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A correlation study of quinoline derivatives and their pharmaceutical behavior by ab initio calculated NQR parameters

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Summary

In this paper, ab initio calculated NQR parameters for some quinoline-containing derivatives are presented. The calculations are carried out in a search for the relationships between the charge distribution of these compounds and their ability to interact with haematin. On the basis of NQR parameters, π-electron density on the nitrogen atom of the quinoline ring plays a dominant role in determining the ability of quinolines to interact with haematin. This point was confirmed with investigation of Fe^{+3} cation-π quinoline ring interactions in 2- and 4-aminoquinoline. However, our results do not show any preference for those carbon atoms of the quinoline ring which previous reports have noted. In order to calculate the NQR parameters, the electric field gradient (EFG) should be evaluated at the site of a quadrupolar nucleus in each compound. EFGs are calculated by the Gaussian 98 program using the B3LYP/6-31G* level of theory.

Introduction

Nuclear quadrupole resonance spectroscopy (NQR) [1] is a very sensitive technique for the measurement of the electronic charge distribution around quadrupolar nuclei ($I \geq 1$). This method can be used as a probe to obtain information about the environment of a given quadrupolar nucleus and consequently to determine the electronic structure of molecules and complexes. Many compounds have been investigated with this method [2].

Malaria is the most serious parasitic disease in man, both from the point of view of mortality and morbidity and from its world-wide occurrence in tropical and subtropical regions. It is estimated that 300 million people are infected annually, with one to two million deaths [3]. For a long time quinoline containing antimalarial drugs have been mainstays in the treatment of the disease.

Numerous studies have been performed on antimalarial-haematin interactions in both aqueous and non-aqueous solution. Many of the earlier studies concentrated on obtaining spectroscopic evidence for haematin–drug interactions [4–7] and association constants, Ks, were also determined [8].

Until the recent appearance of two publications [9, 10] very little was known of the structural requirement for quinolines capable of strong haematin-binding, although it has been shown earlier that quinoline itself and certain simple amino quinolines (3-, 5-, 6- and 8-aminoquinoline) do not form substantial complexes with haematin [11]. It has now been established that 2- and 4-aminoquinolines have a unique ability to form strong complexes with haematin in aqueous DMSO [10]. The association constant of 4-aminoquinoline in particular, $\log K = 4.49 \pm 0.01$, is comparable with some quinoline antimalarial compounds. For example, introduction of a 7-chloro group in 4-amino-7-chloroquinoline has almost no influence on this interaction ($\log K = 4.38 \pm 0.01$) and alkylation of the amino group also has little influence ($\log K = 4.38 \pm 0.03$ for 4-methylaminoquinoline) [10]. A similar association constant for 4-amino-7-chloroquinoline has also been reported in aqueous solution using titration calorimetry [9]. Moving the

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Table 1. Calculated ^{14}N NQCCs at the B3LYP level and with various basis sets.

	χ_N^{calc} (MHz)					$\chi_N^{\exp}$ (MHz)
	6-31G*	6-31+G*	6-31G**	6-31+G**	6-311+G**	
Pyridine	4.887	4.810	4.894	4.824	5.323	4.88
Pyridazine	5.529	5.471	5.528	5.480	6.102	5.65

chloro group from the 7-position to the 6-position, on the other hand, appears to completely destabilize the complex [9].

The underlying electronic and steric factors controlling the ability of these quinolines to form such complexes with haematin are still poorly understood. In this work, ab initio nuclear quadrupole coupling constant (NQCC) calculations on some quinoline-containing antimalarial drugs are carried out so that a possible relationship between their electronic structure and biological activity could be investigated.

Computational details

Quantum chemical calculations were performed using the Gaussian 98 program [12]. All structures were fully optimized without any restriction. To verify the absolute minimum energy structure, their nature was checked with frequency calculation. The absence of imaginary frequency confirms that all conformations were energy minima and did not correspond to a saddle point. Like in many previous studies on quinoline derivatives [13–15], the B3LYP functional was used, which combines Becke's three-parameter [16] exchange functional with the correlation functional of Lee, Yang and Parr [17, 18]. To examine a proper basis set for EFG calculations, a series of basis sets was considered in calculation of ^{14}N NQCC of two analogous aromatic compounds (pyridine and pyridazine); then the calculated NQCC of the nitrogen ring was compared with those measured experimentally (Table 1). Gas-phase ^{14}N NQCCs of pyridine and pyridazine are 4.88 and 5.65 MHz, respectively [19].

Based on the results of Table 1, the difference between calculated and experimentally measured ^{14}N NQCC at the B3LYP level with the 6-31G* basis set is less than the others and therefore, in this work, ab initio calculations were performed at the B3LYP/6-31G* level to compute the components of the EFG tensor in the principal axis system.

