Apparent Dipole Moments and Molar Volumes of β-Carbolines and Carbazole in Dioxane Solution

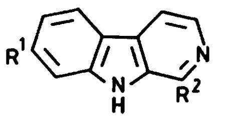
Isidro S. Monzo,* Armando Codoñer, Piedad Medina, Amparo Olba, and Rosa Valero
Departamento de Química Física, Facultad de Ciencias Químicas, Universitat de València, Burjassot (Valencia), Spain

The apparent molecular polarization at infinite dilution, $P_{2\infty}$, molecular refraction, R_D, dipole moment, μ_2, and partial molar volume, $\bar{V}_2^\circ$, of carbazole and some β-carboline derivatives have been determined from dielectric permittivity, specific volume, and refractive index measurements in 1,4-dioxane solutions at 25 °C. Evidence of hydrogen-bonding interaction with solvent has been found from i.r. spectroscopy and the apparent molar volumes. A relation has been found between literature pK_a values of β-carboline derivatives studied in the ground state and their corresponding dipole moments in solution.

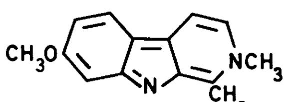
The inhibitor activity of substituted derivatives of β-carboline (9*H*-pyrido[3,4-*b*]indole) on monoamine oxidase (MAO) has been much studied.[1–4] The strong inhibition is of prime interest, since the planar tricyclic conjugated structures would lead one to expect different behaviour by comparison with similar non-hydrazinic inhibitors.[5] However, the presence of pyridine and indole nuclei in the β-carboline structure, and the high tendency of both of them to form very stable charge-transfer complexes (c.t.c.) with flavins,[6–8] suggests that the affinity of MAO for β-carboline could be investigated by association studies of flavins and β-carboline derivatives *in vitro*. Several spectroscopic studies of c.t.c. formation[6,9,10] and acid–base equilibria by Zabala *et al.*[11–13] and Wolfbeis and Furlinger[14] have been undertaken in the last few years, supporting theoretical studies by Aulló and Tomás.[15,16]

The present work is concerned with the set of β-carbolines norharmane (**1**), harmane (**2**), harmine (**3**), 2-methylharmine (**5**), and harmol (**4**) and carbazole (**6**) for which the dipole moment, the apparent molar volumes, the molar refractions, and the apparent molar polarizations have been resolved in 1,4-dioxane solution at 25 °C. This enabled the influence of the substituents and the position of substitution on the physicochemical properties and reactivities to be established.

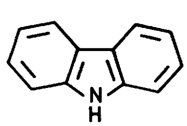
1,4-Dioxane was selected as solvent because of the moderate solubility of the solutes, and the behaviour of the nonpolar solvent; notwithstanding the possible appearance of specific interactions like hydrogen bonds or c.t.c. that may be present.



(**1**) $R^1 = R^2 = H$
(**2**) $R^1 = H, R^2 = CH_3$
(**3**) $R^1 = OCH_3, R^2 = CH_3$
(**4**) $R^1 = OH, R^2 = CH_3$



(**5**)



(**6**)

Experimental

Dioxane (AnalaR; Merck) was further purified following the specifications given by Kraus and Fuoss[17,18] and after three fractional distillations over sodium it was stored over sodium wire. The measured density ρ_1, refractive index n_1, and dielectric permittivity ε_1 of the solvent were 1.027 95 ± 0.000 02, 1.420 09 ± 0.000 05, and 2.1911 ± 0.0001, respectively. All measurements were performed at 25.0 ± 0.1 °C.

Carbazole was supplied by Merck as synthesis grade, 98%, and was purified by three successive recrystallizations in cold benzene followed by resublimation at low pressure. The m.p. was not changed by further sublimation.

The β-carboline derivatives were supplied by Sigma as purum grade reagents of the free base, except harmol (**4**), from Fluka. Except for harmol (**4**), all the β-carbolines were further purified by a standard fractional sublimation method under reduced pressure to avoid possible decomposition. No further changes in the m.p.s were observed. Harmol (**4**) was used without further purification. The m.p.s were measured in a Buchi apparatus by a standard method: norharmane (**1**), 195.7 ± 0.1; harmane (**2**), 233.3 ± 0.1; harmol (**4**), 323.5 ± 0.3, harmine (**3**), 260.4 ± 0.1; 2-methylharmine (**5**), 194.8 ± 0.2, and carbazole (**6**), 242.8 ± 0.1 °C.

