

Crystal and Molecular Structure of 1,1'-Azo-2-phenylimidazo[1,2-a]-pyridinium Dibromide: a New Curariform Agent

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The structure of the title compound, a powerful selective, neuromuscular blocking agent has been determined by a three-dimensional X-ray analysis. Crystals are monoclinic, space-group $P2_1/c$, with lattice parameters $a = 9.15(1)$, $b = 12.05(1)$, $c = 12.61(1)$ Å, $\beta = 121.90(3)^\circ$, and $Z = 2$. The structure was solved by the heavy-atom method and refined by least-squares calculations to R 0.112 for 1698 reflections. The molecule consists of two identical halves joined by a 2-tetrazene link across a centre of symmetry. Phenyl rings are inclined at 47.5° to the rest of the molecule.

THE belief¹ that an interquaternary distance of 12.5 Å is necessary for optimum neuromuscular blocking activity has been refuted by X-ray studies on the potent steroid derivative pancuronium bromide² where the measured distance is 11.08 Å, and the estimated distance of 9.7 Å in the similarly active compound diallylbis(nortoxiferine). Chemical studies on (+)-tubocurarine³ have shown this to be a monoquaternary compound, as is the recently reported steroid derivative conessine ethiodide (stercuronium).⁴ That some conformational requirement may be necessary for effective neuromuscular blockade is suggested by the X-ray structure of acetylcholine⁵ where the $\overset{+}{N}-C-C-O-$ grouping is synclinal (gauche), the conformation held by twelve other related molecules which have been studied crystallographically.⁶ Some of these molecules participate in cholinergic transmission systems. N.m.r. studies on acetylcholine bromide in aqueous (D₂O) solutions⁷ show that this conformation is still held in solution.

The title compound is one of a new class of bisquaternary compounds⁸ which possess potent, selective, short-acting curariform activity in several species.⁹ Some conclusions drawn from the present X-ray study have been published.¹⁰

EXPERIMENTAL

Crystals prepared by the method of ref. 8 were recrystallised from water, m.p. 253—255° (decomp.).

Crystal Data.—[C₂₆H₂₀N₆²⁺]2Br⁻, $M = 576.3$. Monoclinic, $a = 9.15(1)$, $b = 12.05(1)$, $c = 12.61(1)$ Å, $\beta = 121.90(3)^\circ$, $U = 1180(3)$ Å³, $D_c = 1.62$, $Z = 2$, $D_m = 1.63$ (by flotation), $F(000) = 576$. $\mu = 51.0$ cm⁻¹ for Cu-K α radiation, $\lambda = 1.5418$ Å. Space group $P2_1/c$ (C_{2h}^2 , No. 14).

Single crystal Weissenberg equi-inclination photographs, and the multiple-film technique were used for data collection. Crystals smaller than the optimum size (0.4 mm) were used, and no corrections for absorption were applied. The intensities of 1424 reflections were estimated visually

[†] 1 Å = 10⁻¹ nm.

[‡] Final observed and calculated structure factors are listed in Supplementary Publication No. SUP 20538 (14 pp., 1 microfiche). For details see Notice to Authors No. 7 in *J. Chem. Soc. (A)*, 1970, Issue No. 20.

¹ L. S. Goodman and A. Gilman, 'The Pharmacological Basis of Therapeutics', 4th edn., Macmillan, New York, 1970, p. 605.

² D. S. Savage, A. F. Cameron, G. Ferguson, C. Hannaway, and I. R. Mackay, *J. Chem. Soc. (B)*, 1971, 410.

³ A. J. Everett, L. A. Lowe, and S. Wilkinson, *Chem. Comm.*, 1970, 1021.

from layers $hk0-9$ and corrected for Lorentz and polarisation factors. The intensities of 896 reflections were likewise visually estimated from layers $h'0-5l'$, the axis of rotation being b' in the related $P2_1/n$ unit cell, where $a' = a$, $b' = b$, $c = 11.00(1)$ Å, $\beta' = 102.85(3)^\circ$. These intensities, after correction, were re-indexed by use of the transformation $h = -h'$, $k = k'$, $l = h' + l'$ to conform to the $P2_1/c$ cell. Layer scale values were obtained by direct comparison of common reflections from the two sets, which were then merged affording 1698 independent reflections, having a merging R factor [$\sum(F_i - F_{\text{mean}})/\sum F_{\text{mean}}$] of 0.169.

