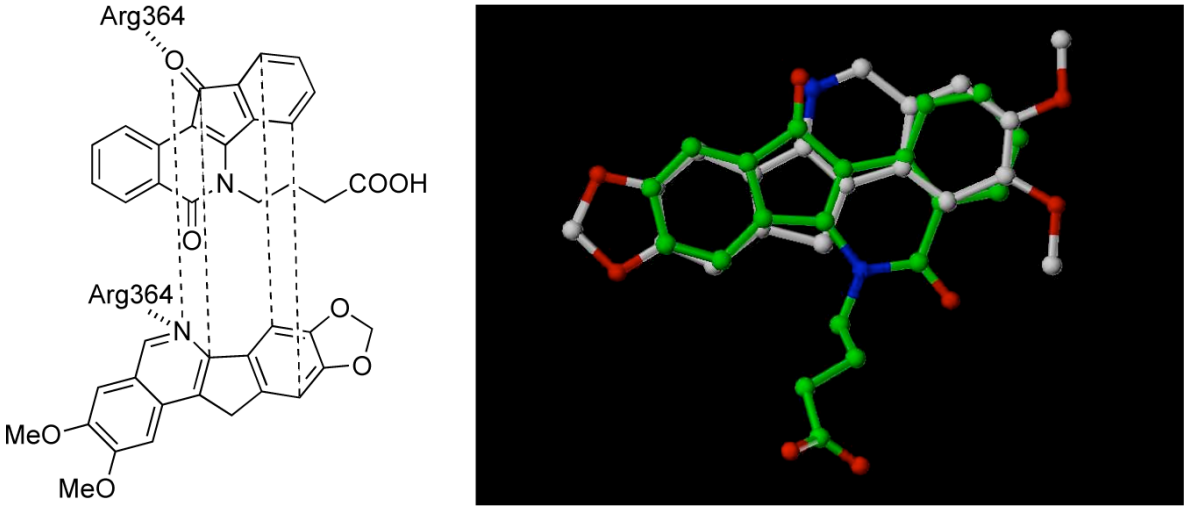

Figure 1.

(Left) The relative orientations of compound **3** (top) and **4** (bottom) observed in the crystal structures of their ternary complexes. The hashed lines indicate hydrogen bonds whereas the dashed lines denote atoms that overlap when the crystal structures are superimposed. (Right) Overlay of the norindenoisoquinoline **3** (green carbon atoms) and **4** (white carbon atoms) in the crystal structures of their ternary complexes with top1 and DNA.

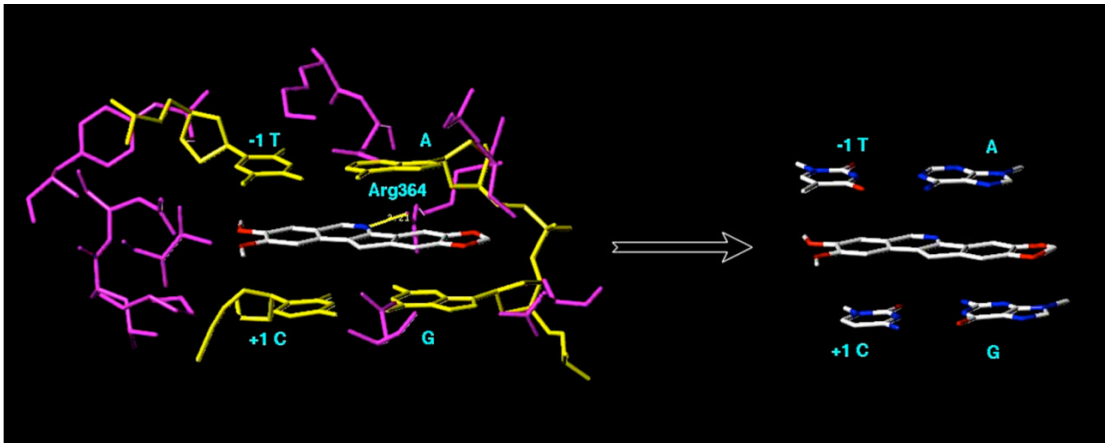

Figure 2.
Model construction for ab initio calculations. Left: X-ray crystal structure of the ternary complex (PDB entry 1TL8[18]) containing compound **4**, DNA and top1. Right: simplified intercalation complex model containing only compound **4** and its flanking base pairs for ab initio calculations.

