Carbon Chemical Shift Tensor Components in Quinolines and Quinoline *N*-Oxides

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Chemical shift calculations are carried out for the quinoline carbons in 1,8-bis(2-isopropyl-4-quinolyl)-naphthalene, 2-isopropylquinoline, amodiaquine, chloroquine, and quinine and the *N*-oxide of each compound. Ab initio calculations of the isotropic shielding values are in agreement with experimental chemical shifts. The calculations indicate that changes to the principal components of the shielding tensor upon N-oxidation are similar for each compound. Carbons 2, 4, 8, and 10 are largely shielded in each case as the nitrogen is oxidized. For C2, C4, and C10, this shielding is due to a large change in σ_{11} and/or σ_{22}, indicating a change in π-electron density. For C8, the large shielding change is due mainly to a change in σ_{33}, indicating a change in σ-electron density. Upon examination and comparison of the calculated ^{13}C shielding tensor components in the antimalarial drugs versus those in unsubstituted quinolines, it is found that amodiaquine and chloroquine have increased π-electron density in the ring containing the amino side chain and quinine has increased π-electron density in the opposite ring, containing the methoxy substituent.

Introduction

The relationship between chemical shielding and electron density has been known for quite some time.[1−7] Proton chemical shifts can be related to the electron-donating or electron-withdrawing nature of a substituent. This is not generally true for carbon shifts, however, due to the dominant paramagnetic shielding term. Nevertheless, carbon chemical shift tensors can still be used to gain information about the electron density surrounding that particular nucleus. Strub et al.[8] have shown that as the π-electron charge increases in the tropylium cation, benzene, and cyclopentadienide anion series, the chemical shift of the aromatic carbons decreases. They also observed that the in-plane components of the chemical shift tensor, δ_{11} and δ_{22}, are particularly sensitive to the change in π-electron density, while the component perpendicular to the aromatic ring, δ_{33}, is largely unaffected by the π-electron charge.[8]

Due to rotational averaging, only the isotropic component of the chemical shift tensor is measured in solution NMR. The magnitudes of the three principal components can be obtained experimentally from powder patterns, but their orientations can usually only be determined from single-crystal studies.[9] However, ab initio methods can be used to calculate both the orientations and magnitudes of chemical shift tensors. Thus, ab initio calculations provide a way to obtain information about the chemical shift that is often difficult to measure experimentally. Following the results of Strub et al.,[8] this information can then be related to the electron density surrounding specific carbons in an aromatic ring.

In the present work, we calculate chemical shift tensors for the quinoline carbons in the various quinolines shown in Figure 1. 1,8-Bis(2-isopropyl-4-quinolyl)naphthalene (**I**) was recently synthesized.[10] The carbon chemical shifts of this compound and its *N*,*N*′-dioxide (**II**) were reported.[11] The change in chemical shift going from **I** to its *N*,*N*′-dioxide was attributed to an increase in π-electron density at certain carbons in the quinoline ring. In the original paper,[11] chemical shifts of 4-iodo-2-isopropylquinoline and its *N*-oxide were compared to those of **I**. Because chemical shifts of carbons directly bound to iodine are strongly influenced by relativistic effects, requiring more complicated ab initio methods,[12] we have chosen instead to compare the chemical shift changes in a similar pair of compounds, 2-isopropylquinoline (**III**) and its *N*-oxide (**IV**). If exploring shielding tensor components of aromatic carbons can indeed provide insights regarding the electronic framework in

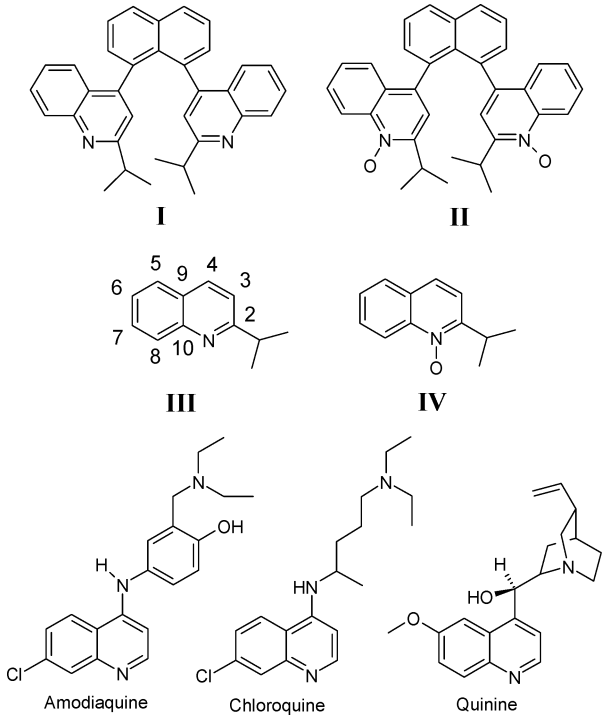

Figure 1. Structures of the compounds studied: **I**, 1,8-bis(2-isopropyl-4-quinolyl)naphthalene; **II**, 1,8-bis(2-isopropyl-4-quinolyl)naphthalene *N*,*N*′-dioxide; **III**, 2-isopropylquinoline; **IV**, 2-isopropylquinoline *N*-oxide. Amodiaquine, chloroquine, and quinine are quinoline-based antimalarial drugs. Quinoline ring carbons are numbered for reference.