The position of the bromide ion was easily found from a three-dimensional Patterson function. An electron-density synthesis phased on this atom, and with 124 poorly phased reflections omitted, revealed the other atom positions. A few spurious peaks, possibly water molecules, were eliminated by full-matrix least-squares refinement with isotropic temperature factors, after which R was 0.16. When all atoms were given anisotropic temperature factors, further refinement reduced R to 0.112. A weighting scheme $1/w = 1 + [F_o - a/b]^2$ with $a = 1000$ and $b = 1250$ was included in all but the initial cycles of refinement.

The absence of any suitable sites for solvent molecules was demonstrated by a Fourier programme¹¹ and a difference-Fourier map did not indicate any chemically reasonable positions for the hydrogen atoms. Each hydrogen atom was positioned on the median line through its bonded carbon atom and in the plane of this carbon atom and its two linked neighbours, assuming C-H 1.08 Å.

RESULTS AND DISCUSSION

The final atomic co-ordinates together with their standard deviations are listed in Table 1 and the interatomic distances and valency angles calculated from these co-ordinates are in Table 2.[‡] Table 3 lists the anisotropic temperature factors. The atomic numbering scheme is shown in Figure 1 and the hydrogen atoms are numbered as the atoms to which they are attached.

⁴ W. Hesse and J. Wieriks, *Biochem. Pharmacol.*, 1971, **20**, 1213 (*Chem. Abs.*, **75**, 86,977g).

⁵ F. G. Canepa, P. Pauling, and H. Sorum, *Nature*, 1966, **210**, 907.

⁶ M. Sundaralingam, *Nature*, 1968, **217**, 35.

⁷ C. C. J. Culvenor and N. S. Ham, *Chem. Comm.*, 1966, 537.

⁸ E. E. Glover and M. Yorke, *J. Chem. Soc. (C)*, 1971, 3280.

⁹ L. Bolger, R. T. Brittain, D. Jack, M. R. Jackson, L. E. Martin, J. Mills, D. Poynter, and M. B. Tyers, *Nature*, 1972, **238**, 354.

¹⁰ D. J. Pointer, J. B. Wilford, and D. C. Bishop, *Nature*, 1972, **239**, 332.

¹¹ D. J. Watkin, *Acta Cryst.*, 1972, *A*, **28**, 33.

TABLE 1

Fractional atomic co-ordinates with their estimated standard deviations in parentheses

Atom	<i>x</i>	<i>y</i>	<i>z</i>
Br	0.4769(2)	0.0427(1)	0.1925(1)
N(1)	0.8910(13)	0.1237(8)	0.4535(10)
C(2)	0.8936(15)	0.2237(10)	0.3955(11)
C(3)	0.7853(16)	0.2933(12)	0.4027(12)
N(4)	0.7168(12)	0.2386(8)	0.4658(9)
C(5)	0.6061(16)	0.2804(12)	0.4966(13)
C(6)	0.5582(16)	0.2130(11)	0.5599(13)
C(7)	0.6227(16)	0.1038(11)	0.5938(12)
C(8)	0.7368(16)	0.0635(10)	0.5613(12)
C(9)	0.7828(15)	0.1328(11)	0.4955(11)
N(10)	1.0069(12)	0.0404(8)	0.4719(9)
C(11)	0.9979(16)	0.2412(10)	0.3400(12)
C(12)	1.0940(17)	0.3387(12)	0.3698(15)
C(13)	1.1916(19)	0.3601(16)	0.3140(17)
C(14)	1.2019(18)	0.2800(16)	0.2414(16)
C(15)	1.1066(20)	0.1804(15)	0.2103(15)
C(16)	1.0030(19)	0.1612(12)	0.2611(14)

TABLE 2

Interatomic distances (Å) and angles (°) with estimated standard deviations in parentheses

(a) Bonded distances

N(1)–C(2)	1.416(17)	C(7)–C(8)	1.395(20)
N(1)–C(9)	1.352(18)	C(8)–C(9)	1.390(19)
N(1)–N(10)	1.388(16)	N(10)–N(10')	1.249(15)
C(2)–C(3)	1.338(20)	C(11)–C(12)	1.395(21)
C(2)–C(11)	1.467(19)	C(11)–C(16)	1.403(22)
C(3)–N(4)	1.410(19)	C(12)–C(13)	1.423(25)
N(4)–C(5)	1.357(19)	C(13)–C(14)	1.367(27)
N(4)–C(9)	1.375(18)	C(14)–C(15)	1.411(26)
C(5)–C(6)	1.363(21)	C(15)–C(16)	1.415(25)
C(6)–C(7)	1.413(21)		

