

Conformation of Some Disubstituted 9-Acridanones

J. BARBE *^x, A.-M. GALY *, R. FAURE †, A. MAHAMOUD ‡, and J.-P. GALY ‡

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Abstract □ Experimental dipole moments of some disubstituted 9-acridanones were compared to the vectorially and theoretically calculated values using CNDO/2 method. Results supported the existence of a presumed folding of these compounds with the prevalence of a quasi-equatorial conformation.

Keyphrases □ Acridanones—disubstituted, dipole moments, conformation as solutes, □ Conformations—disubstituted acridanones as solutes, dipole moments □ Dipole moments—acridanones, disubstituted, conformation as solutes

The special position of acridanone compounds has frequently been mentioned. Their structure has to be situated between those of acridine and acridane (1), since the former is aromatic while the latter is equivalent to a bridged diphenylamine structure. Acridanone derivatives were identified as metabolites of the acridinic drugs (2–4) as well as metabolites of some dibenzazepine-like antiepileptic drugs such as carbamazepine (5–7).

These molecular transformations can modify the biological response if it stems from electronic distribution, and they can also induce side effects due to the new geometrical structures which could eventually carry out stereospecific actions.

Crystallographic data presently are the sole source of information about the acridanones structure (8). Because of this, it becomes worthwhile to define the conformation of acridanones as solutes and molecules isolated theoretically.

In this report the dipole moments of some disubstituted 9-acridanones were measured. They were calculated either by means of incremental vectorial addition or by the CNDO/2 method. Calculations and experimental results were compared to portray the molecular structure of the compounds studied.

EXPERIMENTAL

Materials—The following compounds were studied: 1,10-dimethyl-9-acridanone (I); 2,10-dimethyl-9-acridanone (II); 4,10-dimethyl-9-acridanone (III); 1-methyl-10-benzyl-9-acridanone (IV); 2-methyl-10-benzyl-9-acridanone (V); 2-methoxy-10-methyl-9-acridanone (VI); 2-methoxy-10-benzyl-9-acridanone (VII); 4-nitro-10-methyl-9-acridanone (VIII).

These compounds were prepared using phase transfer catalysis according to the process previously worked out with other acridine (9) or

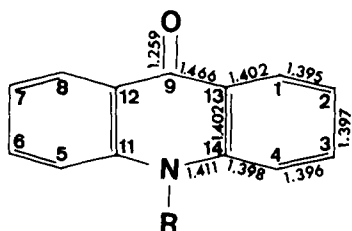


Figure 1—Molecular geometry of the disubstituted acridanones studied.

acridanone (10) derivatives. The purity of the samples studied was checked by HPLC¹.

Methods—The dipole moments of the compounds as solutes in anhydrous benzene were measured at $25.00 \pm 0.05^\circ$. The permittivity² and refractive index³ of the solutions were extrapolated to infinite dilution according to previous reports (11, 12). The quantity $(\epsilon_{12} - n_{12}^2) - (\epsilon_1 - n_1^2)$ was plotted versus the molar concentrations, C , of the solute. The slope of the curve at $C = 0$ was then used to calculate the dipole moment, μ :

$$\mu^2 = \frac{9kT}{4\pi N} \frac{3}{(\epsilon_1 + 2)(n_1^2 + 2)} \frac{(\epsilon_{12} - n_{12}^2) - (\epsilon_1 - n_1^2)}{C} \quad (\text{Eq. 1})$$

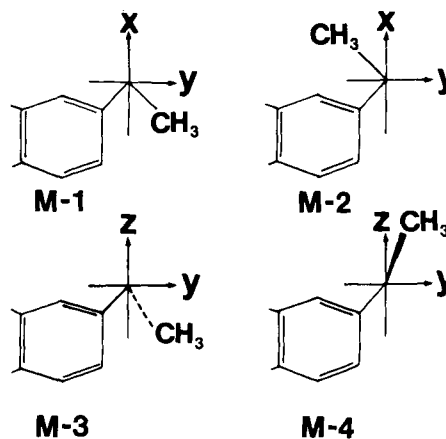
where k is the Boltzmann's constant, N is Avogadro's number, T is the absolute temperature, and ϵ_i and n_i are the permittivities and refraction indexes, respectively, of the solutes (Index 1) and of the solutions (Index 12).

