Monatshefte für Chemie 127, 645–658 (1996)

**Monatshefte für Chemie**
**Chemical Monthly**
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Printed in Austria

# Molecular Modeling of Intercalation Complexes of Antitumor Active 9-Aminoacridine and a [*d*, *e*]-Anellated Isoquinoline Derivative with Base Paired Deoxytetranucleotides

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**Summary.** Intercalators are molecules capable of sliding between DNA base pairs without breaking up the hydrogen bonds between the DNA bases. On the basis of molecular mechanics calculations structural, models of B-DNA tetranucleotide intercalation complexes of some cytostatic active 9-aminoacridines and of a [*d*, *e*]-anellated isoquinoline derivative are presented. The drug complexes are stabilized by energetically favoured *van der Waals* interactions and by selective hydrogen bonds between the side chains of the drugs and the DNA bases. Semiempirical quantum chemistry calculations revealed that the chromophoric system of the intercalators is able to form $\pi,\pi$-charge-transfer interactions with the purine bases of the base paired deoxytetranucleotides. The theoretical findings are of interest for a more specific drug design of cytostatically active agents.

**Keywords.** DNA intercalation; Molecular mechanics; Semiempirical quantum chemistry calculations.

**Molecular Modeling von Interkalationskomplexen antitumoraktiver 9-Aminoacridine sowie eines [*d*, *e*]-anellierten Isochinolinderivates mit basengepaarten Desoxytetranukleotiden**

**Zusammenfassung.** Interkalatoren sind Moleküle, die in der Lage sind, sich zwischen DNA-Basenpaare einzulagern, ohne die Wasserstoffbrücken zwischen den DNA-Basen aufzubrechen. Auf der Basis von molekülmechanischen Rechnungen werden Tetranukleotid-Interkalationskomplexe von verschiedenen zytostatisch aktiven 9-Aminoacridinen und von einem [*d*, *e*]-anellierten Isochinolinderivat präsentiert. Die Komplexe werden durch energetisch günstige *van der Waals*-Interaktionen sowie durch selektive Wasserstoffbrückenbindungen zwischen den Seitenketten der Wirkstoffe und den DNA-Basen stabilisiert. Semiempirische quantenchemische Rechnungen ergaben, daß der Chromophor der Interkalatoren in der Lage ist, $\pi,\pi$-charge-transfer Wechselwirkungen mit den Purinbasen der basengepaarten Desoxytetranukleotide auszubilden. Die theoretischen Ergebnisse sind für ein spezifischeres Wirkstoffdesign zytostatisch aktiver Verbindungen von Interesse.

## Introduction

Selective DNA binding agents are of great interest in medicinal chemistry for the development of antitumor and antibacterial active drugs [1]. One group of these drugs belongs to the DNA intercalating compounds [2]. These molecules insert

between two neighboured (stacked) base pairs of the DNA double helix without breaking up the interstrand hydrogen bonds of the biopolymer. To build up an intercalation site, the distance between the base pairs is increased from 3.4 to 7.0 Å [2]. The principle of intercalation was first discovered by *L. S. Lerman* for acridines [3]. Later, *H. M. Sobell* and coworkers confirmed the intercalation on the basis of several X-ray structures of acridine-dinucleotide complexes [4–8] which gave for the first time detailed geometrical insight in the complex geometries. There exist also several X-ray structures of anthracycline antibiotics, for example of daunorubicin (**1**), intercalatively complexed with base paired hexanucleotides [9–14]. Some of the anthracycline antibiotics and also the structurally related synthetic drug mitoxantrone (**2**) are antitumor active chemotherapeutic drugs for the therapy of several human tumors [15, 16]. Based on mechanistic studies, the intercalation into DNA followed by inhibition of several DNA-dependent enzymes (for example inhibition of DNA-dependent RNA-polymerase or topoisomerase II [17]) seems to play the decisive role for their antitumor activity [16]. In the reported X-ray data on DNA-intercalation complexes with anthracyclines, the aliphatic substituents of ring A of the drugs are throughout inserted into the minor groove of the base paired hexanucleotides, and stabilizing hydrogen bonds between the drugs and the heteroatoms of the base pairs are built up [9–14]. To our knowledge there exists no report that the unsubstituted anthracycline chromophore intercalates anyway. However, it is experimentally proven that daunorubicin loses its cytostatic activity when the C9–OH group is absent [18]. From these results it is obvious that, first of all, functionalities at the drugs which are able to form stable hydrogen bonds with the DNA should contribute significantly to the thermodynamic stability of the intercalation complexes.

In contrast to the drugs **1** and **2**, the mutagenic [19, 20] 9-aminoacridine (**3**) whose intercalation has been experimentally verified [4], cannot build up hydrogen bonds with DNA-bases because of the lack of an appropriate side chain with oxygen or nitrogen atoms. For this drug and other simple acridine derivatives, another stabilization factor must exist to build up an intercalation complex. One further important binding contribution of intercalators to DNA may be the formation of charge-transfer complexes with the electron rich DNA-bases.