(b) Interbond angles

C(2)–N(1)–C(9)	110.4(1.1)	C(7)–C(8)–C(9)	118.4(1.3)
C(2)–N(1)–N(10)	118.8(1.1)	N(1)–C(9)–N(4)	106.0(1.1)
C(9)–N(1)–N(10)	130.3(1.1)	N(1)–C(9)–C(8)	134.5(1.3)
N(1)–C(2)–C(3)	106.4(1.2)	N(4)–C(9)–C(8)	119.5(1.2)
N(1)–C(2)–C(11)	124.2(1.2)	N(1)–N(10)–N(10')	111.1(1.0)
C(3)–C(2)–C(11)	129.4(1.3)	C(2)–C(11)–C(12)	117.9(1.3)
C(2)–C(3)–N(4)	108.1(1.2)	C(2)–C(11)–C(16)	120.9(1.3)
C(3)–N(4)–C(5)	127.5(1.2)	C(12)–C(11)–C(16)	121.2(1.4)
C(3)–N(4)–C(9)	109.0(1.1)	C(11)–C(12)–C(13)	119.3(1.5)
C(5)–N(4)–C(9)	123.5(1.2)	C(12)–C(13)–C(14)	119.1(1.7)
N(4)–C(5)–C(6)	117.8(1.3)	C(13)–C(14)–C(15)	122.3(1.8)
C(5)–C(6)–C(7)	121.3(1.4)	C(14)–C(15)–C(16)	118.5(1.6)
C(6)–C(7)–C(8)	119.6(1.3)	C(11)–C(16)–C(15)	119.3(1.5)

(c) Some intramolecular non-bonded distances

N(1) ... N(4)	2.179(16)	N(4) ... N(10)	3.542(16)
N(1) ... N(10')	2.177(16)	N(4) ... N(10')	4.027(16)
N(1) ... N(1')	3.430(16)	N(4) ... N(1')	5.396(16)
N(1) ... N(4')	5.396(16)	N(4) ... N(4')	7.481(16)

(d) Intermolecular non-bonded distances

Br ... N(1)	3.600	Br ... C(13 ^{III})	5.293
Br ... C(2)	3.941	Br ... C(14 ^{III})	4.066
Br ... C(3)	4.026	Br ... C(15 ^{III})	3.886
Br ... N(4)	3.779	Br ... C(6 ^{IV})	4.517
Br ... C(5)	4.417	Br ... C(7 ^{IV})	3.716
Br ... C(6)	4.752	Br ... Br ^v	6.159
Br ... C(7)	4.560	Br ^v ... C(6 ^I)	4.517
Br ... C(8)	3.957	Br ^v ... C(7 ^I)	3.716
Br ... C(5 ^I)	3.890	Br ^v ... C(8 ^I)	4.639
Br ... C(6 ^I)	3.652	Br ^v ... C(13 ^{III})	3.782
Br ... C(3 ^{II})	3.630	Br ^v ... C(14 ^{III})	4.094
Br ... C(5 ^{II})	3.786		

Roman numerals refer to equivalent positions relative to the reference molecule at *x*, *y*, *z*:

I <i>x</i> , $\frac{1}{2} - y$, $z - \frac{1}{2}$	IV $1 - x$, $-y$, $1 - z$
II $1 - x$, $y - \frac{1}{2}$, $\frac{1}{2} - z$	V $1 - x$, $y + \frac{1}{2}$, $\frac{1}{2} - z$
III $x - 1$, <i>y</i> , <i>z</i>	

