DETERMINATION OF THE AGGREGATION OF 9-AMINOACRIDINES IN AQUEOUS SOLUTION BY AN ION SELECTIVE ELECTRODE

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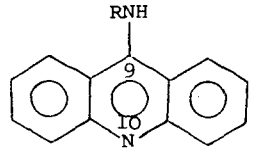
9-Aminoacridines have been used for their antimicrobial and antifungal properties in a variety of pharmaceutical applications. There are numerous reports that aminoacridines self-associate in solution (Moulik et al 1976) but this effect has not been taken into account in their mode of action. The object of this work was to determine the degree of aggregation of the 9-aminoacridines by ion selective electrodes so that the monomer concentrations may be determined.

Ten 9-(N-alkyl amino) derivatives of acridine were synthesised by the method of Albert et al (1943). CH and N analysis gave good agreement with theoretical values. Ion selective electrodes were prepared by the method of Shinbo (1978) using PVC membranes containing di-nonylphthalate plasticizer and the 9-alkyl-aminoacridine tetraphenylboron complex. Electrodes were preconditioned overnight by immersion in 10^{-3} M aqueous solutions of the aminoacridine salt. The electrodes were then immersed in distilled water and measurements made over a concentration range of 10^{-5} to 10^{-3} M at 15, 25 and 37°C. Readings were done in duplicate using a Beckman Research pH meter. Selectivity constants were determined with respect to H^+, K^+, Na^+ and NH_4^+. Values of 8 x 10^{-2}, 3.2 x 10^{-6}, 4.0 x 10^{-7} and 3.7 x 10^{-6} were obtained respectively. Slopes approaching Nernstian, 58 to 61 mv, were obtained at the lower concentrations.

The experimental results were analysed by computer using a least squares interactive technique, assuming that dimerization only occurred in the concentration ranges studied, that dimers did not elicit an electrode response and that the aminoacridines existed in the cationic form. Good correlation was obtained between the experimental plots of EMF as a function of concentration and predicted values of EMF for the dimerization model. Values calculated were within 1 mv of the experimental values, except at concentrations greater than 10^{-3} M when deviations of up to 3 mv were obtained. Some of the results are given in Table 1.

Table 1 Log dimerization constants at 25°C and 37°C; standard error in brackets

Acridine Derivative	25°C	37°C
9-NH_2	6.60 (0.39)	8.25 (0.10)
9-$NH_2$10CH_3	4.53 (0.41)	7.96 (0.62)
9-$NHCH_3$	3.87 (0.43)	7.71 (0.55)
9-NHC_3H_7	3.55 (0.04)	3.38 (0.06)
9-NHC_5H_{11}	3.06 (0.03)	2.91 (0.19)
9-NHC_6H_{13}	3.07 (0.06)	2.69 (0.04)
9-NHC_7H_{15}	2.80 (0.25)	2.40 (0.17)
9-NHC_8H_{17}	3.06 (0.16)	3.46 (0.09)
9-$NHC_{10}H_{21}$	-	0.89 (0.60)
9-$NHC_{12}H_{25}$	-0.30 (0.04)	-0.093 (0.008)
9-$NHC_{16}H_{33}$	1.64 (0.40)	3.48 (0.18)



9-alkylaminoacridine

An ion selective electrode has been developed and used to determine the dimerization constant for the 9-aminoacridines and indicate that at 37°C in concentrations of 10^{-4} to 10^{-3} M, the amount of monomer varies between 1 and 100% depending on the length of the alkyl chain in the 9 position. Therefore self-association of the 9-aminoacridines may be a significant factor which should be considered when determining their mode of action on microbial and fungal cells.

Moulik, S.P. et al (1976) Indian J. Chem. 14A(S): 306-310
Albert, A. et al (1943) J. Chem. Soc.: 651-654
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