RESULTS AND DISCUSSION

Experimental dipole moments and the theoretical moments, calculated using vectorial incremental addition, are given in Table I. For these calculations, the following molecular increments were used: anisole, 1.25 D; diphenylamine, 1.08 D; nitrobenzene, 3.98 D; toluene, 0.40 D (13); and 4-pyridone, 5.30 D (14).

Molecules were examined as being planar. Nitrogen hybridization was successively considered as sp^2 and sp^3 , and in each case a possible conjugation of the nitrogen lone-pair was taken into account. It must be kept in mind that conjugation modifies the value of dipolar increments because of the alteration of the electronic density at the level concerned. The values used are those previously given (15).

The molecules were assumed to be folded, which occurs along a fictitious N—O axis. Calculations were performed for different values of the angle, α , between each benzo ring of the heterocycle. The folding involves two limit-conformers known as R extra (quasi-axial) or R intra (quasi-equatorial) in accordance with the spatial orientation of the N—R bond. The conjugation concerns only the intra structure, because of the electronic hindrances in the extra structure. Four limit structures also were studied in the methoxy substituent: in structures M-1 or M-2, the methyl group is in the benzo plane, while in structures M-3 or M-4 it is out of the



¹ Pump, M 6000 A, Waters Associates; column, 25-cm μ Bondapak C-18 Waters Associates; detector, variable wavelength UV spectrometer Cecil CE 212. Detection was operated at 254 nm. The mobile phase flow rate (methanol RP) was 3 ml/min⁻¹, i.e., ~2000 psi.

² W.T.W. DM 01 dipolmeter with a DFL 1 cell.

³ O.P.L. Abbe-type refractometer.

Table I—Experimental and Calculated Dipole Moments ^a

Compounds	μ exp.	μ lit.	μ CNDO/2	μ Vectorial Calculation ^b									
				Planar Structure		Folded Structure				R extra			
				N sp ²	N sp ³	R intra		R extra		R extra		R extra	
$\alpha = 170^\circ$	160°	150°	140°	170°	160°	150°	140°						
<i>N</i> -methyl acridanone	5.20	5.38(13) 3.50(13)	5.05	5.90	5.57	5.85	6.09	6.32	6.48				
I	4.85		4.69	5.50	4.82	4.99	5.19	5.44	5.65	4.70	4.63	4.62	4.68
II	5.37		4.90	5.71	4.43	5.47	5.72	5.98	6.15	4.30	4.24	4.26	4.35
III	5.34		4.95	6.30	5.32	5.68	5.94	6.21	6.40	5.10	5.02	4.99	5.03
IV B-1	5.28			5.38	4.64	4.82	5.05	5.33	5.59	4.52	4.43	4.42	4.48
IV B-2	5.28			5.38	5.22	5.38	5.56	5.76	5.97	5.10	5.02	4.99	5.03
V B-1	5.32		5.14	5.52	4.89	5.25	5.51	5.78	5.96	3.93	3.84	3.88	4.03
V B-2	5.32		5.14	5.52	4.11	4.42	4.62	4.89	5.13	4.53	4.55	4.63	4.76
VI M-1	4.66		4.44	7.15	4.61	4.37	4.64	5.16	5.24	4.14	4.03	4.04	4.15
VI M-2	4.66		4.44	5.49	5.10	5.46	5.73	6.01	6.21	4.73	4.74	4.79	4.87
VI M-3	4.66		4.44	6.33	4.32	4.63	4.84	5.13	5.38	5.95	5.85	5.79	5.78
VI M-4	4.66		4.44	6.33	6.06	6.22	6.36	6.54	6.68	4.37	4.28	4.27	4.34
VI M-5	4.66		4.44	6.33	4.51	4.67	4.84	5.09	5.29	5.30	5.40	5.52	5.65
VII B-1, M-1	4.60		4.44	7.02	5.44	5.19	5.16	5.17	5.19	5.14	4.83	4.54	4.36
VII B-1, M-2	4.60		4.44	5.41	5.56	5.62	5.70	5.81	5.91	5.49	5.30	5.14	5.06
VII B-1, M-3	4.60		4.44	6.34	6.50	6.86	7.06	7.27	7.40	4.01	3.90	3.91	4.04
VII B-1, M-4	4.60		4.44	6.20	5.74	6.05	6.19	6.38	6.52	4.91	5.00	5.16	5.34
VII B-1, M-5	4.60		4.44	6.53	4.94	5.30	5.51	5.75	5.91	4.80	4.45	4.14	3.99
VII B-2, M-1	4.60		4.44	7.13	4.18	4.48	4.64	4.89	5.09	5.15	4.91	4.74	4.69
VII B-2, M-2	4.60		4.44	5.54	5.90	6.25	6.41	6.57	6.66	6.16	6.15	6.14	6.18
VII B-2, M-3	4.60		4.44	6.23	5.21	5.50	5.57	5.68	5.78	4.58	4.59	4.63	4.73
VII B-2, M-4	4.60		4.44	6.58	7.13	6.79	7.06	7.34	7.36	5.57	5.74	5.90	6.05
VII B-2, M-5	4.60		4.44	6.58	6.41	5.95	6.17	6.45	6.51	5.27	5.08	4.86	4.73
VIII	2.55		0.72 ^c 10.06 ^d	1.91	6.54	5.29	5.57	5.89	5.96	5.66	5.56	5.47	5.44
					5.32	5.48	5.69	5.72	5.72	0.74	1.12	1.85	2.54
					2.40	2.91	3.48	3.92	3.92				
					1.54	2.17	2.90	3.51	3.51				

