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Acta Cryst. (1990). B**46**, 860–862

Structure and Conformational Features of 9-(4-Diethylaminophenyl)acridine

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(*Received* 8 *February* 1990; *accepted* 9 *August* 1990)

Abstract

$C_{23}H_{22}N_2$, $M_r = 326{\cdot}44$, triclinic, $P\bar{1}$, $a = 10{\cdot}525\ (7)$, $b = 10{\cdot}538\ (9)$, $c = 9{\cdot}177\ (2)$ Å, $\alpha = 105{\cdot}42\ (5)$, $\beta = 95{\cdot}96\ (6)$, $\gamma = 63{\cdot}57\ (6)°$, $V = 878{\cdot}5$ Å^3, $Z = 2$, $D_x = 1{\cdot}234$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, $\mu = 0{\cdot}52$ mm^{-1}, $F(000) = 348$, $T = 294$ K, final $R = 0{\cdot}056$ for 1299 observed reflections. The acridine ring is highly planar. The 9-phenyl substituent is oriented [dihedral angle 74·5 (3)°] in a similar manner to the analogous 5-phenyl structures. Extensive molecular-orbital (MNDO) calculations on the model 9-phenylacridine system have confirmed that this geometry is energetically favoured, and have revealed the shape of the energy surface for rotation about the C—C bond connecting the phenyl ring and acridine chromophore.

Introduction

A large number of acridines substituted at the 9-position have been studied with respect to potential DNA-binding affinity and anti-tumour activity (Baguley, Denny, Atwell & Cain, 1981; Baguley & Finlay, 1988). In particular, 9-arylamino substitution has resulted in a number of biologically active and DNA-intercalative compounds, with the 3′-methoxy-4′-methanesulfonanilide derivative ('amsacrine') having outstanding activity.

We have previously shown that direct attachment of a phenyl group to the aromatic acridine chromophore, without an intervening amino linkage, results in compounds that retain DNA-binding activity (Abraham, Neidle & Acheson, 1987; Abraham, Agbandje, Neidle & Acheson, 1988). The present paper extends this type of linkage to the 9-position. In particular, we examine the conformational properties of the 9-phenylacridine series with respect to the linking C—C bond.

Experimental

The title compound was synthesized by reflux condensation of 9(10*H*)-acridone, phosphoryl chloride and *N*,*N*-diethylaniline using a literature procedure (Albert, 1966). Recrystallization from petroleum (313–333 K fraction) afforded brownish-yellow plates, m.p. 470·5–471 K (literature 470 K). A crystal of dimensions 0·20 × 0·20 × 0·15 mm was used. The space group was $P\bar{1}$ (No. 2, triclinic). Cell dimensions were obtained from least-squares refinement of 25 2θ values measured on an Enraf–Nonius CAD-4 diffractometer; graphite-monochromated Cu $K\alpha$ radiation (λ = 1·54178 Å) was used. Intensity data were collected using an ω–2θ scan technique and a maximum scan time of 120 s per reflection, for $1{\cdot}5 \le \theta \le 60{\cdot}0°$ and $-13 \le h \le 13$, $-17 \le k \le 17$, $0 \le l \le 11$; 2603 unique reflections were measured of which 1299 had $I \ge 2\sigma(I)$. Three intensity standard reflections were monitored every 200 reflections of X-ray exposure during the data collection and showed no statistically significant crystal decay. An empirical *DIFABS* absorption correction was applied (Walker & Stuart, 1983); minimum and maximum absorption correction factors of 0·91 and 1·15, respectively, were used. The structure was solved by direct methods with *MULTAN*82 (Main *et al.*, 1982) and refined by full-matrix least-squares techniques on *F*. H-atom positions were generated from geometric considerations and were kept fixed during the refinement. The final R was 0·056 and wR was 0·064 with $w = 1/[\sigma^2(F) + 0{\cdot}04(F)^2]$. The maximum Δ/σ was 0·01 and the e.s.d. of observation of unit weight was 1·81; the maximum and minimum electron density levels in

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0108-7681/90/060860-03$03.00

Table 1. *Non-H-atom positional and equivalent isotropic parameters, with e.s.d.'s in parentheses*