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TABLE 1: Calculated and Experimental Chemical Shifts of 1,8-Bis(2-isopropyl-4-quinolyl)naphthalene (I) and 1,8-Bis(2-isopropyl-4-quinolyl)naphthalene *N*,*N*′-Dioxide (II), ppm

	calcd absolute shielding		exptl chemical shift[a]		chemical shift difference	
carbon	**I**	**II**	**I**	**II**	calcd	exptl
2	6.40	20.60	165.5	152.2	−14.20	−13.3
3	56.12	54.37	119.8	119.4	1.75	−0.4
4	25.08	37.89	147.9	137.5	−12.81	−10.4
5	50.88	50.74	125.3	126.4	0.14	1.1
6	52.48	50.50	128.4	127.8	1.98	−0.6
7	49.21	48.54	125.1	129.8	0.66	4.7
8	47.06	54.69	129.4	120.8	−7.63	−8.6
9	47.71	45.68	126.4	128.9	2.03	2.5
10	27.16	31.38	146.7	140.9	−4.21	−5.8

[a] From refs 10 and 11.

TABLE 2: Principal Components of Shielding Tensors for 1,8-Bis(2-isopropyl-4-quinolyl)naphthalene (I), 1,8-Bis(2-isopropyl-4-quinolyl)naphthalene *N*,*N*′-Dioxide (II), 2-Isopropylquinoline (III), and 2-Isopropylquinoline *N*-Oxide (IV)

	I-ring 1				**II**-ring 1				difference			
carbon	σ_{11}	σ_{22}	σ_{33}	isotropic	σ_{11}	σ_{22}	σ_{33}	isotropic	σ_{11}	σ_{22}	σ_{33}	isotropic
2	−88.18	−35.71	141.20	5.77	−44.12	−27.93	134.05	20.67	44.05	7.78	−7.15	14.90
3	−43.43	55.12	153.44	55.04	−40.45	57.19	147.55	54.76	2.98	2.07	−5.89	−0.28
4	−73.01	−10.34	154.71	23.79	−47.08	6.40	154.71	38.01	25.93	16.74	0.00	14.22
5	−54.15	35.47	169.06	50.12	−52.63	36.39	168.95	50.90	1.52	0.92	−0.11	0.78
6	−58.86	44.31	171.46	52.30	−62.27	41.38	172.12	50.41	−3.41	−2.93	0.66	−1.90
7	−62.03	38.88	170.47	49.11	−60.33	34.32	171.69	48.56	1.70	−4.56	1.22	−0.55
8	−50.97	38.50	154.18	47.24	−46.70	29.66	181.09	54.68	4.27	−8.84	26.91	7.45
9	−27.84	−17.39	187.62	47.46	−25.39	−16.41	179.75	45.98	2.45	0.99	−7.88	−1.48
10	−49.83	−28.40	159.86	27.21	−36.18	−11.17	141.65	31.43	13.66	17.23	−18.21	4.23
	I-ring 2				**II**-ring 2				difference			
carbon	σ_{11}	σ_{22}	σ_{33}	isotropic	σ_{11}	σ_{22}	σ_{33}	isotropic	σ_{11}	σ_{22}	σ_{33}	isotropic
2	−84.25	−35.75	141.10	7.03	−44.26	−28.42	134.27	20.53	39.99	7.33	−6.82	13.50
3	−36.72	55.20	153.12	57.20	−41.40	57.60	145.76	53.99	−4.67	2.39	−7.36	−3.21
4	−67.16	−7.51	153.78	26.37	−47.76	5.82	155.26	37.77	19.40	13.33	1.47	11.40
5	−51.50	37.50	168.92	51.64	−53.57	35.88	169.40	50.57	−2.07	−1.62	0.48	−1.07
6	−58.71	45.32	171.35	52.65	−62.00	41.22	172.55	50.59	−3.30	−4.09	1.20	−2.06
7	−61.97	39.40	170.50	49.31	−60.77	34.49	171.86	48.53	1.20	−4.91	1.36	−0.78
8	−51.22	37.93	153.97	46.89	−47.12	29.71	181.50	54.69	4.10	−8.22	27.53	7.80
9	−26.14	−17.31	187.33	47.96	−26.19	−16.36	178.67	45.37	−0.05	0.95	−8.67	−2.59
10	−50.65	−28.00	160.00	27.12	−36.11	−11.31	141.37	31.32	14.54	16.69	−18.63	4.20
	III				**IV**				difference			
carbon	σ_{11}	σ_{22}	σ_{33}	isotropic	σ_{11}	σ_{22}	σ_{33}	isotropic	σ_{11}	σ_{22}	σ_{33}	isotropic
2	−86.66	−33.42	136.58	5.50	−45.07	−26.13	130.03	19.61	41.58	7.29	−6.55	14.11
3	−45.70	62.04	155.22	57.19	−49.26	61.78	150.81	54.44	−3.56	−0.26	−4.41	−2.74
4	−63.27	28.90	157.91	41.18	−39.12	45.73	159.25	55.29	24.15	16.84	1.34	14.11
5	−50.80	42.22	156.53	49.32	−52.02	41.98	158.08	49.35	−1.22	−0.24	1.55	0.03
6	−58.19	41.54	170.55	51.30	−62.00	38.39	171.72	49.37	−3.81	−3.15	1.16	−1.93
7	−64.45	38.69	169.98	48.07	−61.71	34.16	170.92	47.79	2.74	−4.53	0.94	−0.28
8	−50.95	38.73	153.20	46.99	−46.94	31.02	180.35	54.81	4.01	−7.71	27.15	7.82
9	−27.32	−15.53	189.88	49.01	−27.56	−14.15	181.26	46.52	−0.24	1.38	−8.62	−2.49
10	−51.03	−29.30	158.06	25.91	−35.92	−12.91	139.11	30.09	15.11	16.39	−18.95	4.18