I.r. spectra in CCl_4 (Merck Uvasol grade), and CCl_4–1,4-dioxane were taken with a Pye–Unicam SP1000 double-beam spectrophotometer for qualitative purposes.

The dielectric permittivities ε_{12}, densities ρ_{12}, and refraction indices n_{12} of solutions, as well as the details of apparatus, methods, and equations used to derive the molar properties, are in ref. 19.

The apparent molar polarization at infinite dilution $P_{2\infty}$ was calculated from equation (1) where M_2 is the molecular weight

$$P_{2\infty} = M_2[3\alpha v_1/(\varepsilon_1 + 2)^2 + (v_1 + \beta)(\varepsilon_1 - 1)/(\varepsilon_1 - 2)] \quad (1)$$

of solute and α and β are limiting values of $(\partial\varepsilon_{12}/\partial\varepsilon_2)_{\omega_2 = 0}$ and $(\partial v_{12}/\partial\omega_2)_{\omega_2 = 0}$, respectively; subscripts 1, 2, and 12 refer to the solvent, solute, and solution, respectively.

The apparent molecular refraction of solute at the sodium D line, R_D, appears to be constant in the concentration range studied, so we have used the mean value given by equation (2)

$$R_D = M_2[r_1 + \sum_{i=1}^{j} (r_{12i} - r_1)/\sum_{i=1}^{j} \omega_{2i}] \quad (2)$$

where r_{12_i} is the specific refraction of the *i*th solution.

To calculate the dipole moment of solutes μ_2, we used relationship (3) where μ_2 is expressed in Debye units.

Table. Polarization data of β-carboline and carbazole in 1,4-dioxane solution at 25 °C. pK_a Values from the literature

Compound	α	$-\beta$	γ	$P_{2\infty}$/cm^3	R_D/cm^3	$\bar{V}_2^\circ$/cm^3 mol^{-1}	μ_2/D	pK_a
Norharmane	8.02	0.196	0.77	260.8 ± 0.3	56.3 ± 0.5	133.3 ± 0.2	3.16 ± 0.03	7.2
Harmane	8.23	0.134	0.72	292.4 ± 0.3	61.1 ± 0.5	152.7 ± 0.2	3.36 ± 0.03	7.7
Harmol	7.74	0.222	0.88	296.9 ± 0.5	63.8 ± 0.7	149.6 ± 0.2	3.37 ± 0.04	8.0
Harmine	9.10	0.173	0.56	370.0 ± 0.3	65.0 ± 0.5	168.9 ± 0.2	3.86 ± 0.02	8.0
2-Methylharmine	21.11	0.176	0.66	872.0 ± 0.4	72.3 ± 0.5	179.8 ± 0.2	6.25 ± 0.02	11.5
Carbazole	3.88	0.134	0.76	147.3 ± 0.3	58.2 ± 0.5	139.5 ± 0.2	2.09 ± 0.03	−5.9
Pyridine							2.22 ± 0.02*	5.25†

* From ref. 32. † See ref 31.

$$<\mu_2^2> = (0.0128)^2 (P_{2\infty} - R_D)T \qquad (3)$$

The partial molar volume of solute $\bar{V}_2^\circ$/cm^3 mol^{-1} at infinite dilution can be derived from plots of molar volumes of solution $\bar{V}_{12}$ against the molar fractions f_2 which in all cases showed no deviation from linearity.

$$\bar{V}_{12} = \bar{V}_1^\circ + (\bar{V}_2^\circ - \bar{V}_1^\circ)f_2 \qquad (4)$$

Results and Discussion

The values of the parameters α, β, and γ [calculated as the limit of $(\partial n_{12}^2/\omega_2)_{\omega_2 = 0}$] along with $P_{2\infty}$, R_D, $\bar{V}_2^\circ$, and the dipole moments derived from the appropriate equations (1)—(4) are listed in the Table.

It is worth noting, from R_D data for benzene,[20] pyridine,[21] 2-methylpyridine,[22,23] anisole,[24] and phenol,[24,25] that in all cases the molar refraction results for β-carboline and carbazole follow the additivity rule.

Molar volumes are generally in accord with those calculated on the basis of group additivity. Exceptionally, the molar volume of harmol (**4**) is smaller than that of harmane (**2**), but corresponds to the similar decrease of phenol[26,27] from benzene,[20] caused by hydrogen-bond formation.[28,29] For harmine (**3**) and 2-methylharmine (**5**), comparison of molar volumes is complicated by changes in both electron distribution and hydrogen bonding.