	x	y	z	B_{eq} (Å²)*
C1	0·5405 (4)	0·2022 (4)	0·1732 (5)	3·9 (1)
C1*A*	0·4106 (4)	0·2256 (4)	0·2303 (4)	3·3 (1)
C2	0·5619 (5)	0·1751 (5)	0·0224 (5)	5·0 (1)
C3	0·4545 (5)	0·1689 (5)	−0·0794 (5)	5·6 (2)
C4	0·3271 (5)	0·1934 (5)	−0·0295 (5)	5·0 (1)
C4*A*	0·3000 (4)	0·2240 (4)	0·1264 (5)	3·7 (1)
C5	0·0091 (4)	0·3022 (4)	0·3627 (6)	4·8 (1)
C5*A*	0·1471 (4)	0·2749 (4)	0·3164 (5)	3·8 (1)
C6	−0·0206 (4)	0·3282 (5)	0·5088 (6)	5·3 (1)
C7	0·0804 (4)	0·3290 (5)	0·6202 (5)	4·9 (1)
C8	0·2113 (4)	0·3035 (4)	0·5829 (5)	4·0 (1)
C8*A*	0·2494 (4)	0·2770 (4)	0·4289 (4)	3·3 (1)
C9	0·3843 (4)	0·2501 (4)	0·3855 (4)	3·1 (1)
N10	0·1696 (3)	0·2474 (3)	0·1687 (4)	4·2 (1)
C11	0·4978 (4)	0·2474 (4)	0·4983 (4)	3·0 (1)
C12	0·4971 (4)	0·3738 (4)	0·5941 (5)	3·6 (1)
C13	0·6035 (4)	0·3697 (4)	0·6971 (5)	3·6 (1)
C14	0·7157 (4)	0·2381 (4)	0·7103 (4)	3·1 (1)
C15	0·7167 (4)	0·1107 (4)	0·6128 (5)	3·5 (1)
C16	0·6104 (4)	0·1163 (4)	0·5094 (5)	3·6 (1)
N17	0·8230 (3)	0·2340 (3)	0·8133 (4)	4·0 (1)
C20	0·8237 (4)	0·3665 (5)	0·9113 (5)	4·6 (1)
C21	0·7310 (5)	0·4265 (5)	1·0472 (6)	6·2 (2)
C22	0·9279 (4)	0·0954 (5)	0·8430 (5)	4·4 (1)
C23	1·0567 (5)	0·0215 (5)	0·7438 (7)	6·2 (2)

*The equivalent isotropic thermal parameter, for atoms refined anisotropically, is defined by the equation: $1{\cdot}333(a^2B_{11} + b^2B_{22} + c^2B_{33} + bcB_{23}\cos\alpha + acB_{13}\cos\beta + abB_{12}\cos\gamma)$.

Table 2. *Intramolecular bond lengths* (Å) *and bond angles* (°), *with e.s.d.'s in parentheses*

C1—C2	1·358 (5)	C8—C7	1·344 (5)
C1—C1*A*	1·409 (4)	C8*A*—C9	1·398 (4)
C2—C3	1·403 (5)	C9—C11	1·493 (4)
C3—C4	1·354 (5)	C11—C12	1·384 (4)
C4—C4*A*	1·410 (5)	C11—C16	1·384 (4)
C4*A*—C1*A*	1·429 (5)	C12—C13	1·381 (4)
C4*A*—N10	1·361 (4)	C13—C14	1·390 (4)
C1*A*—C9	1·412 (4)	C14—C15	1·398 (4)
C5—C5*A*	1·437 (5)	C14—N17	1·389 (4)
C5—C6	1·336 (5)	C15—C16	1·381 (4)
C5*A*—C8*A*	1·415 (4)	N17—C20	1·448 (4)
C5*A*—N10	1·332 (4)	N17—C22	1·463 (4)
C6—C7	1·397 (5)	C20—C21	1·480 (5)
C8—C8*A*	1·430 (4)	C22—C23	1·487 (5)

C2—C1—C1*A*	120·9 (4)	C1*A*—C9—C11	120·5 (3)
C1—C2—C3	120·2 (4)	C8*A*—C9—C11	121·7 (3)
C2—C3—C4	120·9 (4)	C4*A*—N10—C5*A*	116·3 (3)
C3—C4—C4*A*	120·6 (4)	C9—C11—C12	122·3 (3)
C4—C4*A*—C1*A*	118·8 (4)	C9—C11—C16	120·6 (3)
C4—C4*A*—N10	117·4 (4)	C12—C11—C16	117·1 (3)
C1*A*—C4*A*—N10	123·8 (3)	C11—C12—C13	121·6 (3)
C1—C1*A*—C4*A*	118·6 (3)	C12—C13—C14	121·5 (3)
C1—C1*A*—C9	123·2 (3)	C13—C14—C15	116·8 (3)
C4*A*—C1*A*—C9	118·2 (3)	C13—C14—N17	121·5 (3)
C5*A*—C5—C6	120·2 (4)	C15—C14—N17	121·7 (3)
C5—C5*A*—C8*A*	118·4 (4)	C14—C15—C16	121·2 (3)
C5—C5*A*—N10	116·8 (4)	C11—C16—C15	121·8 (3)
C8*A*—C5*A*—N10	124·7 (4)	C14—N17—C20	121·6 (3)
C5—C6—C7	121·6 (4)	C14—N17—C22	120·9 (3)
C8*A*—C8—C7	120·7 (4)	C20—N17—C22	117·0 (3)
C5*A*—C8*A*—C8	118·4 (3)	N17—C20—C21	113·9 (3)
C5*A*—C8*A*—C9	119·1 (3)	N17—C22—C23	114·2 (3)
C8—C8*A*—C9	122·5 (3)	C6—C7—C8	120·6 (4)
C1*A*—C9—C8*A*	117·8 (3)		

the final difference Fourier map were 0·4 and −0·3 e Å^{-3}, respectively.

Atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV). Calculations were performed on a VAX 11/750 computer using the *SDP* system (Frenz, 1980).

MNDO Hamiltonian calculations were performed on an Alliant FX40/3 computer using the *AMPAC* semi-empirical molecular-orbital package (Quantum Chemistry Program Exchange No. 506, Department of Chemistry, Indiana University) with corrected parameter values for nitrogen (Stewart, 1989). Graphics visualization and modelling was carried out using the *GEMINI*1.02 (Beveridge, 1990) molecular-modelling program on a Silicon Graphics 4D-20G workstation.

Discussion

Atomic coordinates and equivalent isotropic thermal parameters for non-H atoms are given in Table 1* and Table 2 contains intramolecular bond lengths and angles. The molecular geometry is shown in Fig. 1.

The acridine chromophore is planar within the limits of experimental error ($\chi^2 = 324$), with the maximum deviation from the least-squares plane, defined by the 14 ring atoms, being 0·036 (4) Å. The two outer rings of the chromophore are inclined at angles of 2·3 (4) and 1·5 (4)°, respectively, to the central heterocyclic ring. The substituent 9-phenyl ring is non-coplanar with the acridine; the values of the C1*A*—C9—C11—C12 and C8*A*—C9—C11—C12 torsion angles are 104·9 (5) and −74·9 (5)°, and the C9—C11 bond length is 1·493 (4) Å. The dihedral angle between the planes defined by the acridine and phenyl components is 74·5 (3)°. The bond geometry in this structure does not differ significantly, within the limits of experimental error, from that found in

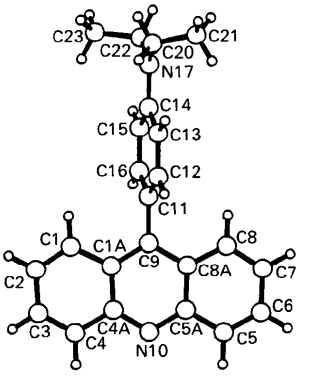

Fig. 1. Molecular structure of the molecule.

* Tables of structure factors, anisotropic thermal parameters for non-H atoms, calculated H-atom coordinates, least-squares planes and additional refinement details have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53475 (43 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

other acridines (Abraham, Neidle & Acheson, 1987; Jones & Neidle, 1975), or 9-aminoacridine (Talacki, Carrell & Glusker, 1974).

The orientation of the 9-phenyl ring with respect to the acridine nucleus is similar to that in two analogous 5-phenylacridine structures, where torsion angles about the sp^2–sp^2 bond linking the two aromatic systems are 114·5 (9) and 104·5 (6)° (Abraham, Neidle & Acheson, 1987). The C(phenyl)—C(acridine) bond lengths in these molecules [1·483 (8) and 1·491 (6) Å, respectively] are also similar. The implication of a degree of torsional flexibility in the 5-phenyl series can presumably be ascribed to the asymmetric steric hindrance from H atoms at C6 and N10.

MNDO calculations on geometry-optimized 9-phenylacridine, where a self-consistent field was achieved with final convergence to ≤ 4 J mol^{-1} and a final energy gradient of ≤ 10 J mol^{-1} Å^{-1}, reveal that rotation about the C9—C11 bond is feasible despite steric interference between the *ortho*-H atoms H12 and H16 on the phenyl ring and H1 and H8 of the acridine. Calculations of enthalpies of formation (ΔH_f) for 9-phenylacridine (Fig. 2) show that the torsion angle in the crystal structure [75·1 (5)°, equivalent by symmetry to 104·9 (5)°] is energetically favoured since the base of the enthalpic well is broad. Indeed, this conformation is only 3·7 kJ mol^{-1} higher in energy (enthalpy) than that for the optimal, fully orthogonal structure. The bond length determined for C9—C11 in the optimized molecule using this procedure (1·4915 Å) is also similar to that found in the crystal structure.

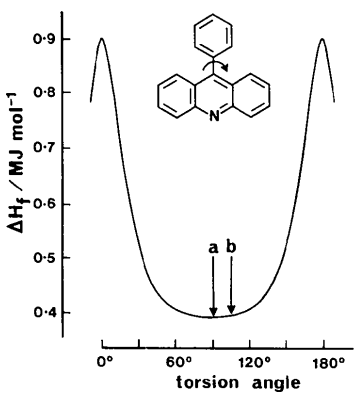

Fig. 2. Calculated enthalpy of formation (ΔH_f) for 9-phenylacridine with variation of C1*A*—C9—C11—C12 torsion angle: (*a*) computed enthalpy minimum and (*b*) crystallographic conformation determined for the title compound.

Partial rotation about the C9—C11 sp^2–sp^2 bond may thus be facile, suggesting that the acridine portion of this type of molecule may have similar nucleic acid intercalative ability compared to fully coplanar molecules. Molecular-modelling studies and solution binding experiments are currently addressing this issue and will be reported elsewhere.

We are grateful to the Cancer Research Campaign and the Department of Education (Northern Ireland) for research studentships (to MA and AWM, respectively).

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