these systems, then similar studies can be employed to characterize further systems that involve $\pi-\pi$ interactions. Amodiaquine, chloroquine, and quinine are quinoline-based antimalarial drugs. These drugs are believed to function by binding to heme and preventing hemozoin formation in the digestive vacuole of the parasite.[13] Electronic properties of these drugs, which can be elucidated by studying the components of chemical shift tensors, may be related to the binding between the drugs and heme.

Computational Details

All calculations were performed using the Gaussian 98 program[14] on an SGI Origin 2000 workstation (Silicon Graphics, Inc.; Mountain View, CA) with four processors. The structures for 1,8-bis(2-isopropyl-4-quinolyl)naphthalene, 2-isopropylquinoline, amodiaquine, chloroquine, quinine, and the corresponding *N*-oxide for each compound were geometry optimized using the B3LYP[15,16] functional and a 6-31G[17] basis set. Shielding tensors were calculated at the optimized geometries using GIAO[18] with the B3LYP functional and a 6-311G(2d, 2p)[19] basis set.

Results and Discussion

Table 1 presents the calculated isotropic shielding of each quinoline carbon in 1,8-bis(2-isopropyl-4-quinolyl)naphthalene, and 1,8-bis(2-isopropyl-4-quinolyl)naphthalene *N*,*N*′-dioxide, along with the experimental values from refs 10 and 11. Carbon numbers refer to those shown in Figure 1. Experimentally, only one peak is observed for each quinoline carbon, so the calculated values are an average over the two quinoline rings in the static optimized structure. The experimental shifts for each compound,