Evaluation of NQCCs

The formulation employed in the evaluation of NQR parameters can be found elsewhere [19]. Briefly, the electric field gradient (EFG) is a traceless, symmetric second-rank tensor whose principal axes are chosen so that its components satisfy $|q_{ZZ}| \geq |q_{YY}| \geq |q_{XX}|$ ($eq_{ij} = \dfrac{\partial^2 V}{\partial i \partial j}$ where $i, j = X, Y$ and Z, e is electron charge and V is the external electronic potential) [20]. The quantities usually determined experimentally are the NQR frequencies, v_Q; these frequencies lead to NQCC(χ) which is given by: $\chi = \dfrac{e^2 Q q_{ZZ}}{h}$, where Q is the nuclear electric quadrupole moment.

Like in many previous studies [2, 21], here we assume that the nuclear quadrupole moments act as a simple constant or scaling parameter, and we do not parameterize them. Among the wide range of $Q(^{14}N)$ and $Q(^{2}H)$ standard values published, we have selected the recent values $Q(^{14}N) = 20.44\ mb$ and $Q(^{2}H) = 2.86\ mb$ reported by Pyykko [22].

Results and discussion

Previous studies on some quinoline derivatives have concluded that 2-aminoquinolines and 4-aminoquinolines (Figure 1; series A) interact with haematin and their association constants were reported [8]. However, when the amino group is placed on the 3, 5, and 6 positions of the quinoline ring (Figure 2; series B), there is no interaction between haematin and these derivatives and consequently they lack treatment effect.

More recently the electrostatic potential surfaces of chloroquine and several chloroquine analogues have been calculated using *ab initio* quantum mechanical methods [9]. That study indicates that the π-electron density at C_8, C_{8a}, C_4 and C_{4a} of the quinoline ring (Figure 3) may play an important role in determining the ability of quinolines to interact with haematin.

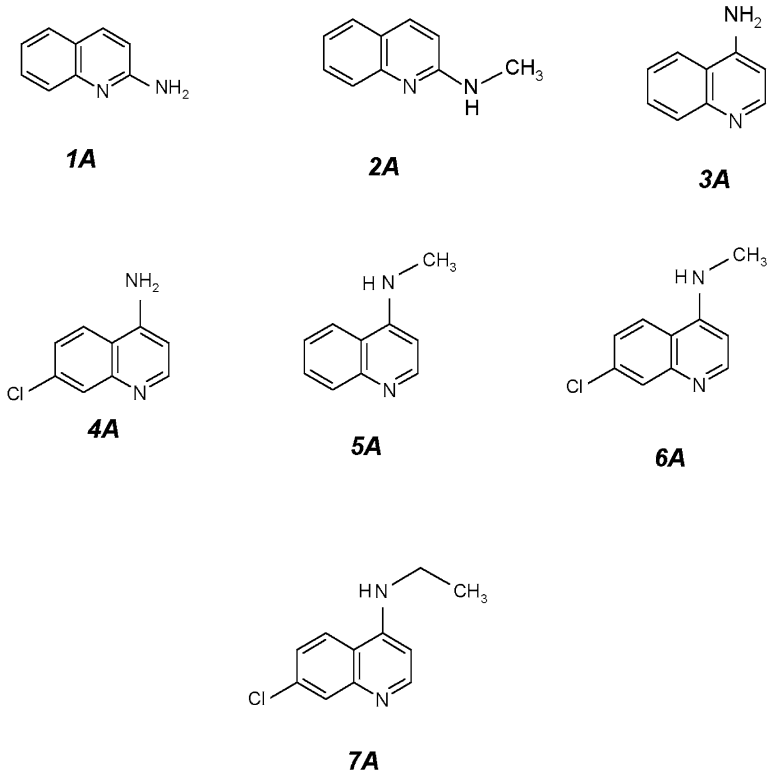

Figure 1. Structures of series A molecules.

Therefore it is expected that the charge density and consequently NQCC of deuteriums connected to these carbons (D_4 and D_8) should be different from the others. The numbering of deuteriums and carbons of the quinoline ring is shown in Figure 3.

The relation between the electronic structure of aminoquinolines and their ability for interaction with haematin can be considered using NQR parameters, because these parameters are highly sensitive to the local charge distribution. For this purpose, the NQR parameters of ^{14}N and ^{2}H were calculated for all compounds. The electric field gradient at the site of quadrupolar nuclei was calculated. The calculated NQCC parameters of ^{2}H and ^{14}N are shown in Tables 2 and 3. It is evident that since the bond properties depend on electrons, it is possible to replace hydrogen atoms by deuterium, assuming no structural changes will occur.