The knowledge of the threedimensional structure of the biologically relevant drug-receptor complexes in a therapy group should be the starting point for a rational design of new drugs. In the present paper, we report about detailed structural aspects of DNA intercalation complexes of the antiprotozoic drug quinacrine (**4**) and the antitumor active compounds 9-aminoacridine-4-carboxylic acid 2-(dimethylamino)-ethylamide (**5**; in the present paper called carboxamide throughout) and the benzo[*d*, *e*]isochinolin-1,3-dione derivative mitonafide (**6**). The results were derived from model building, interactive computer graphics and, molecular mechanics calculations. All of these drugs bind tightly to double-stranded DNA by intercalation of the chromophore [21–25]. We discuss the geometrical (conformational) and energetical characteristics of low energy complexes, the sequence selectivity, and – on the basis of semiempirical quantum-mechanical calculations – the ability of these drugs to form charge-transfer complexes with the nucleic acid bases. On a molecular level, all three compounds should be able to build up hydrogen bonds with the amino group of the side chain and provide an electron

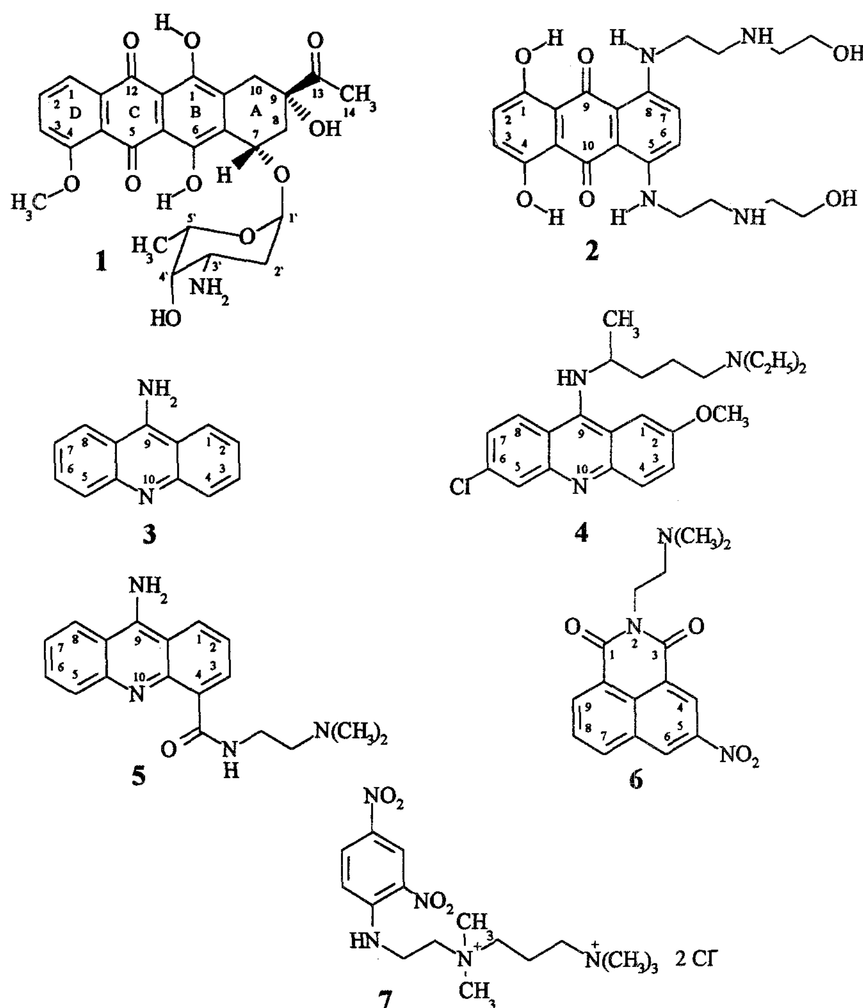



**Fig. 1** Chemical structures of daunorubicin (**1**), mitoxantrone (**2**), 9-aminoacridine (**3**), quinacrine (**4**), carboxamide (**5**), mitonafide (**6**) and a 2,4-dinitroaniline derivative (so-called *reporter* molecule, **7** [33, 34])

deficient chromophore (for **4** and **5** only in the N10-protonated form) which is able to act as electron acceptor in a charge-transfer complex with a DNA base. No X-ray structures of the respective drug-DNA complexes being available, the theoretical results should reveal reliable models for the geometrical and electronical requirements for optimal drug binding in the given series, help to understand the drug action mechanism of these classes of heterocycles, and allow to design new chemotherapeutic congeners.

## Materials and Methods

All operations were performed with the aid of the molecular modeling program packet SYBYL 6.0 [26], installed on a VAX 4000/90 DEC. The molecular mechanics calculations were realized with AMBER [27] and TAFF [28] (TRIPOS associated force field) in SYBYL using the *Powell* minimizer. For base

paired B-DNA, oligonucleotide specific parameters from *P. A. Kollman* were used [27], whereas the calculations of the intercalation complexes including the non nucleic structure of the drug were performed with TRIPOS force field parameters as implemented in SYBYL. The validation and the success of calculations of drug-receptor complexes using the TRIPOS parameters in comparison to using the AMBER parameters is well documented [28]. For the electrostatic term in force field calculations for refinement of oligonucleotides, the nucleinic charge from the AMBER program was used [27]; the atomic charges of the drug-DNA complexes were calculated by the method of *Gasteiger* and *Hückel* [29]. The molecular mechanics calculations revealed no significant differences for the DNA complex geometries by using alternatively MOPAC-AM1 charges [30] for the drug; thus, *Gasteiger* and *Hückel* charges were used. A distance dependent dielectric constant of the form $\varepsilon = cR_{ij}$ $(c = 4)$ was employed throughout in the electrostatic term [26]. The complex was further energy minimized with TAFF until the energy gradient was less than 0.01 kcal/mol. The graphical visualizations were performed with an Evans & Sutherland PS 390 system.