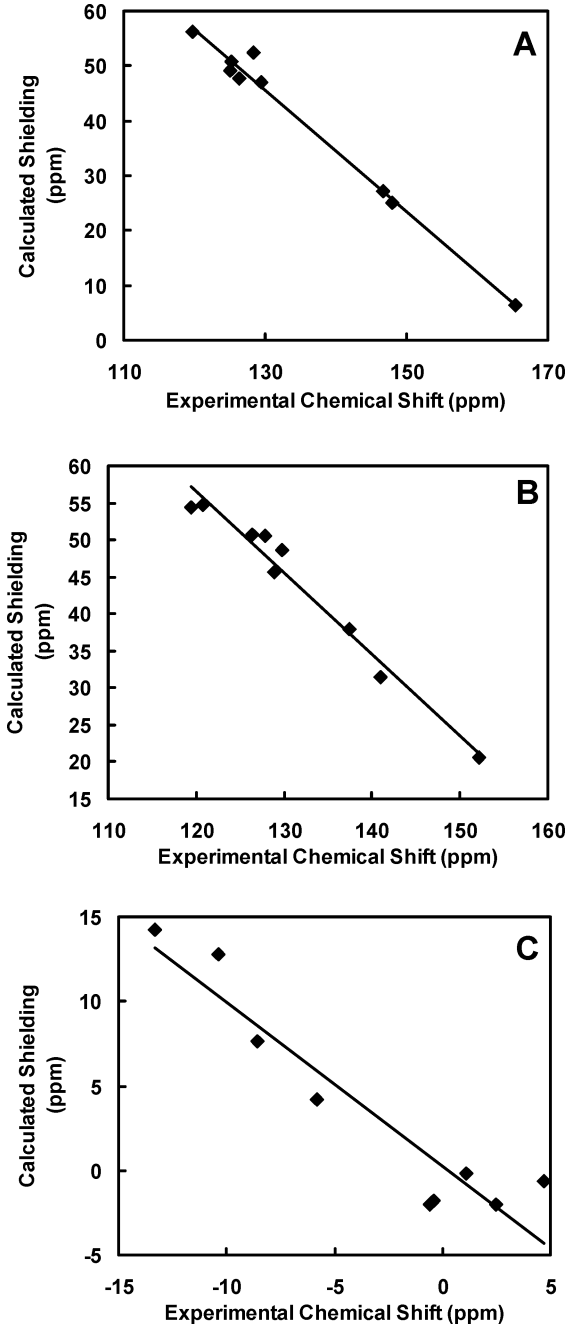

Figure 2. Comparison of experimental chemical shifts and calculated absolute isotropic shielding values for 1,8-bis(2-isopropyl-4-quinolyl)-naphthalene and 1,8-bis(2-isopropyl-4-quinolyl)naphthalene *N*,*N*′-dioxide. (A) 1,8-Bis(2-isopropyl-4-quinolyl)naphthalene (**I**), slope = −1.10, $R^2 = 0.98$. (B) 1,8-Bis(2-isopropyl-4-quinolyl)naphthalene *N*,*N*′-dioxide (**II**), slope = −1.10, $R^2 = 0.97$. (C) Difference between **I** and **II**, slope = −0.97, $R^2 = 0.89$.

as well as the changes to the quinoline carbon chemical shifts upon N-oxidation, are well reproduced by the calculations. The calculated shielding versus experimental chemical shift is plotted in Figure 2 for each case: **I**, **II**, and the difference between the two compounds. Linear regression lines for these plots have slopes between −0.97 and −1.10 and R^2 values between 0.89 and 0.98. The agreement between calculation and experiment is quite good. This agreement allows us to study elements of the shielding tensor with confidence that the calculations are probably consistent with experiment.

The three principal components of the shielding tensor for each quinoline carbon of 1,8-bis(2-isopropyl-4-quinolyl)naphthalene, 2-isopropylquinoline, and their corresponding *N*-oxides are presented in Table 2. The individual tensor components, as well as the differences in the tensor components upon N-oxidation, show similar trends for each quinoline ring of **I** and for 2-isopropylquinoline. Thus, the isolated 2-isopropylquinoline is a good model for the N-oxidation of the bis-quinolyl compound. The changes in chemical shielding of the quinoline ring carbons in **I** are not significantly influenced by the presence of the other quinoline ring or by the naphthalene ring bound to C4.

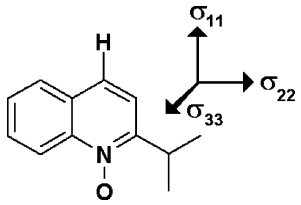

Figure 3. Orientation of the principal components of the chemical shift tensor, shown here for C4 of 2-isopropylquinoline *N*-oxide. σ_{11} is in the plane of the quinoline ring and radial to the ring (e.g., for protonated carbons σ_{11} is oriented along the C−H bond), σ_{22} is tangential to the quinoline ring, and σ_{33} is coming out of the paper toward the viewer, perpendicular to the plane of the quinoline ring.

The principal axis system for these quinolines is oriented as in Figure 3, with σ_{11} in the plane of the quinoline ring and oriented in a radial direction. The intermediate component σ_{22} is oriented tangentially to the quinoline ring, and σ_{33} is perpendicular to the plane of the quinoline ring. This is in agreement with tensor orientations obtained previously from single-crystal studies of other aromatic carbons[20] and from calculations of carbon chemical shift tensors in substituted naphthalenes.[21] Because σ_{33} is perpendicular to the quinoline plane, it is not significantly affected by the π-electron density.[8,20,22] On the other hand, σ_{11} and σ_{22} are in the plane of the quinoline ring, so changes in π-electron density should be manifested mostly in changes to σ_{11} and σ_{22}.[8,22] In the case of the compounds considered in Table 2, the carbons that experience a large isotropic chemical shift change upon N-oxidation are C2, C4, C8, and C10. For C2 (ortho to the nitrogen), this large change in the isotropic shift is due mainly to a large change in σ_{11}. Upon N-oxidation, the increase in σ_{11} is approximately 40−44 ppm in each case, while σ_{22} and σ_{33} increase and decrease, respectively, by less than 8 ppm, leading to an increase in the isotropic shielding of 13−15 ppm. C4 (para to the nitrogen) also experiences an increase in isotropic shielding between 11 and 15 ppm. For this carbon, the large change is due to σ_{11} and σ_{22}. The σ_{11} and σ_{22} components are shielded by 13−26 ppm, while σ_{33} is shielded by less than 2 ppm. C10, also ortho to the nitrogen, experiences a change in all of the principal tensor components. The σ_{11} component becomes more shielded by approximately 14 ppm, σ_{22} is more shielded by approximately 17 ppm, and σ_{33} is deshielded by approximately 19 ppm. The change in σ_{33} is opposite in sign compared to the changes in σ_{11} and σ_{22}, and thus the isotropic value is shielded by only 4 ppm, as σ_{33} partially cancels effects from σ_{11} and σ_{22}. C8, which is two bonds removed from the nitrogen, also experiences a large increase in isotropic shielding (between 7 and 8 ppm), but in this case the isotropic change is due mainly to σ_{33}. The σ_{33} component increases by around 27 ppm, while σ_{11} increases by only 4 ppm and σ_{22} decreases by only about 8 ppm.