TABLE 3

Anisotropic temperature factors (Å²) *

	$10^3 U_{11}$	$10^3 U_{22}$	$10^3 U_{33}$	$2 \times 10^3 U_{12}$	$2 \times 10^3 U_{23}$	$2 \times 10^3 U_{13}$
Br	63(1)	45(1)	67(1)	-19(1)	-10(1)	87(1)
N(1)	51(5)	38(5)	47(6)	18(9)	11(9)	65(10)
C(2)	39(6)	34(6)	42(7)	12(10)	0(11)	40(11)
C(3)	51(7)	56(8)	45(8)	20(12)	2(13)	64(12)
N(4)	42(5)	42(5)	43(6)	8(9)	0(9)	50(9)
C(5)	38(6)	57(8)	56(9)	9(11)	-2(14)	51(12)
C(6)	43(6)	49(7)	59(9)	10(11)	-3(14)	63(13)
C(7)	37(6)	53(7)	45(8)	0(11)	7(13)	42(11)
C(8)	44(6)	40(6)	41(7)	0(10)	-5(11)	48(11)
C(9)	34(6)	51(7)	40(7)	3(11)	5(12)	46(11)
N(10)	42(5)	39(5)	45(6)	20(9)	22(9)	47(9)
C(11)	42(6)	37(6)	42(7)	6(10)	17(11)	36(11)
C(12)	43(7)	52(8)	72(10)	2(12)	18(14)	67(14)
C(13)	52(8)	85(12)	87(12)	30(17)	73(21)	86(17)
C(14)	43(7)	98(13)	76(11)	30(16)	85(21)	63(15)
C(15)	56(9)	87(11)	59(10)	47(17)	28(17)	64(16)

* In the form: $T = \exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{32}hkb^{*c^*} + 2U_{12}hka^{*b^*} + 2U_{13}hla^{*c^*})]$.

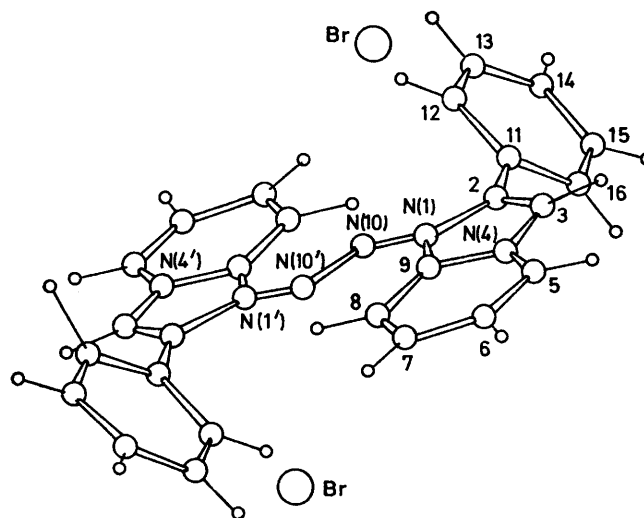


FIGURE 1 Molecular structure viewed along the *a* axis. Carbon atoms have numbers only; other elements have chemical symbols, and small circles represent hydrogen atom positions

The molecule consists of two identical halves related by a centre of symmetry located on the N(10)–N(10') bond

TABLE 4

Least-squares planes given in the form $lX' + mY' + nZ' = d$ where *X'*, *Y'*, and *Z'* are co-ordinates in Å. Deviations (Å) of atoms from the planes are given in parentheses

Plane (1):* Azoimidazopyridinium ring system

$$0.7385X + 0.3837Y + 0.5545Z = 8.00$$

[N(10) -0.012, N(1) 0.086, C(9) 0.081, C(8) 0.082, C(7) 0.017, C(6) -0.053, C(5) -0.069, N(4) 0.001, C(3) -0.020, C(2) 0.022]

Plane (2): Phenyl ring

$$-0.4219X + 0.4386Y - 0.7935Z = -5.76$$

[C(11) 0.003, C(12) -0.022, C(13) 0.031, C(14) -0.020, C(15) 0.000, C(16) 0.009]

* The centroid of this plane was the centre of symmetry at 1, 0, 1/2. Atoms related to those given by inversion in this centre of symmetry were included in calculation of the plane equation and deviate from the plane by equal amounts, opposite in sign, from those given.