^a In Debye units, D. ^b For each compound, there are the dipole moments calculated with (first line) and without (second line) conjugation. ^c Nitrogen dioxide and benzo plane are perpendicular. ^d Nitrogen dioxide and benzo ring-carriers are in the same plane.

benzo plane. Free rotation M-5 was also studied for this group. Conversely, free rotation was inconceivable for the benzyl substituent. So, only structure B-1 or B-2 was considered.

The molecular geometry was used for the CNDO/2 calculations (Fig. 1). Substituents are located along the bisector axis.

Bond length and angles are those drawn from the literature (16). Calculations were performed for a planar structure only. Dipole moments are given in Table I while bond indexes of some compounds are collated in Table II. These indexes can be compared to those corresponding to acridine derivatives (17). Average values of bond indexes in each case are summarized in Fig. 2. Comparison shows that the aromatic character of benzo rings is greater in acridanones than in acridines, unlike the aromatic

character of the central ring which is lower in acridanones than in acridines. Consequently, the acridanone heterocycle can be assumed to be folded. Moreover, this statement agrees with the result of the comparison between experimental dipole moments and the vectorially calculated ones. There is also an agreement with UV spectra (18).

But, added to this, according to the latter comparison, a particular orientation of the methyl group of the methoxy substituent is involved: lone pairs of the extracyclic oxygen should be conjugated with the π cloud of the ring-carrier. Similarly, the most probable structure for the benzyl substituent seems to be the previously noted structure, B-1. This is in close agreement with the NMR spectra⁴ presented in Table III. Indeed, structure B-1 is consistent with the deshielding of the benzylic protons, CH₂, (5.52 < δ < 5.57 ppm) referring to those of the φ -CH₂-NR₂ like compounds (3.30 < δ < 3.96 ppm) (19).