Changes in carbon chemical shift due to substituent effects have been shown to correlate with the $2p_z$ electron densities.[23] Carbons that are one and three bonds away from the nitrogen would be expected to experience a change in π-electron density

TABLE 3: Principal Components of Shielding Tensors for Quinoline-Based Antimalarials

	amodiaquine				amodiaquine *N*-oxide				difference			
carbon	σ_{11}	σ_{22}	σ_{33}	isotropic	σ_{11}	σ_{22}	σ_{33}	isotropic	σ_{11}	σ_{22}	σ_{33}	isotropic
2	−87.08	22.5	137.97	24.46	−42.25	41.36	122.75	40.62	44.84	18.86	−15.22	16.16
3	−18.79	68.7	175.20	75.04	−28.93	63.91	168.74	67.91	−10.14	−4.80	−6.45	−7.13
4	−58.21	22.6	135.59	33.35	−31.85	43.10	134.19	48.48	26.36	20.42	−1.40	15.13
5	−43.18	50.2	171.37	59.48	−45.51	47.95	169.40	57.28	−2.33	−2.31	−1.97	−2.20
6	−48.83	42.5	151.78	48.49	−53.02	38.60	152.17	45.92	−4.19	−3.92	0.39	−2.57
7	−65.60	35.9	103.26	24.55	−62.57	30.39	102.13	23.32	3.04	−5.59	−1.13	−1.23
8	−40.59	37.7	137.84	45.01	−36.20	32.89	162.11	52.93	4.39	−4.90	24.27	7.92
9	−9.45	0.65	183.32	58.17	−15.07	0.16	174.21	53.10	−5.62	−0.49	−9.11	−5.07
10	−50.21	−28.10	149.16	23.62	−35.65	−9.27	134.72	29.93	14.56	18.84	−14.44	6.32

	chloroquine				chloroquine *N*-oxide				difference			
carbon	σ_{11}	σ_{22}	σ_{33}	isotropic	σ_{11}	σ_{22}	σ_{33}	isotropic	σ_{11}	σ_{22}	σ_{33}	isotropic
2	−88.65	22.84	137.54	23.91	−43.68	40.88	122.73	39.98	44.97	18.04	−14.80	16.07
3	−9.07	71.25	174.73	78.97	−11.36	67.08	171.78	75.83	−2.30	−4.16	−2.95	−3.14
4	−55.00	3.19	141.40	29.86	−33.60	20.83	141.41	42.88	21.40	17.64	0.02	13.02
5	−43.33	51.45	173.50	60.54	−45.07	49.33	172.66	58.97	−1.74	−2.12	−0.85	−1.57
6	−46.37	45.81	151.86	50.44	−50.83	41.67	152.32	47.72	−4.46	−4.14	0.45	−2.72
7	−64.08	38.41	102.76	25.70	−61.41	32.56	101.71	24.28	2.67	−5.85	−1.06	−1.41
8	−40.00	37.85	137.54	45.13	−36.36	31.40	161.95	52.33	3.64	−6.45	24.41	7.20
9	−4.94	1.90	182.91	59.96	−9.33	4.30	175.00	56.66	−4.39	2.39	−7.91	−3.30
10	−48.59	−27.24	149.63	24.60	−34.23	−9.05	136.43	31.05	14.36	18.19	−13.20	6.45

	quinine				quinine *N*-oxide				difference			
carbon	σ_{11}	σ_{22}	σ_{33}	isotropic	σ_{11}	σ_{22}	σ_{33}	isotropic	σ_{11}	σ_{22}	σ_{33}	isotropic
2	−81.36	27.53	140.60	28.92	−38.69	45.96	123.53	43.60	42.67	18.43	−17.07	14.67
3	−45.74	52.98	177.06	61.43	−50.26	53.91	171.68	58.44	−4.52	0.93	−5.39	−2.99
4	−53.93	18.17	156.99	40.41	−22.58	39.96	156.95	58.11	31.35	21.79	−0.04	17.70
5	−5.97	66.84	159.09	73.32	−8.12	65.28	159.54	72.23	−2.15	−1.56	0.45	−1.09
6	−66.66	−2.30	107.09	12.71	−68.73	−3.87	106.25	11.22	−2.07	−1.57	−0.84	−1.49
7	−36.01	44.36	173.24	60.53	−30.62	41.82	173.89	61.70	5.39	−2.53	0.65	1.17
8	−59.01	26.49	154.02	40.50	−52.53	22.26	178.02	49.25	6.47	−4.24	24.00	8.75
9	−23.93	−11.83	183.59	49.28	−24.65	−11.87	172.54	45.34	−0.71	−0.03	−11.05	−3.93
10	−43.70	−25.03	156.39	29.22	−31.70	−2.41	138.41	34.77	12.00	22.62	−17.98	5.54

when the nitrogen is oxidized, due to resonance effects. On the other hand, carbons that are two bonds away from the nitrogen feel the effects of oxidation mainly through the σ framework. Thus the large change in chemical shift for C4 is due mainly to a change in π-electron density as the nitrogen is oxidized, while the change in C8 is due to a change in σ-electron density. C2 and C10 should experience a change in both the σ- and π-electron density, being only one bond removed from the nitrogen. Although the isotropic changes for C2 and C10 are dominated by changes to σ_{11} and σ_{22}, there is still some change to the σ_{33} component in each case. In both C2 and C10, the change to σ_{33} is opposite in sign to that of σ_{11} and σ_{22}, indicating that there is a decrease in σ-electron density and an increase in π-electron density as the quinoline nitrogen is oxidized.