(Figure 1). The imidazo[1,2-*a*]pyridinium ring system is nearly planar, and both halves of the molecule connected by the 2-tetrazene linkage deviate only slightly from planarity (Table 4). The atoms of the phenyl ring are reasonably close to the least-squares best plane (Table 4), but the molecule as a whole is non-planar since the phenyl and the imidazo[1,2-*a*]pyridinium rings are mutually inclined at an angle of 47.5° (Figure 1). The angle is large in comparison with those of 7.6, 10.9,

form with bond lengths 1.39(1) and 1.25(1) Å for the N=N=N bonds, and the bond angle N(1)-N(10)-N(10') is 111(1)°. Very few crystal structures having tetrazene chains have been reported but that of 1,4-bis-(*N*-ethyl-1,2-dihydrobenzthiazol-2-ylidene)tetrazene¹⁶ has the chain in the *trans*-*N*-*trans*-*trans*-*N* form with N=N 1.257(4), N-N 1.400(4) Å, and N-N=N 110.6(3)°. None of these values differ markedly from those quoted for similar systems; the N=N bond length in aromatic

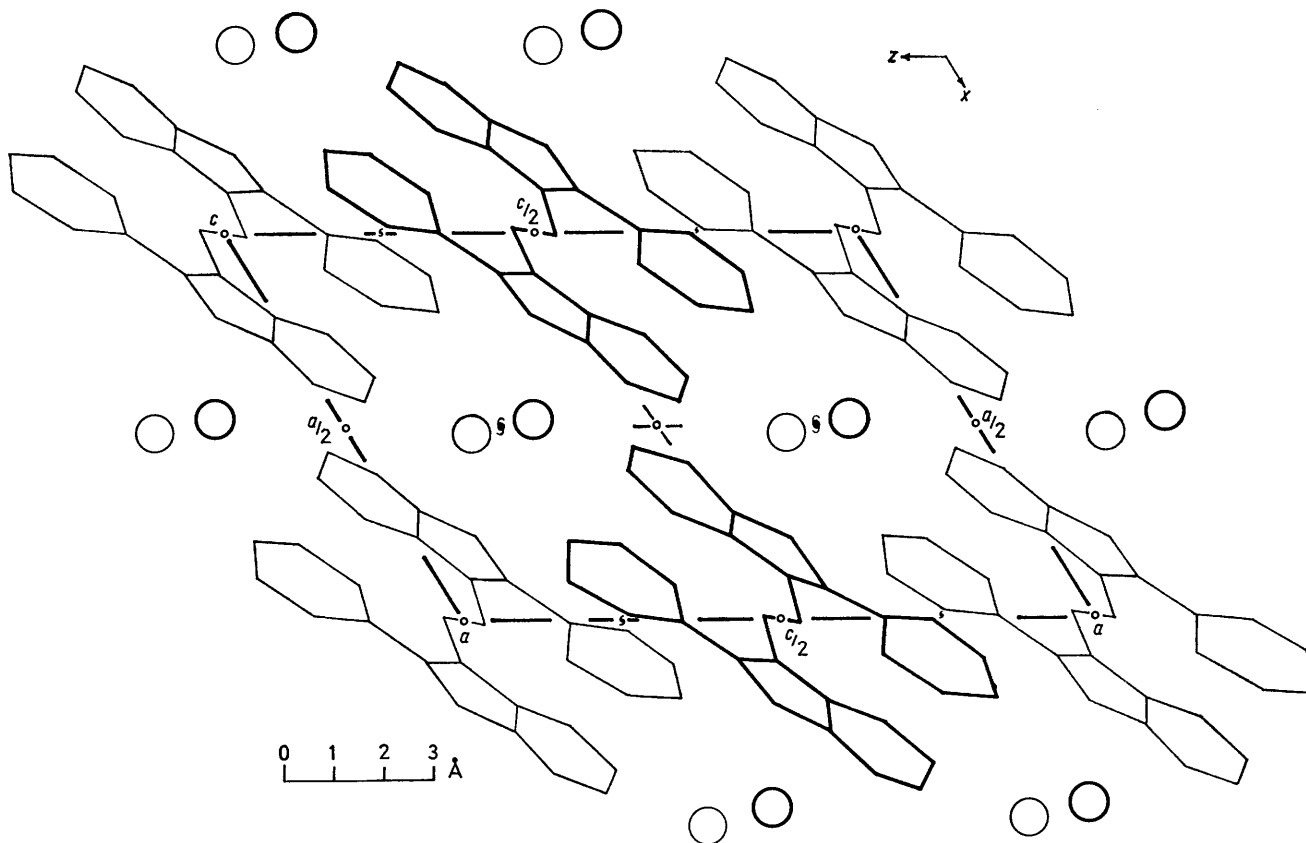


FIGURE 2 The molecular packing viewed along the *b* axis

and 6.9° in the comparable *s*-triphenyltriazine,¹² although the hydrocarbon systems biphenyl¹³ (0°) and binaphthyl¹⁴ (68°) show a wide variation.