The interaction energy *E-inter* of the various complexes is calculated by

$$E\text{-}inter = E\text{-}tot - E\text{-}oligo - E\text{-}drug. \quad (1)$$

The potential energy term for the whole complex is *E-tot*, for its tetranucleotide it is *E-oligo*, and for mitoxantrone or other intercalators, it is *E-drug*. *Van der Waals* and electrostatic contributions to the interaction energy *E-inter* between DNA and the drug are given as *E-int-vdW* and *E-int-elec*, respectively. All changes in the conformational energy are summed up in *E-int-conf*. It should be noted that

$$E\text{-}inter = E\text{-}int\text{-}elec + E\text{-}int\text{-}vdW + E\text{-}int\text{-}conf. \quad (2)$$

In this paper, only the energy values of Eq. 2 are given, because only these values are relevant to the discussion of the complexes. It has also to be noted that the calculated values have no physical meaning and thus should only be considered for comparing the different drug-DNA complexes to find optimal binding geometries.

## Results and Discussion

### *Model building and energy minimization*

The exact geometry of quinacrine dihydrochloride (salt of **4**) was derived from an X-ray structure [31]. Carboxamide (**5**) and mitonafide (**6**) were built using the SYBYL building modul. In the case of carboxamide, the 9-aminoacridine X-ray structure [4] was used and adequately modified. The mitonafide starting geometry was obtained completely from the SYBYL building modul. The amino groups at the end of the side chains of these drugs were constructed in the protonated form. Additionally, the basic acridine chromophores of quinacrine and carboxamide were protonated at N10. These protonations are in agreement with the conditions in physiological environment where the cationic forms of these 9-aminoacridine derivates predominate very clearly in the equilibrium [32].

Before starting to build up the drug-DNA complexes, an appropriate base paired deoxytetranucleotide with an enlarged intercalation site was constructed. Acridines insert best parallel to the long axis of the base pairs [4–8], anthracyclines like **1** and mitoxantrone (**2**) approximately perpendicular [9–14, 33]; therefore, the intercalation site must be geometrically slightly different. Thus, the construction of base paired B-DNA oligonucleotides with an appropriate intercalation site must be done carefully and has to be adapted in each case to the intercalating heterocycle. Here,

the base paired tetranucleotide $d(\mathrm{TCGA})_2^{\#}$[a] with an increased distance of 6.7 Å between the second and the third base pair was derived from the X-ray structure of the 9-aminoacridine-$d(\mathrm{CG})_2$ intercalation complex [4] and the tetranucleotide duplex $d(\mathrm{TCGA})_2$, built up as described in our previous paper [33]. The central $d(\mathrm{CG})_2$ part of $d(\mathrm{TCGA})_2$ (base pairs 2 and 3) was substituted by the dinucleotide of the X-ray structure with an enlarged base pair distance. Then, a full geometry optimization of the thus constructed tetranucleotide was performed using the AMBER force field [28]. The resulting base paired $d(\mathrm{TCGA})_2^{\#}$ tetranucleotide duplex retains the B-DNA conformation. By appropriate substitution of the bases of the second and third base pair of the modified $d(\mathrm{TCGA})_2^{\#}$ and a subsequent AMBER geometry optimization, a further base paired tetranucleotide $d(\mathrm{TTAA})_2^{\#}$ was constructed.

The model building of the intercalation complexes was done by docking the drugs **4**, **5**, and **6** into the enlarged intercalation site of base paired deoxytetranucleotides. Two structural modes are taken into consideration during the insertion of chromophore and side chain of the drugs into the DNA cavity. According to the reported intercalation geometry of 9-aminoacridine [4], the chromophores of **4** and **5** were inserted parallel to the long axis of the base pairs (edge-on alignment orientation). The orientation of the side chains was achieved such that the construction of hydrogen bonds between the protonated amino group of the side chain as hydrogen bond donor and the heteroatoms of the second or third base pair as hydrogen bond acceptors was possible (Fig. 2). In this way, four intercalation