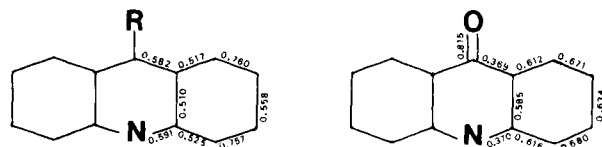
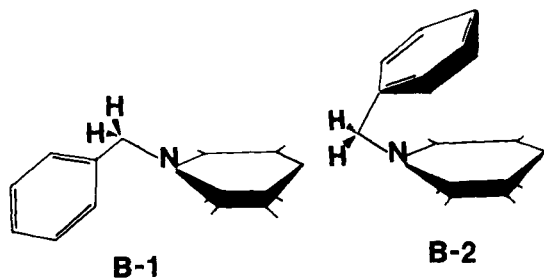


Figure 2—Acridines and acridanones: diagrams with the averaged π bond indexes.

⁴ Varian XL 100 Spectrometer.

Table II—Bond Indexes of Some Compounds Studied

Bonds	Compounds					
	I	II	III	V	VI	VII
C ₁ —C ₂	0.6616	0.6710	0.6849	0.6709	0.6692	0.6692
C ₂ —C ₃	0.6499	0.6293	0.6441	0.6293	0.6256	0.6256
C ₃ —C ₄	0.6758	0.6846	0.6695	0.6845	0.6849	0.6849
C ₄ —C ₁₄	0.6190	0.6186	0.6037	0.6180	0.6187	0.6181
C ₁₄ —N ₁₀	0.3784	0.3690	0.3769	0.3713	0.3621	0.3643
N ₁₀ —C ₁₁	0.3747	0.3767	0.3767	0.3791	0.3784	0.3808
C ₁₁ —C ₅	0.6184	0.6179	0.6178	0.6045	0.6173	0.6040
C ₅ —C ₆	0.6819	0.6822	0.6825	0.6890	0.6826	0.6894
C ₆ —C ₇	0.6423	0.6418	0.6415	0.6347	0.6413	0.6342
C ₇ —C ₈	0.6851	0.6855	0.6858	0.6908	0.6860	0.6913
C ₈ —C ₁₂	0.6152	0.6144	0.6141	0.6076	0.6138	0.6069
C ₁₂ —C ₁₁	0.5842	0.5831	0.5832	0.5874	0.5826	0.5868
C ₁₂ —C ₉	0.3668	0.3683	0.3686	0.3697	0.3691	0.3705
C ₉ —O	0.8090	0.8168	0.8165	0.8163	0.8172	0.8166
C ₉ —C ₁₃	0.3832	0.3667	0.3671	0.3668	0.3659	0.3660
C ₁₃ —C ₁₄	0.5800	0.5832	0.5879	0.5828	0.5877	0.5873
C ₁₃ —C ₁	0.5954	0.6182	0.6119	0.6182	0.6139	0.6140

Table III—Chemical Shifts and Assignment of Protons ^a

Compounds	Aromatics	—CH ₂ —	2-OCH ₃	N—CH ₃	φ-CH ₃
I	8.5–7.0(m, 7H)			3.90(s, 3H)	3.10 (s, 3H)
II	8.0–7.2(m, 7H)			3.80(s, 3H)	2.45(s, 3H)
III	8.5–7.2(m, 7H)			3.85(s, 3H)	2.70(s, 3H)
IV	8.5–6.9(m, 12H)	5.45(s, 2H)			3.00(s, 3H)
V	8.6–7.1(m, 12H)	5.55(s, 2H)			2.45(s, 3H)
VI	8.7–7.2(m, 7H)		3.95(s, 3H)	3.85(s, 3H)	
VII	8.5–7.2(m, 12H)	5.55(s, 2H)	3.90(s, 3H)		
VIII	8.7–7.1(m, 7H)			3.60(s, 3H)	

^a Solvent, dimethyl sulfoxide; internal standard, tetramethylsilane; temperature, ambient; multiplicity: m, multiplet; s, singlet.

No information is available, however, about the nitro group from the vectorial pattern, because of the supposed free rotation of this substituent. But, inclination of the latter upon the ring-carrier plane is close to 70°, according to the CNDO/2 calculations.

The agreement found between quantum mechanics calculations and incremental vectorial addition must be emphasized. Similar results were previously noted with some other acridine derivatives (17).

As for acridanones, they are presumably slightly folded, the angle of folding being close to 170°. Moreover, the prevailing structure should be the intrastucture.

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