A similar calculation was carried out for amodiaquine, chloroquine, and quinine (shown in Figure 1). These compounds have been shown to have utility as antimalarial drugs. Amodiaquine and chloroquine are substituted 7-chloroquinolines, and quinine is a 6-methoxyquinoline. The principal components of the shielding tensors calculated for the three drugs and for their *N*-oxides are presented in Table 3. The differences in the principal components upon oxidation show the same trends as those for the 1,8-bis(2-isopropyl-4-quinolyl)naphthalene and 2-isopropylquinoline. C2, C4, C8, and C10 are largely shielded upon oxidation of the quinoline nitrogen. In the case of C2, C4, and C10 this large isotropic difference is due mostly to changes in σ_{11} and σ_{22}, while for C8 the difference comes mainly from a large change in σ_{33}.

Comparing the isotropic chemical shifts of the unoxidized form of the three drugs may provide insight into properties that may influence the potency of antimalarial drugs. In Figures 4 and 5, the isotropic shielding and the three principal components of the shielding tensor are plotted against the carbon number. In Figure 4, the shielding values for quinine are compared to those of a quinoline ring bearing no substituents for reference, and in Figure 5, shielding values for amodiaquine and chloroquine with the quinoline nitrogen protonated are compared to those for a protonated quinoline ring. At physiologically relevant pH (5.2−5.6),[24] amodiaquine[25] and chloroquine[26] are expected to have the quinoline nitrogen protonated, while that of quinine[26] is not. From Figure 4, it is evident that σ_{33} is sensitive to changes in the σ-electronic structure. The only carbon for which the σ_{33} component of quinine substantially differs from that of the quinoline ring is C6, which bears the methoxy substituent. A similar trend is seen in Figure 5 for the σ_{33} component of amodiaquine and chloroquine. The carbons that are substantially deshielded relative to the protonated quinoline ring are C7, which bears the chloro substituent, C4, which bears the amino side chain, and to a lesser extent C6 and C8, ortho to the carbon bearing the chlorine.

The σ_{11} component of the shielding tensor is expected to be sensitive to changes in π-electron density. This can be seen in Figures 4 and 5 as well. In Figure 4, C5 and C7 have σ_{11} components that are significantly shielded relative to those of the unsubstituted quinoline ring. C5 and C7 are ortho to the methoxy substituent of quinine and thus experience increased π-electron density due to the resonance electron-donating effect of this substituent. In Figure 5, the σ_{11} component of amodiaquine and chloroquine is shielded relative to that of the quinoline ring for C3 and C9. These carbons are ortho to the amino side chain at C4. Unlike the case of quinine, for these drugs the amino side chain appears to have more of an effect