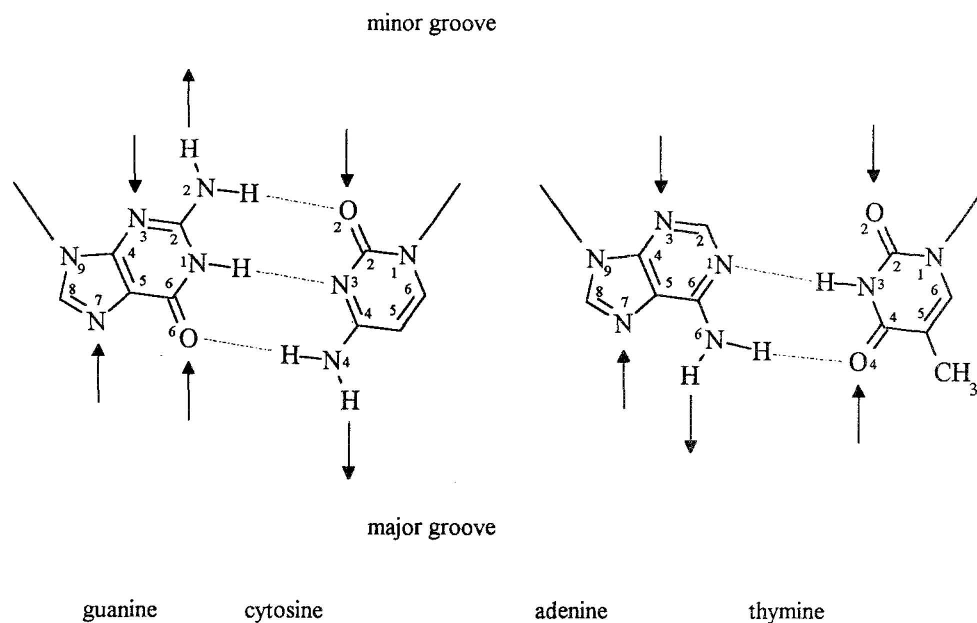



**Fig. 2** Guanine-cytosin and adenine-thymine base pair; heteroatoms which can act as hydrogen bond donors or acceptors are marked by arrows

[a] The base paired deoxytetranucleotides marked by "#" were constructed for building up intercalation complexes with 9-aminoacridines in contrast to the not specially marked deoxytetranucleotides for building up complexes with anthracycline derivates

complexes of each drug were constructed by orientation of the side chains into the major or the minor groove (see Fig. 2) of *d*$(TCGA)_2^{\#}$ or *d*$(TTAA)_2^{\#}$. During the TAFF minimization of the complexes, the base paired tetranucleotides kept are fixed, restricting a conformational change. This is justified on the basis of the rational conformation of the constructed tetranucleotides *d*$(TCGA)_2^{\#}$ and *d*$(TTAA)_2^{\#}$. Both have B-DNA geometry like the base-paired oligonucleotides in the intercalation complexes of the reported X-ray structures [9–14]. Therefore, only the conformation of the intercalator is fully minimized by the calculations. Details of the calculated complexes are given in Table 1.

**Table 1.** Geometries of the hydrogen bonds between the base paired drug-deoxytetranucleotide intercalation complexes after energy refinement by molecular mechanics (TAFF)

| Drug | Base sequence of the tetranucleotides | Complexes (abbreviations see[a,b]) | Hydrogen bonds of the protonated side chain amino group with specification of the participated bond partners and of angles[c] (°) and distances[d] (Å) |
|---|---|---|---|
| **4** | *d*$(TCGA)_2$ | Q-tcga-ma | G–N7/G–O6<br>124 2.0/125 1.9 |
| **4** | *d*$(TCGA)_2$ | Q-tcga-mi | C–O2<br>154 2.1 |
| **4** | *d*$(TTAA)_2$ | Q-ttaa-ma | A–N7<br>156 2.1 |
| **4** | *d*$(TTAA)_2$ | Q-ttaa-mi | T–O2<br>154 1.9 |
| **5** | *d*$(TCGA)_2$ | Ca-tcga-ma | G–N7/G–O6<br>128 2.6/130 1.7 |
| **5** | *d*$(TCGA)_2$ | Ca-tcga-mi | C–O2<br>142 2.4 |
| **5** | *d*$(TTAA)_2$ | Ca-ttaa-ma | A–N7<br>166 2.5 |
| **5** | *d*$(TTAA)_2$ | Ca-ttaa-mi | T–O2<br>144 2.3 |
| **6** | *d*$(TCGA)_2$ | M-tcga-ma | G–N7/M–O3<br>134 2.0/124 1.9 |
| **6** | *d*$(TCGA)_2$ | M-tcga-mi | G–N3/M–O3<br>139 2.8/122 1.7 |
| **6** | *d*$(TTAA)_2$ | M-ttaa-ma | T–O4/M–O3<br>133 2.1/123 1.8 |
| **6** | *d*$(TTAA)_2$ | M-ttaa-mi | A–N3/M–O3<br>127 2.0/130 1.9 |

[a] ma: implementation of the side chain into the **MA**jor groove, mi: implementation of the side chain into the **MI**nor groove; [b] Q = **Q**uinacrine, Ca = **Ca**rboxamide, M = **M**itonafide; [c] angle heteroatom-hydrogen-heteroatom; [d] distance between hydrogen and acceptor-heteroatom

*Molecular mechanics calculations*

The calculations based on the modes described above revealed reliable DNA complex geometries for each of the drugs **4**, **5**, and **6**. The relevant energy values are given in Fig. 3. The intercalation complexes are stabilized by *E-int-vdW* and *E-int-elec*. The gain of *E-int-vdw* is induced by the enlargement of the *van der Waals* contact area by the insertion of the chromophore between the two base pairs, and the gain of *E-int-elec* is caused by the electrostatic attraction between the cationic drugs and the polyanionic tetranucleotides. Additionally, energy contribution of the hydrogen bonds in the drug-DNA interaction are taken into consideration by calculation of the *van der Waals* energy in the Tripos associated force field [28]. The energy requirement for conformational changes of the intercalators *E-int-conf* is well compensated by the energy gain of *E-int-vdw* and *E-int-elec* in most cases.

