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ORIGINAL PAPER

Theoretical studies of the anti-tumor drug FR900482

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Abstract Hartree-Fock and density functional theory (B3LYP) calculations were applied to the study of the anti-tumor drug FR900482 and some of its analogs. Optimum geometries were obtained and it was found that the most stable conformations feature the N-H bond of the aziridine ring nitrogen "down" and the oxygen bridge and aziridine nitrogen "up". It was also found that the analog containing NH_2 (in place of the -CHO of the natural product) is the most prone to oxidation.

Keywords FR900482 · Oxidation · Hartree · Fock · B3LYP (Density functional theory)

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It seems that a simple name for FR900482 has not been adopted so far because there is still a search for the most stable analog.

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Introduction

A class of highly significant chemotherapeutic agents includes DNA interstrand cross-linking compounds. These chemicals exhibit anticancer and antibacterial properties due to their ability to stop the DNA replication by covalently binding the two strands of DNA. Among these agents, aziridine-containing drugs such as mitomycin C are clinically employed. However, it was found [1] that mitomycin C is myelosuppressive and its activity is associated with cardiotoxicity.

Another aziridine-containing drug, the antitumor, antibiotic FR900482 was isolated from Streptomyces sandaensis No. 6897 by Imanaka et al. [2]. This class of compounds also cross-links DNA and exhibits the same level of activity as mitomycin C [3]. The presence of a hydroxylamine hemiacetal had added attraction for the synthetic chemists [4].

In order to cross-link DNA, these compounds are reductively activated *in vivo*, and a mitosene moiety is formed (5). Due to structural and mechanistic differences between mitomycin C and FR900482, the later does not produce the superoxide radical anion during the reductive activation and does not feature oxidative scission of DNA [5].

The reduction energies of the FR900482 and some of its analogs were reported by us [6].

This work investigates the eventual oxidation of these compounds.

Even though the role of an oxidation to a quinone ring is not clear, we deemed it of interest to investigate the energetics of this oxidation reaction, as dependent on the substituent in different analogs of FR900482. The various compounds studied here correspond to varied groups, -G, taking the place of the aldehydic -CHO group of the natural product at position C3 (conventional numbering; this is

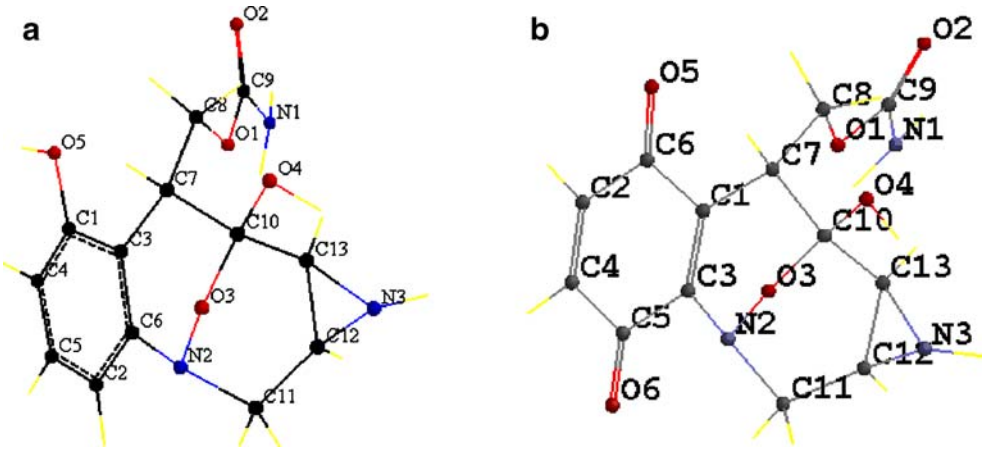

Fig. 1 **a**) Non-oxidized Compound, **b**) Oxidized compound

position C5 for compounds a, and C4 for compound b, according to our computational numbering seen in the Tables and Figs.). The compounds examined here include the parent system of FR900482 (compound 2, G=CHO); compound 3 (G=F); compound 4 (G=CF3); compound 5 (G=NH2); compound 6 (G=OCH_3); compound 7 (G=CH2OH), and compound 8 (G=OCH2OH). Compound 1 features a hydrogen atom instead of the substituents at C5. For these eight systems, calculations were performed for the corresponding phenol, series **a**, and for the derived 2,5-quinone (conventional numbering; 3,6-quinone by our computational numbering), series **b**.

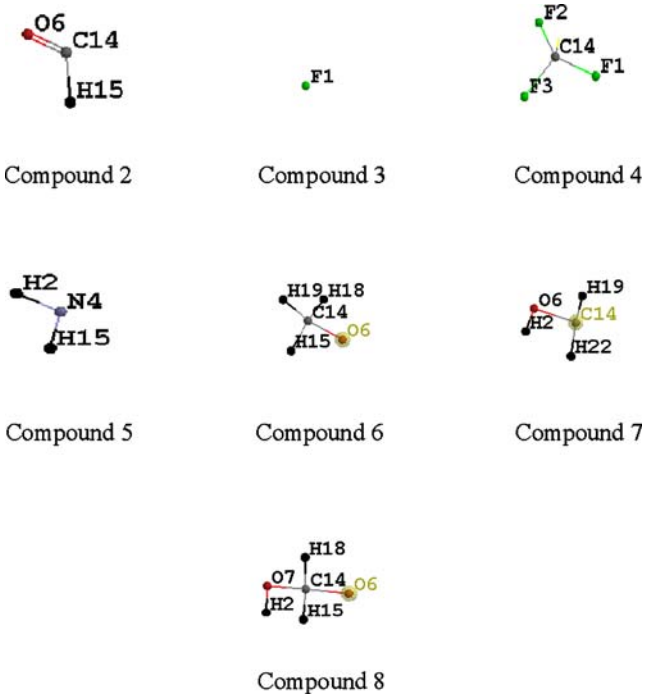

Fig. 2 Substituents of investigated compounds

To this purpose, we apply quantum chemical calculations to FR900482 itself and to some of its analogs.