Our results show that NQCCs of the nitrogen atom in the quinoline ring in the B series substantially differ from those of the A series (the mean values of ^{14}N NQCCs in the A and B series are 4.2 and 4.7 MHz, respectively), while the NQCCs of deuteriums in both series are rather the same. In other words, the major difference among molecules in series A and B is the charge density on nitrogen of the quinoline ring. This indicates that the charge density on the nitrogen ring may play an important role in determining the ability of quinolines to interact with haematin. Considering the negative resonance effect of an amino group, when an amino group is placed *ortho* or *para* relative to the nitrogen of the ring, the symmetry of EFG around the nitrogen atom increases. In other words, the effect of the nonbonding electron pair of the nitrogen atom becomes modest and the values of q_{ZZ} and consequently the NQCC of nitrogen decrease. This is evident, since the electric field gradient around a given nucleus arises from charge distribution of the surrounding atoms and the contribution of nonbonding electrons is more than that of bonding electrons. But the larger NQCC of the nitrogen atom in the quinoline ring in the B series indicates that the charge density on the nitrogen atom is less than that of the A series.

Considerable data now support the hypothesis that antimalarial quinolines inhibit parasite growth by binding to haematin [23–25]. Regarding the investigation of the nature of π-π interaction [26], it is the properties of the atoms at the points of intermolecu-

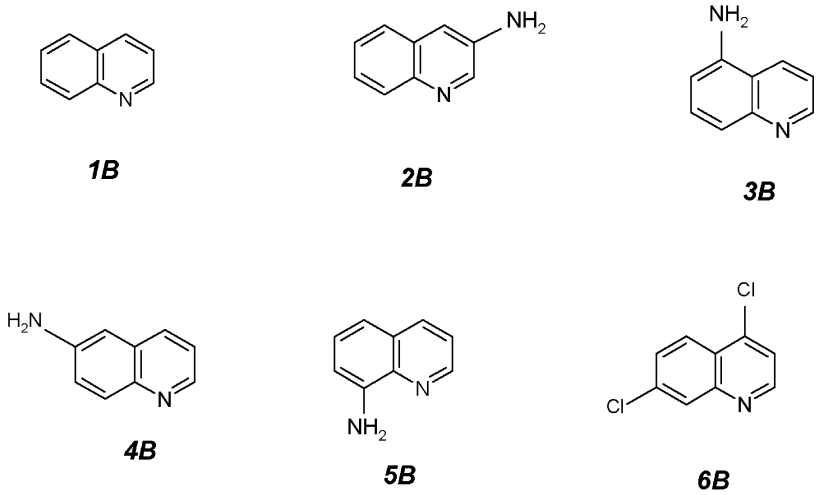

Figure 2. Structures of series B molecules.

Table 2. Calculated values of NQCC of ^{2}H and ^{14}N atoms in series A molecules.

Compound	$\chi(D_2)$ (KHz)	$\chi(D_3)$ (KHz)	$\chi(D_4)$ (KHz)	$\chi(D_5)$ (KHz)	$\chi(D_6)$ (KHz)	$\chi(D_7)$ (KHz)	$\chi(D_8)$ (KHz)	$\chi(^{14}N)$ (MHz)
1A	–	201.032	198.411	199.370	201.497	200.380	201.586	3.880
2A	–	203.006	198.298	199.346	201.606	200.333	201.682	3.803
3A	200.914	201.224	–	201.139	200.885	200.461	200.914	4.245
4A	194.390	201.170	–	201.047	201.525	–	201.651	4.236
5A	194.470	200.335	–	201.178	200.743	200.438	200.991	4.400
6A	194.318	200.320	–	200.871	201.285	–	201.603	4.391
7A	194.331	200.488	–	200.977	201.436	–	201.695	4.362

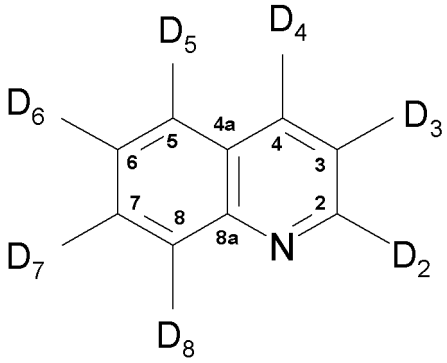

Figure 3. The numbering of deuteriums and carbons of the quinoline ring.

lar contact rather than the overall molecular properties which are important and therefore in this case (the interaction between haematin and quinoline-containing drugs) the charge density on the nitrogen atom is essential. Therefore, the NQCC of the nitrogen ring may be considered as a probe to determine the extent of interaction between haematin and these drugs.