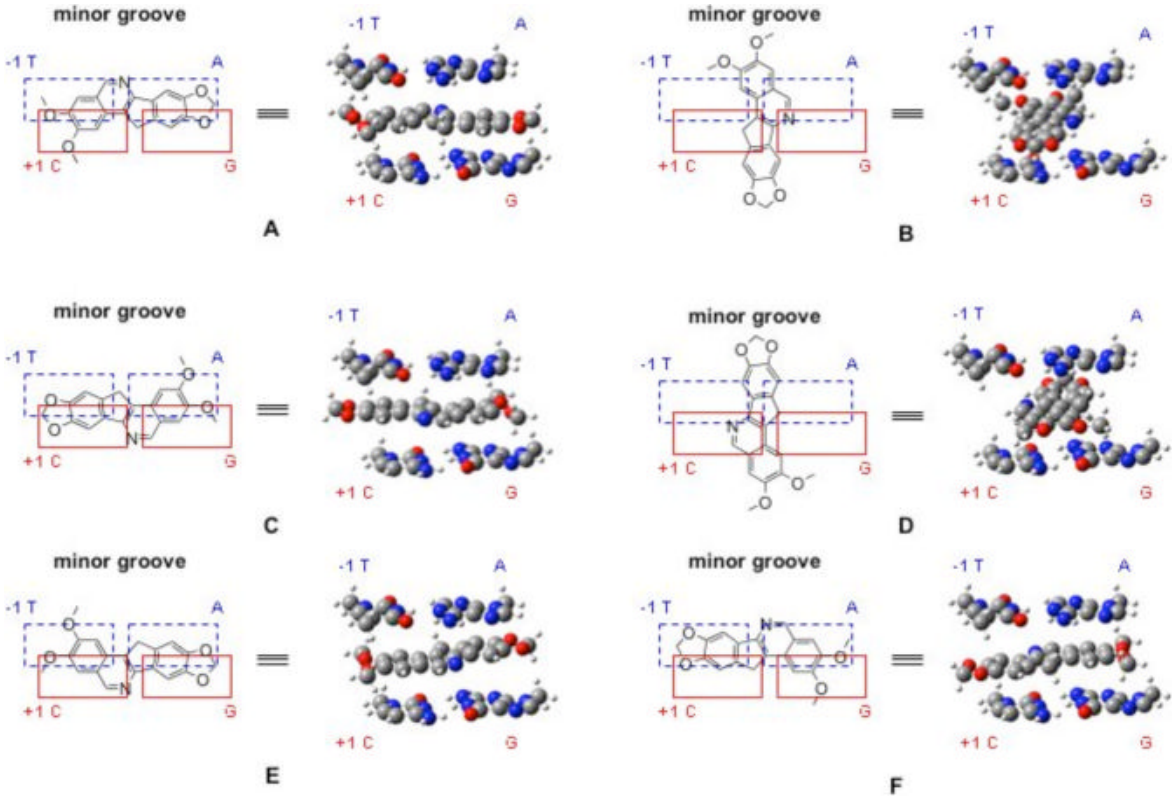

Figure 3.
Six different orientations of compound **4** in the intercalation complex.

Table 1

The Calculated MP2 Energies of Models A-F

Models[a]	$E_{MP2/6-31G*}$[b] (au)	ΔE_1[bc] kcal/mol	$E_{MP2/6-31G*}$[d] with BSSE (au)	ΔE_2[cd] kcal/mol	$E_{MP2/6-31G*(0.25)}$[b] (au)	ΔE_3[bc] kcal/mol	$E_{MP2/6-31G*(0.25)}$[d] with BSSE (au)	ΔE_4[cd] kcal/mol
A	-3095.662602	0	-3095.622004	0	-3093.316949	0	-3093.234935	0
B	-3095.644519	11.35	-3095.616253	3.61	-3093.276539	25.36	-3093.221051	8.71
C	-3095.656892	3.58	-3095.612156	6.18	-3093.313178	2.37	-3093.226218	5.47
D	-3095.647623	9.4	-3095.619197	1.76	-3093.280033	23.17	-3093.224158	6.76
E	-3095.651893	6.72	-3095.607820	8.90	-3093.307916	5.67	-3093.221720	8.29
F	-3095.655316	4.57	-3095.611744	6.44	-3093.310299	4.17	-3093.225337	6.02

[a] Model A: extracted from the crystal structure; models B-D: ligand-rotated 90°, 180°, 270° relative to model A; model E: ligand-flipped orientation of model A; model F: ligand-rotated 180° relative to model E.

[b] MP2 energies without BSSE.

[c] ΔE_1 and ΔE_2 refer to the energy difference (kcal/mol) between model A and other models calculated at MP2/6−31G*, while ΔE_3 and ΔE_4 refer to the energy difference (kcal/mol) between model A and other models calculated at MP2/6−31G*(0.25).

[d] MP2 energies with BSSE correction.

Table 2

The Solvation Energies (kcal/mol) from MP2/6−31G*(0.25) and B3LYP/6−31G* Using the PCM Model

Models	$\Delta G_{solvation}$(MP2)[a]	$\Delta E_{solvation}$[b]	ΔE[c]	$\Delta G_{solvation}$(DFT-UAKS)[ad]	$\Delta G_{solvation}$(DFT-UAHF)[ae]
A	-40.25	0	0	-43.52	-39.47
B	-40.55	-0.3	8.41	-43.90	-41.33
C	-35.41	4.84	10.31	-38.08	-35.29
D	-35.61	4.64	11.40	-39.24	-36.37
E	-40.23	0.02	8.31	-42.96	-40.10
F	-36.11	4.14	10.16	-39.49	-36.22

[a] $\Delta G_{solvation(MP2)} = E_{PCM\text{-}MP2} - E_{MP2}$, $\Delta G_{solvation(DFT)} = E_{PCM\text{-}DFT} - E_{DFT}$

[b] $\Delta E_{solvation}$ was the relative solvation energy of the models investigated at the MP2 level.

[c] ΔE was the relative energy in aqueous solution of the models investigated at the MP2 level, which was computed as the sum of the relative energy in gas-phase (ΔE_4 in Table 1) and relative solvation energy ($\Delta E_{solvation}$).

[d] The results were obtained using B3LYP/6−31G* and the UAKS radii scheme.

[e] The results were obtained using B3LYP/6−31G* and the UAHF radii scheme.

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Table 3

The Binding Energies (kcal/mol) of Models A-F

Models	$E_{int(MP2)}$ [a]	$E_{int(HF)}$ [a]	E_{corr} [b]	E_{CT} [c]
A	-31.56	33.25	-64.81	-60.00
B	-22.85	23.20	-46.05	-24.23
C	-26.09	42.94	-69.03	-76.42
D	-24.80	22.43	-47.23	-38.15
E	-23.27	46.85	-70.12	-87.34
F	-25.54	41.66	-67.20	-85.21

[a] From MP2/6−31G*(0.25) calculations with BSSE.

[b] $E_{corr} = E_{int(MP2)} — E_{int(HF)}$.

[c] E_{CT} was calculated from HF/6−31G**.