Methods and results

The Titan [7] program was used to perform Hartree-Fock and density functional theory (at B3LYP level) calculations in order to obtain the energies and the optimum geometrical parameters of FR900482 and some of its analogs which have the aldehydic group replaced by other substituents. In addition, the quinone species of these compounds were also investigated. Figure 1a shows the non-oxidized compound, and Fig. 1b shows the oxidized compound with G=H. Figure 2 shows the different substituents.

The 6–31G** basis set, which sets d orbitals on non-hydrogen atoms and p orbitals on hydrogens, was used for the Hartree-Fock calculations. The density functional theory (DFT) method, B3LYP, also used the 6–31G** basis set.

The compound shown in Fig. 1a represent the lowest energy structures, as determined by the HF/6–31G**calculations. This features the aziridine ring cis-fused and the N-H

Table 1 Energies (au) of the compounds

	Structure a		Structure b	
Compound	HF	B3LYP	HF	B3LYP
1	−1038.63986	−1044.72970	−1112.31426	−1118.71916
2	−1151.36967	−1158.05501	−1225.03813	−1232.03738
3	−1137.49005	−1143.96109	−1211.15701	−1217.94632
4	−1374.25993	−1381.76620	−1447.92773	−1455.74904
5	−1093.67670	−1100.08846	−1167.35824	−1174.08987
6	−1152.52372	−1159.25393	−1226.19535	−1233.24224
7	−1152.53275	−1159.25913	−1226.20908	−1233.24959
8	−1227.39045	−1234.47615	−1301.06165	−1308.46394

Table 2 Solvation energies (kcal mol^{-1}) for the HF/6-31G** and the B3LYP optimized structures b

Compound	Solvation energy	
	HF/6-31G**	B3LYP
1	−15.63	−17.35
2	−15.60	−17.46
3	−13.63	−15.23
4	−12.50	−14.05
5	−18.79	−20.82
6	−14.75	−16.33
7	−18.55	−20.69
8	−17.72	−20.30

hydrogen of the aziridine ring "down". Calculations have shown that the most stable conformations feature the oxygen bridge "up". Figure 1b shows the same structure with the quinone instead of phenol.

Table 1 shows the energies of these structures at both HF/6–31G** and B3LYP/6–31G** levels. Table 2 shows the solvation energies of the compounds [8]. Table 3 shows the energy of the oxidation reaction:

$$Phenol\ species + 1/2(O2) - H2 = Quinone\ species$$

at both HF/6-31G** and B3LYP levels.

Some optimum geometric parameters of the investigated compounds, as obtained by HF/6-31G** calculations are shown in the Supplementary Material.

Discussion

Examining the Supplementary Material, it is interesting to note that the phenol species for compounds 3, 5, 6, 7, and 8 show a longer C5-X (where X is the attached atom of the substituent) bond length than the C4-X bond lengths in the quinone species. This is due to the delocalization of the π electrons on the C-X bond from the quinone ring. In the original compound 2 and in compound 4 the trend is reversed.

Table 3 The Energies (kcal mol^{-1}) of Oxidation Reactions of the Investigated Compounds

Compounds	HF/6-31G**	B3LYP/6-31G**
1	−4.142	−6.234
2	−0.414	−1.785
3	0.527	−3.580
4	0.000	−2.080
5	−8.622	−13.733
6	−2.403	−5.513
7	−5.353	−6.862
8	−2.133	−5.186

As mentioned before, the most stable configuration of the compounds feature the aziridine ring cis-fused, with the hydrogen of the aziridine ring "down". The oxygen bridge is "up". At both calculational levels, configurations with the oxygen bridge "down", the aziridine ring trans-fused or the NH hydrogen of the aziridine ring "up" proved to be higher in energy. These results are in agreement with the fact that the isomer of FR900482 featuring the oxygen bridge "up" exists in the majority of cases [9].

Among the compounds investigated, both at HF/6-31G** and at B3LYP/6-31G** levels, the NH_2-containing analog is the most prone to oxidation. The least prone to oxidation are the FR900482 compound itself (at B3LYP/6-31G** level) and the F- and CF_3-containing analogs, as can be seen from Table 3. As seen in Table 2, the solvation energy of the phenol species is larger than the one of the quinone species [6]. The difference has a negative effect on the oxidation, so the larger it is, the harder it is for the compound to oxidize. The highest difference is for the original compound and for compound 6 (3.48 and 3.85 kcal mol^{-1}, respectively). However, the differences for compounds 3 and 4 which, besides the original compound are the least prone to oxidation are also substantial (2.48 and 2.62 kcal mol^{-1}, respectively). Compound 5 (NH2, which is the most prone to oxidation, exhibits a smaller difference (2.06 kcal mol^{-1}). These are the B3LYP results and the HF results show the same trend.

As shown in previous work [6] the most prone to reduction are, besides the original compound, compounds containing fluorine substituents. Since the NH2 containing compound is more prone to oxidation (which might increase its toxicity) and less prone to reduction (which might allow for increased activity) it might not prove a useful analog. However, it might be beneficial to investigate experimentally the fluorine-containing analogs from the points of view of activity and toxicity.

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