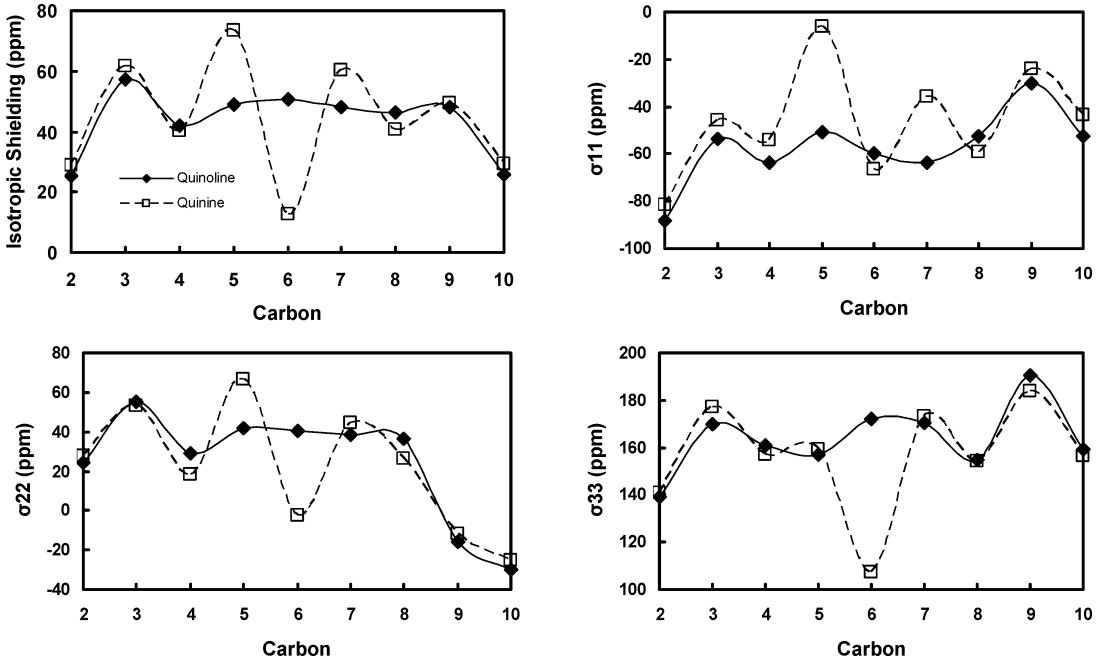

Figure 4. Absolute isotropic shielding and tensor components, σ_{11}, σ_{22}, and σ_{33} for each carbon of quinine and an unsubstituted quinoline ring.

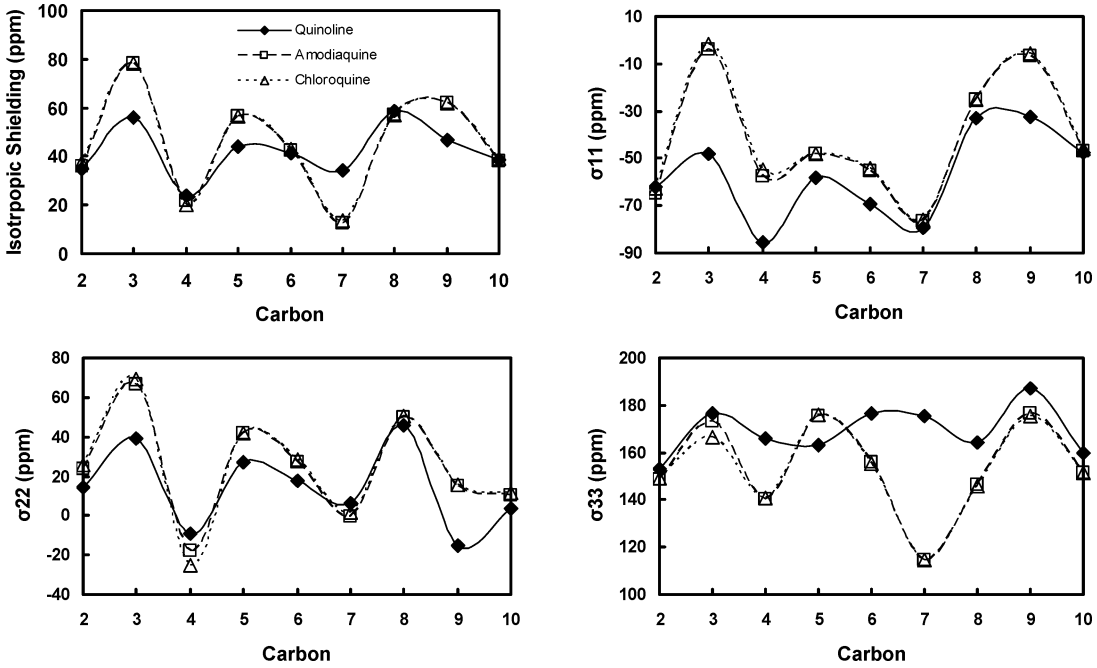

Figure 5. Absolute isotropic shielding and tensor components, σ_{11}, σ_{22}, and σ_{33} for each carbon of amodiaquine, chloroquine, and an unsubstituted quinoline ring with the quinoline nitrogen protonated.

on the π-electronic structure of the quinoline ring than does the chloro substituent.

The σ_{22} component is tangential to the quinoline ring, so σ_{22} will demonstrate changes in both the σ- and π-electron density at each carbon. This can be seen in Figure 4 for quinine; C5 is shielded due to an increase in π-electron density, and C6 is deshielded due to a decrease in σ-electron density from the methoxy substituent at C6. In Figure 5, σ_{22} is shielded at C3 and C9 relative to that of the quinoline ring. The data in Figures 4 and 5 indicate that in amodiaquine and chloroquine there is an increase in π-electron density in the ring containing the amino side chain, whereas for quinine there is an increase in π-electron density in the opposite ring.

The oscillatory nature of the plots in Figures 4 and 5 indicates that the π-electron density is not distributed evenly over the quinoline ring in the drugs. Instead, alternating carbons have more or less electron density. The plots for the unsubstituted quinoline rings are less oscillatory. Figure 6 is a graphical representation of the π-electron distribution in the amodiaquine, chloroquine, and quinine quinoline rings, as demonstrated by the shielding in σ_{11}. In this figure, the size of each carbon is proportional to σ_{11}, with larger spheres representing more shielded carbons. The nonuniform π-electron distribution seen in Figure 6 probably plays a role in the ability of these drugs to bind to heme.