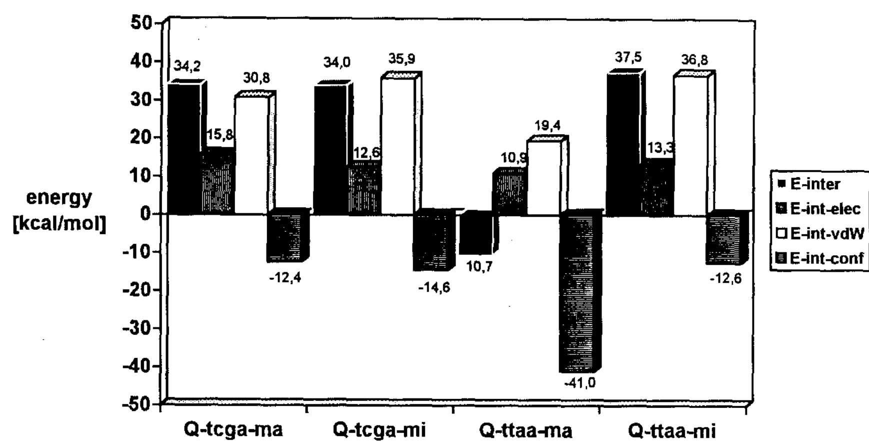
For **4** (Q) and **5** (Ca), an energetically favoured complex conformation could be calculated if the side chains were inserted into the major groove of a CG base pair (Fig. 3a, b, Fig. 4). In this case, the side chains of both drugs form a three-centered hydrogen bond which connects guanine N7, the amino group of the side chain, and guanine O6 (see Fig. 4). The energy gain of the quinacrine complex Q-tcga-ma is compensated because of energetically favoured *van der Waals* contacts of the bulky quinacrine side chain during insertion into the minor groove. So the complexes Q-tcga-mi and Q-ttaa-mi also seem to be favoured because of the gain of *E-int-vdW*. The complex Q-ttaa-ma seems to be energetically less favoured, probably due to the greater steric repulsion of the quinacrine side chain and the methyl group of thymine in the major groove.

Mitonafide (**6**) does not show a clear energetical preference for one of the studied insertion modes (Fig. 3c). In every mitonafide intercalation complex, a three-centered hydrogen bond is formed involving the amino group of the mitonafide side chain and the carbonyl-oxygen O3 of the amide group of the mitonafide chromophore. Because of the attractive *van der Waals* contacts, the mitonafide intercalation complexes with the side chain lying in the minor groove are energetically slightly favoured.

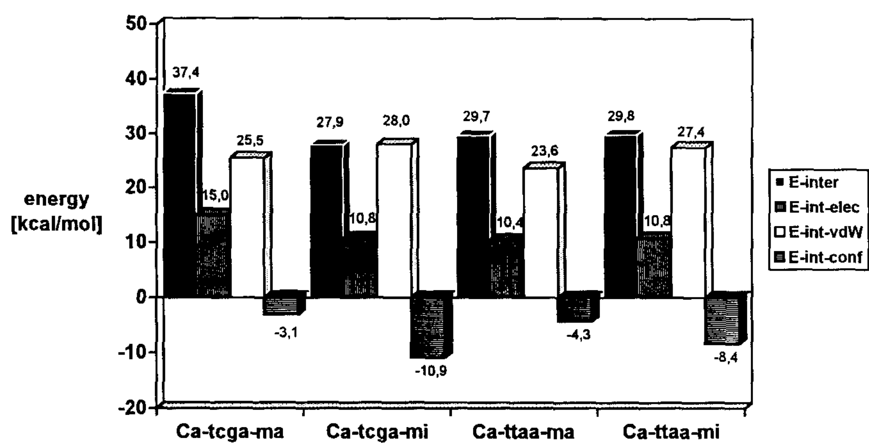
*Semiempirical MO calculations of charge-transfer complexes*

The contribution of charge-transfer interactions in DNA intercalation complexes has been discussed first in the studies of *E. J. Gabbay* and coworkers [34, 35] on interactions between DNA and electron deficient 2,4-dinitroaniline molecules like **7** (so called *reporter* molecules). In a later work, *D. Sharples* and *J. R. Brown* proved the existences of electron donor-acceptor complexes between acridinium cations and guanosine monophosphate by UV/Vis spectroscopy [32]. In a report on the spectroscopic properties of N10-protonated quinacrine and its interaction with polynucleotides [32], a fluorescence quenching in presence of the $d(\mathrm{CG})_n$-nucleotides is described which may be caused by an electron transfer from guanine to the quinacrine cation.

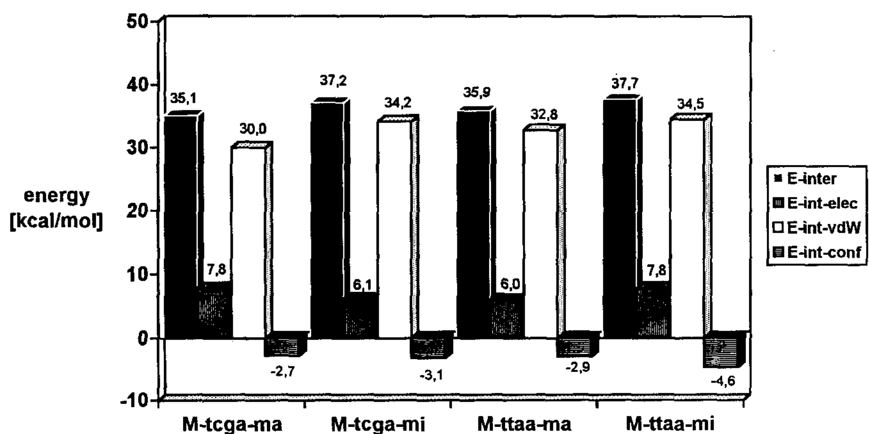
From these experimental results it seems reasonable that in the case of sufficient electron deficient chromophores (cationic systems, nitroarenes) also charge-transfer interaction in the DNA intercalative binding plays a significant role for complex




a




b




c

**Fig. 3** Potential energy values (kcal/mol) of drug-tetranucleotide complexes deduced from TAFF-calculations; abbreviations of complexes: see Table 1