The bond length of 1.47(2) for the C(2)-C(11) bond agrees well with the corresponding value in *s*-triphenyltriazine¹² [1.475(7)] and in 2-(1-imidazol-2-yl)benzophenone¹⁵ [1.49(3)] and is not dissimilar to the 1,1'-bond in biphenyl [1.497(2)] and binaphthyl [1.475(5) Å].

The tetrazene chain >N=N=N< is in the *N*-*trans*-*N*

azo-compounds ranges from 1.243 to 1.276 Å¹⁷ and the N=N=N bond angles from 111 to 113°^{17,18} while the N-N bond length in salicylaldehyde azine¹⁹ is 1.407(4) Å. The fused pyridinium ring has bond lengths close to the average values quoted in ref. 20, and to values recently reported for 8a-azonia-3,4-diazaphenanthrene cation²¹ and anhydro-7-methyl-1-phenyl-3-phenylimino-*s*-triazolo[4,3-*a*]pyridinium zwitterion.²² The imidazole ring

¹⁷ H. Hope and D. Victor, *Acta Cryst.*, 1969, *B*, **25**, 1849, and references therein.

¹⁸ C. J. Brown, *Acta Cryst.*, 1966, **21**, 146; **21**, 153.

¹⁹ G. Arcovito, M. Bonamico, A. Domenicano, and A. Vacigato, *J. Chem. Soc. (B)*, 1969, 733.

²⁰ *Chem. Soc. Special Publ.*, No. 18, 1965.

²¹ J. A. Elix, M. Sterns, W. S. Wilson, and R. N. Warrener, *Chem. Comm.*, 1971, 426.

²² M. W. Partridge, R. J. Grout, and T. J. King, *Chem. Comm.*, 1971, 898.

¹² A. Damiani, E. Giglio, and A. Ripamonti, *Acta Cryst.*, 1965, **19**, 161.

¹³ G. B. Robertson, *Nature*, 1961, **191**, 593; **192**, 1026.

¹⁴ K. A. Kerr and J. M. Robertson, *J. Chem. Soc. (B)*, 1969, 1146.

¹⁵ J. S. McKechnie and Iain C. Paul, *J. Chem. Soc. (B)*, 1968, 984.

¹⁶ R. Allmann, *Acta Cryst.*, 1967, **22**, 246.

has much more localised bonds C(9)-N(4) and C(9)-N(1) [1.38(2) and 1.35(2) Å] which are comparable with those in pyrrole²⁰ (1.383 Å); C(3)-N(4) and C(2)-N(1) [1.42(2)] are slightly longer as in imidazole²³ itself while the C(2)-C(3) bond is short [1.34(2) Å] as in imidazole (1.356 Å).

The closer approach of the anion to N(1) than to N(4) [N(1) ··· Br 3.60, and N(4) ··· Br 3.78 Å] suggests that the quaternary centre may be closer to N(1). The values agree well with that calculated (3.43 Å) from the sum of the ionic radii $\overset{+}{\text{N}}\text{H}_2$ (1.48) and Br⁻ (1.95 Å).²⁴

The packing diagram (Figure 2) shows that the anions

²³ S. Martinez-Carrera, *Acta Cryst.*, 1966, **20**, 783. See also F. P. van Ramoortere and F. P. Boer, *J. Chem. Soc. (B)*, 1971, 976.

pack in layers parallel to *b*. The atoms of one layer have *x* co-ordinates close to *a*/2, although they are not in contact [Table 2(d)]. Molecules at *x*, *y*, *z* and *x*, $\frac{1}{2} - y$, *z* - $\frac{1}{2}$ pack together with the plane of the phenyl ring at *x*, *y*, *z* nearly parallel with that of the heterocyclic rings of the other molecule. The anion position prevents coplanarity of the phenyl rings with the rest of the molecule, but it seems reasonable that the molecule would be nearly planar in solution.

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²⁴ L. Pauling, 'The Nature of the Chemical Bond,' 3rd edn., Cornell University Press, Ithaca, New York, 1960, pp. 514, 518.