Conclusions

Chemical shift tensors have been used to examine the change in π-electron density of the aromatic carbon atoms of several

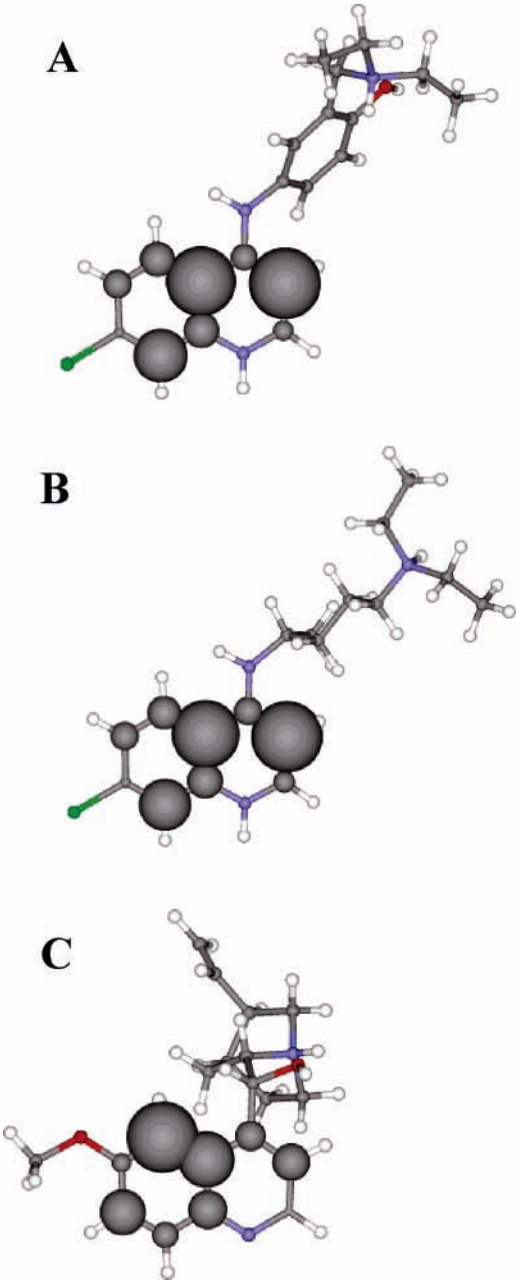

Figure 6. Graphical representation of π-electron density, as suggested by the principal shielding component σ_{11}, in quinoline carbons of (A) amodiaquine, (B) chloroquine, and (C) quinine. The size of each quinoline carbon is proportional to σ_{11}, with larger spheres representing more shielded carbons, corresponding to greater π-electron density. Note that data are not shown for the quinoline nitrogen.

quinolines when the nitrogen is oxidized. Experimental isotropic shieldings and shielding changes upon oxidation were shown to be consistent with experimental chemical shifts for 1,8-bis-(2-isopropyl-4-quinolyl)naphthalene and 1,8-bis(2-isopropyl-4-quinolyl)naphthalene *N*,*N*′-dioxide. It was shown that the changes in the principal components of the carbon shielding tensors were similar for 2-isopropylquinoline and for 1,8-bis-(2-isopropyl-4-quinolyl)naphthalene, indicating that changes in electron density at the quinoline carbons are not significantly influenced by the presence of the central naphthalene ring in the latter.

Carbons three bonds removed from the nitrogen were shown to experience large changes in electron density due to resonance effects, carbons two bonds removed generally experienced only small changes due to inductive effects, while carbons adjacent to the nitrogen experienced both resonance and inductive effects. These results are consistent with previous observations involving substituent effects on the chemical shift in substituted benzenes.[2] The changes to the principal shielding components when the quinoline nitrogen is oxidized followed the same pattern for all of the compounds studied. The various substituents on the quinoline rings of the antimalarial drugs and bis-quinolyl compound did not significantly affect the changes in electron density upon oxidation of the quinoline nitrogen.

Principal components of the chemical shielding tensors were also used to examine the difference in electron density at the quinoline ring among a series of antimalarial drugs. From the σ_{11} shielding values, it was seen that the methoxy substituent leads to an increase in π-electron density at C5 and C7 for quinine and that the amino substituent leads to an increase in π-electron density at C3, C4, and C9 in amodiaquine and chloroquine. Compared to unsubstituted quinoline rings, all three drugs demonstrated increased or decreased π-electron density on alternating quinoline carbons. Egan et al. have examined structure−function relationships for various substituted quinolines in terms of their in vitro antiplasmodial activity (IC_{50}), ability to inhibit β-hematin formation, and strength of binding to heme.[27] These parameters were related to the Hammett constant (σ) and lipophilicity constant (π) for various substituents at the 7-position of *N*,*N*-diethyl-(4-quinolyl)-1,2-ethanediamine.[28] The π-electron density at various carbons on the quinoline ring, as examined through the σ_{11} component of the chemical shielding tensor, is another structural parameter that may prove advantageous to consider along with the Hammett and lipophilicity constants in a structure−activity relationship among quinoline antimalarials.

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