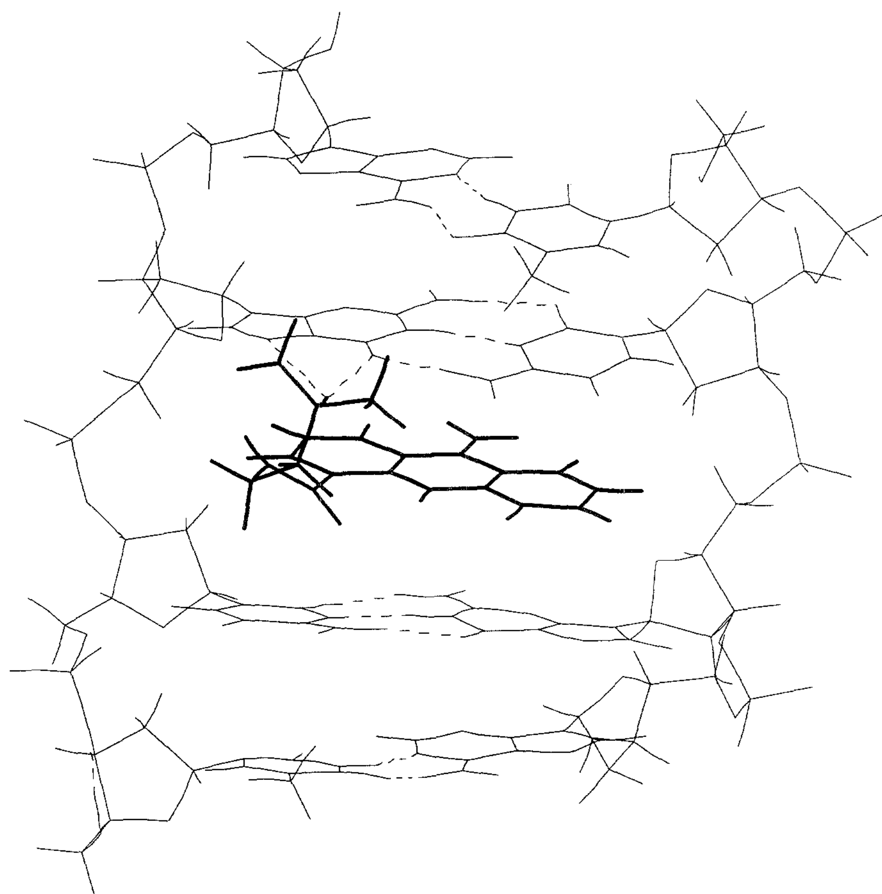


**Fig. 4** DNA-intercalation complex Ca-tcga-ma, stabilized by hydrogen bonds between intercalator and DNA base pairs; view nearly perpendicular to the helix axis

stabilization. However, standard force field calculations do not consider charge-transfer interactions explicitly. To predict charge-transfer interactions for the molecules **4**, **5**, and **6**, semiempirical quantum chemistry calculations with the program MOPAC 6.0 using AM1 Hamiltonian parameters [30] were performed.

A charge-transfer interaction is characterized by an electron-transfer from an electron rich subsystem of a complex to an electron deficit subsystem. According to the frontier molecular orbital concept, the charge is transferred from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO) of the complex. Therefore, electron distribution and density of the frontier orbitals of charge-transfer complexes play a significant role for the possibility of an electron transfer [37, 38]. In the case of nucleic acid intercalation complexes, the orbital distribution of HOMO must be localized at the purine base as one subsystem ($\pi$-electron donor), and the orbital distribution of LUMO must be localized at the chromophore of the intercalator as the other subsystem ($\pi$-electron acceptor). Figure 5 represents the threedimensional orbital distribution of HOMO and LUMO of the cytosine-guanine/9-aminoacridinium complex whose geometry is