Since 1,4-dioxane reduces the molar volumes of hydrogen-bonding solutes, i.r. spectra of all the molecules were taken in CCl_4 and in CCl_4–1,4-dioxane. For cases of carbazole, norharmane, and harmane, broad, weak bands were found at 3 370, 3 300, and 3 340 cm^{-1} respectively. The intensity increased with the concentrations of solutes in 15% dioxane–CCl_4. In the remaining cases, no bands were found at similar frequencies. This is expected for 2-methylharmine as no N–H • • • O bond is feasible. Harmine and harmol were abnormal. In harmol, a strong intermolecular hydrogen bond (see the high m.p., low apparent molar volume, i.r. spectrum in solid KBr *etc.*) is expected. This apparent anomaly can be understood if we assume that strong hydrogen-bond interactions with 1,4-dioxane cause a relatively large shift to a lower frequency, and consequently, the characteristic broad band of the hydrogen bond will be overlapped by the highest stretching band of 1,4-dioxane at 3 000 cm^{-1}, Harmol has two different hydrogen-bonding possibilities (O–H • • • O and N–H • • • O) in support of the above arguments. For harmine, the occurrence of a high electric dipole moment is crucial in explaining the trend.

The apparent molar polarizations given in the Table suggest that the addition of a second heteroatom in the tricyclic structure considerably increases the electronic density of these aromatic systems. Thus, the break in symmetry from carbazole to norharmane leads to an increase of *ca.* 130 cm^3 in the value of $P_{2\infty}$, similar to the value for pyridine in cyclohexane solution at 25 °C.[21] On the other hand, the presence in these aromatic systems of differently polar substituent groups considerably influences the electronic density. Therefore, the presence of a CH_3 group in harmane involves an increase of 32 cm^3 relative to norharmane (without a methyl group), which is considerably higher than the corresponding value found by Cumper and Vogel[23] for 2-methylpyridine relative to pyridine in benzene solution at 25 °C. In the case of 2-methylharmine, electronic reorganization must occur, indicating that the highest value of $P_{2\infty}$ will increase the basicity in the ground state at the highest level, as found by Zabala *et al.*[11] from measurements of pK_a values. Also, the high electronic density confirms the tendency to form very stable charge-transfer complexes with electronic acceptors, such as flavins. This is in line with ΔH° values obtained by us in a recent study.[10]

A value of *ca.* 4 D for the dipole moment of harmine explains the non-appearance of the characteristic broad, weak stretching band for the hydrogen bond between the solute and solvent in the sense given above. The value of μ 6.38 D for 2-methylharmine accounts for the internal electronic organization resulting from detaching the pyrrole and pyridine structures and interchanging them. The similar values for harmol and harmane, μ 3.40 D, suggest a change in the direction of the $\vec{\mu}$ vector, probably due to the presence of the hydroxy group in the benzene ring.

In the Table, the pK_a values of carbazole, β-carbolines, and pyridine reported by Chen *et al.*,[30] Zabala *et al.*,[11–13] and Linell[31] for the equilibrium $BH^+ \rightleftharpoons B + H^+$ have been shown for comparative purposes. A value of the dipole moment for pyridine in dioxane solution at 25 °C has been reported by Barassin and Lumbroso.[32] A good relation exists between the value of $\mu^{\frac{1}{2}}$ and pK_a, which indicates once more that the electronic structure is quite involved in the acid–base mechanism for protonated β-carbolines in the ground state. The negative pK_a value for carbazole denotes its basic strength, since protonated carbazole can only occur in very strong acid.[30] Thus, this pK_a corresponds to the loss of a second H^+ ion from a nitrogen atom, and consequently it cannot be used for comparisons with the other compounds. The pK_a of harmol is slightly larger than that obtained from the value of $\mu^{\frac{1}{2}}$ because the pK_a (8.0) was not experimentally determined; the authors[13] assumed that the pK_a values for harmol and harmine were the same. If there is a straight-line relation between $\mu^{\frac{1}{2}}$ and pK_a (as in this case, *r* 0.997), pK_a 7.4 for harmol should be expected, in good agreement with the u.v.–visible absorption spectra bands recorded[13] for pH 6.0—8.4. From the data reported by Perrin[33] for pyridine, quinoline, and isoquinoline derivatives, in which methoxy is replaced by hydroxy in the same position, a general tendency for the pK_a value to decrease has been confirmed, supporting our expected pK_a value for harmol.