Based on these results, it is expected that each substitute in any position on the quinoline ring that increases the charge density on nitrogen, increases the interaction with haematin and vice versa.

Interaction between iron cation and π-quinoline ring

Cation-π interactions are important from the molecular recognition point of view, as they play a major role in the determination of structures of macromolecules such as drug–receptor interactions. The present study also attempts to advance our understanding of the active site in π-π interaction between 2- and 4- aminoquinolines (series A) and haematin. Thus, to determine the role of aromatic π-electrons of the quinoline ring in series A, two hypothetical complexes, *Fe^{+3}-1A* and *Fe^{+3}-3A*, were designed as a

Table 3. Calculated values of NQCCs of ^{2}H and ^{14}N atoms in series B molecules.

Compound	$\chi(D_2)$ (KHz)	$\chi(D_3)$ (KHz)	$\chi(D_4)$ (KHz)	$\chi(D_5)$ (KHz)	$\chi(D_6)$ (KHz)	$\chi(D_7)$ (KHz)	$\chi(D_8)$ (KHz)	$\chi(^{14}N)$ (MHz)
1B	194.364	201.100	198.209	199.229	200.461	200.238	200.772	4.700
2B	192.701	–	198.862	199.871	200.501	201.190	200.947	4.772
3B	194.434	201.519	199.659	–	200.258	200.366	202.980	4.704
4B	195.432	201.155	198.857	199.711	–	199.390	200.815	4.708
5B	195.365	201.297	198.442	202.091	200.325	201.017	–	4.541
6B	194.090	201.233	–	199.109	200.381	–	201.025	4.653

Table 4. Comparison of NQCCs of ^{2}H and ^{14}N atoms in complexed and uncomplexed cationic models.

Compound	$\chi(D_2)$ (KHz)	$\chi(D_3)$ (KHz)	$\chi(D_4)$ (KHz)	$\chi(D_5)$ (KHz)	$\chi(D_6)$ (KHz)	$\chi(D_7)$ (KHz)	$\chi(D_8)$ (KHz)	$\chi(^{14}N)$ (MHz)
1A	–	201.032	198.411	199.370	201.497	200.380	201.586	3.880
Fe^{+3}-*1A*	–	182.459	181.976	182.459	183.169	179.822	171.154	2.158
$\Delta\chi$	–	18.573	16.435	16.911	18.328	20.558	30.432	1.722
3A	200.914	201.224	–	201.139	200.885	200.461	200.914	4.245
Fe^{+3}-*3A*	182.893	17.943	–	187.725	183.849	183.668	170.853	1.974
$\Delta\chi$	18.021	17.943	–	13.414	17.036	16.793	30.061	2.271

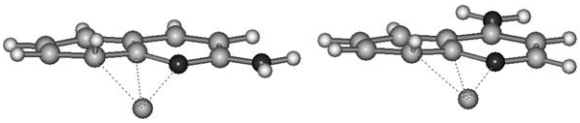

Figure 4. The optimum structures of the Fe^{+3}-*1A* (left) and Fe^{+3}-*3A* (right) complexes.

model. The optimum structures (NIMG=0) of these complexes are shown in Figure 4.

Using calculated components of the EFG tensor, the NQCCs of deuteriums and nitrogen of the ring in these complexes were determined. The calculated NQCCs of quadrupolar nuclei in 2- and 4-aminoquinolines (1A and 3A) and their complexes with Fe^{+3} were compared to find the active site in these antimalarial drugs (Table 4).

Table 4 indicates that $\overline{\Delta\chi}(D)$s are 20.21 and 18.88 KHz for Fe^{+3}-*1A* and Fe^{+3}-*3A* respectively, but $\Delta\chi(^{14}N)$s are 1722 and 2271 KHz for those complexes. These results suggest that the change of charge density on nitrogen is greater than that of deuteriums. Therefore, the interaction between the nitrogen ring and Fe^{+3} is greater than the rest. In other words, the nitrogen ring has a dominant role in the interaction with haematin and its charge density is more affected after complexation.

Conclusions

This study indicates that:
– Calculation of the NQCC parameter of the nitrogen atom in a quinoline ring is a useful tool to compare the behavior of quinoline-containing antimalarial drugs.
– π-electron density at the nitrogen atom of the quinoline ring may play a dominant role in determining the ability of quinolines to interact with haematin.
– Finally, evaluation of charge density and consequently NQCC of the nitrogen ring in Fe^{+3}-quinoline antimalarial complexes could be considered as a characteristic property to investigate the pharmaceutical effects of such drugs.

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