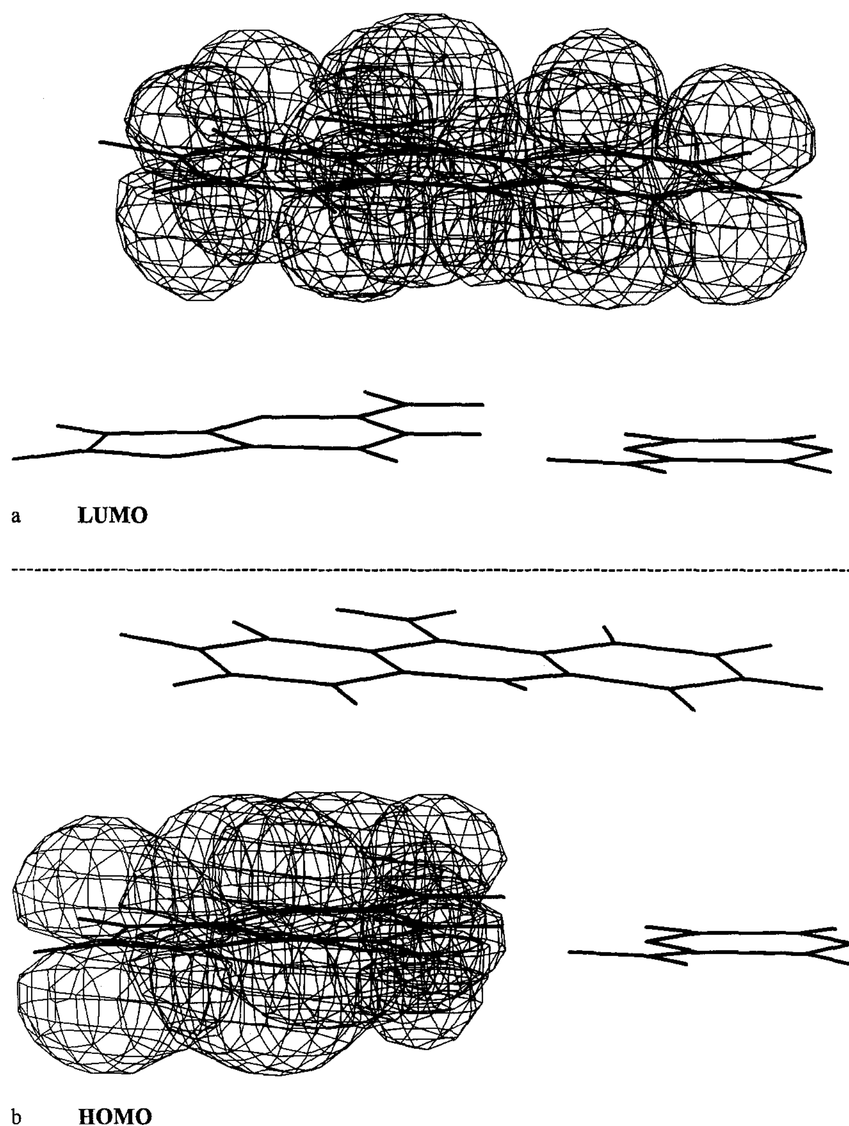



**Fig. 5** LUMO (a) and HOMO (b) of the cytosine-guanine/9-aminoacridinium complex showing the threedimensional orbital distribution; the direction of the charge-transfer is given by the localization of these orbitals; the average distance of the complex partners is about 3.4 Å

based on a part of its X-ray structure [4]. The HOMO of this complex is localized at the guanine base (Fig. 5b), the LUMO is localized at the acridinium cation (Fig. 5a). Cytosine is not involved in building up the charge-transfer interaction. The direction of charge-transfer is given by the localization of these orbitals. FMO-calculations of cationic **4** and **5** complexes give similar results of a $\pi,\pi$-charge-transfer interaction with nucleic bases. Figure 6 shows the orbital distribution for the same complex with the 9-aminoacridine base as an example. In this case, HOMO and LUMO are both localized at the 9-aminoacridine subsystem, and therefore the possibility for a charge-transfer between the complex partners is excluded.