References

1 E. A. Zeller, J. Barsky, J. R. Fouts, W. F. Kirchreimer, and L. S. Van Orden, *Experientia*, 1952, **8**, 349.

2 E. A. Zeller and J. Barsky, *Proc. Soc. Exp. Biol. Med.*, 1952, **81**, 459.

3 B. T. Ho, W. M. McIsaac, K. E. Walker, and V. Estévez, *J. Pharm. Sci.*, 1968, **57**, 269.

4 B. T. Ho, P. M. Gardner, S. F. Pong, and K. E. Walker, *Experientia*, 1973, **29**, 527.

5 B. T. Ho, *J. Pharm. Sci.*, 1972, **61**, 821.

6 M. A. Slifkin, 'Charge Transfer Interactions of Biomolecules,' Academic Press, London, 1971.

7 R. Foster, 'Molecular Association,' Academic Press, London, 1975, ch. 3 and 4.

8 B. Pullman, 'Molecular Association in Biology,' Academic Press, New York, 1968.

9 A. Codoñer, I. S. Monzó, F. Tomás, and R. Valero, *Spectrochim. Acta, Part A*, 1986, **42**, 765.

10 A. Codoñer, I. S. Monzó, F. Tomás, and R. Valero, *Spectrochim. Acta*, in the press.

11 F. Tomás Vert, I. Zabala Sánchez, and A. Olba Torrent, *J. Photochem.*, 1983, **23**, 355.

12 J. Romero Berto, I. Zabala Sánchez, J. M. Aulloá Reverte, F. Tomás Vert, and A. Olba Torrent, *J. Photochem.*, 1985, **29**, 405.

13 F. Tomás, I. Zabala, and A. Olba, *J. Photochem.*, 1985, **31**, 253.

14 O. S. Wolfbeis and E. Furlinger, *Z. Phys. Chem. (Frankfurt)*, 1982, **129**, 171.

15 J. M. Aulló and F. Tomás, *An. Quim.*, 1979, **75**, 11.

16 F. Tomás and J. M. Aulloá, *J. Pharm. Sci.*, 1979, **68**, 772.

17 C. A. Kraus and R. M. Fuoss, *J. Am. Chem. Soc.*, 1933, **55**, 21.

18 A. Weissberger, 'Technique of Organic Chemistry,' vol. VII, 'Organic Solvents,' Interscience, New York, 1955, ch. V, p. 372.

19 A. Codoñer, I. S. Monzó, F. Tomás, and R. Valero, *J. Phys. Chem.*, 1986, **90**, 2244.

20 I. S. Monzó, Ph. D. Thesis, University of Valencia.

21 A. Codoñer, I. S. Monzó, F. Tomás, and R. Valero, *J. Chem. Soc., Perkin Trans. 2*, 1986, 573.

22 R. Smets and P. Huyskens, *Bull. Soc. Chem. Fr.*, 1978, 173.

23 C. W. N. Cumper and A. I. Vogel, *J. Chem. Soc.*, 1956, 3621.

24 S. Nagakura and H. Baba, *J. Am. Chem. Soc.*, 1952, **74**, 5693.

25 B. Eric, E. V. Goode, and D. A. Ibbitson, *J. Chem. Soc.*, 1960, 55.

26 'International Critical Tables,' McGraw-Hill, New York and London, 1933.

27 'Handbook of Chemistry and Physics,' The Chemical Rubber Publishing Co. Cleveland, 1973, 54th edn.

28 G. C. Pimentel and A. L. McClellan, 'The Hydrogen Bond,' Freeman, San Francisco, 1960, ch. 2, p. 52.

29 E. A. Moelwyn-Hughes, 'Physical Chemistry,' Pergamon, Oxford, 1961, ch. XVII.

30 H. J. Chen, L. E. Hakka, R. L. Hinman, A. J. Kresge, and E. B. Whipple, *J. Am. Chem. Soc.*, 1971, **93**, 5102.

31 R. H. Linell, *J. Org. Chem.*, 1960, **25**, 290.

32 J. Barassin and H, Lumbroso, *Bull. Soc. Chim. Fr.*, 1961, 492.

33 D. D. Perrin, 'Dissociation Constants of Organic Bases in Aqueous Solution,' Butterworths, London, 1965.

Received 28*th November* 1986; *Paper* 6/2292