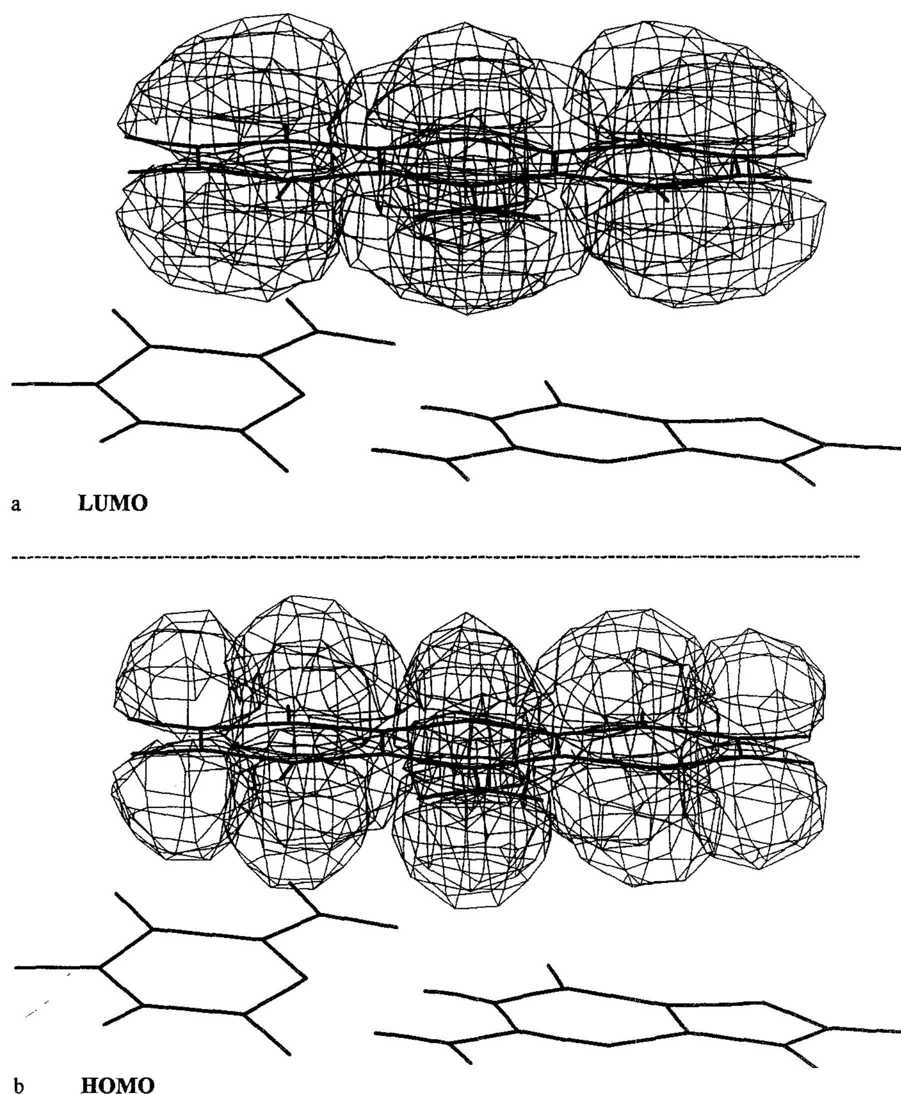



**Fig. 6** LUMO (a) and HOMO (b) of the cytosine-guanine/9-aminoacridine complex showing the threedimensional orbital distribution; no electron transfer is possible because both frontier orbitals are localized exclusively at the 9-aminoacridine subsystem

These theoretical results agree with the report of *D. Sharples* and *J. R. Brown* [32], whose experimental findings indicate that it is the cationic form of the ligand which is responsible for the $\pi,\pi$-charge-transfer interaction with the purine base.

According to our calculations, mitonafide (**6**) is also able to form an electron donor acceptor complex with the purine bases of DNA. It possesses an electron deficient ring system due to the nitro group and the carbonyl oxygens. However, the chromophore is very electron deficient, and in fact mitonafide forms an intramolecular charge transfer complex involving the lone pair of the dimethylamino nitrogen and the chromophor ring system as is evidenced by the bright yellow color of the free base compared to the colorless salt [21].

**Table 2.** AM1 calculated energies of the frontier orbitals (eV)

| subsystem | HOMO-energy | LUMO-energy |
|---|---|---|
| guanine | −8.69 | −0.32 |
| adenine | −8.78 | −0.12 |
| cytosine | −9.41 | −0.15 |
| thymine | −9.61 | −0.29 |
| 9-aminoacridinium/cation | −12.35 | −5.11 |
| 9-aminoacridinin/base | −7.99 | −0.81 |
| hydroquinone | −8.73 | 0.23 |
| benzoquinone | −10.88 | −1.73 |
| quinacrine | −12.10 | −5.17 |
| carboxamide | −12.33 | −5.14 |
| mitonafide | −10.06 | −2.08 |

For the strength of a charge-transfer complex, both the energy difference between the frontier orbitals and the extent of the orbital overlap of the HOMO of a donor with the LUMO of the acceptor are responsible. In Table 2, the energy values of the frontier orbitals of the drug chromophore and the DNA-bases are given. Additionally, the values for hydrochinone and *p*-benzoquinone, which form a stable quinhydrone complex, have been calculated for validation of the method and for comparison.

On the basis of the AM1 calculated values for the energies of the frontier orbitals of the DNA-bases it can be explained why a purine base and not a pyrimidine base is the $\pi$-electron donor in the charge-transfer complex: the pyrimidine bases cytosine and thymine reveal much lower HOMO energy values than the pyrimidine bases, so that a $\pi$-electron transfer from a pyrimidine base to the drug chromophore is energetically not favoured. It is remarkable that the HOMO energy value of adenine is lower than the corresponding value of guanine. This could be a reliable explanation for the experimentally verified favoured intercalation of acridines into $d(CG)_2$-dinucleotides [4–8]. As expected, the LUMO energy values of the acridine cations are much lower than the corresponding energy values of the bases. These results support our suggestions that a charge-transfer interaction with the purine bases of the DNA is only possible for acridinium cations.

## *Conclusion*

The presented results of model building and calculations show the stabilizing effect of hydrogen bonds and of charge-transfer interactions for drug-DNA intercalation complexes on the basis of molecular mechanics and semiempirical molecular orbital calculations in the acridine and benzo[*d*, *e*]isoquinolin-1,3-dione series. The importance of hydrogen bonds for the intercalation process of anthracyclines and of mitoxantrone has been demonstrated in our previous paper [33]. The intercalation complexes of the drugs **4**, **5**, and **6** are additionally stabilized by $\pi,\pi$-electron transfer between a DNA purine base and the electron deficient drug chromophore; this is in agreement with experimental studies for 9-aminoacridines [22, 32].

These two types of binding seem to play a very important role for the intercalative interaction of anticancer drugs. The known DNA intercalators possess either an aliphatic side chain, substituted in most cases with a highly basic amino group which is able to form hydrogen bonds with the hetero atoms of the purine bases, and/or a sufficient electron deficient chromophore which is involved as an electron acceptor in a charge-transfer complex. The electron deficient chromophore is formed by protonation or alkylation of basic heterocycles, as for example in the acridine, phenanthroline [6], or ellipticine [39] series. Other compounds like mitonafide (**6**) or *Gabbay*'s *reporter* molecules of type **7** possess a nitro group which induces electronically the same effect. So we propose that – beside a planar chromophore – a compound must have at least one of these structural features to be an effective DNA-intercalator with pronounced antitumour activity.

Although our model calculations are quite successful in predicting correct complex geometries, they do not reflect the balance of driving forces for intercalation. Moreover, our calculations are not able to consider hydrophobic interactions between drug and DNA bases mainly responsible for the stabilization effect of base-drug stacking *in vitro* and *in vivo* [33].

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*Received August 10, 1995. Accepted (revised) January 30, 1996*