Tetrahedron Letters No. 15, pp 1279 - 1282, 1975. Pergamon Press. Printed in Great Britain.

THE REACTIVITY OF IMIDAZOLE DERIVATIVES ON THEIR BEING ACYLATED IN THE SURFACE LAYER OF CATIONIC MICELLES

Karel MARTINEK, A. P. OSIPOV, A. K. YATSIMIRSKI, V. A. DADALI and I. V. BEREZIN

Laboratory of Bioorganic Chemistry, Lomonosov State University, Moscow 117234, USSR

(Received in UK 6 January 1975; accepted for publication 5 March 1975)

The imidazole group, which is a part of the active centre of many enzymes, often displays an unusual reactivity [1]. It is interesting to find out which role in this phenomenon is played by the effects of the microenvironment. It is known that there are certain analogies between the structure of protein globules and surfactant micelles [2-4]. Hence we believed it feasible to elucidate how the reactivity of imidazole derivatives is affected by the environment of the surface layer of cetyltrimethylammonium bromide (CTAB) micelles.

We have measured the liberation of p-nitrophenate ion on acylation of a series of imidazole derivatives (see legend to the figure) by p-nitrophenylheptanoate, under conditions when the concentration of the nucleophile greatly exceeds that of the ester. The true rate constants for this reaction in micelles were calculated from the observed reaction rate vs. CTAB concentration profiles. To this end we used the kinetic method [5-7] developed previously for other reactions. It should be emphasized that this approach to the analysis of the overall kinetic data makes it possible to estimate the contribution to the micellar effect of the partition of the reagents between the bulk and micellar phases. The second order rate constants found reflect the true reactivity of the reagents in the micellar environment. Study of the pH dependence allowed

characterization of the reactivity of both the electroneutral form of the nucleophile and/or the corresponding anion. Some details of the procedure are given in ref. 8, but we generally proceeded from the considerations used in ref. 7 for benzimidazole.

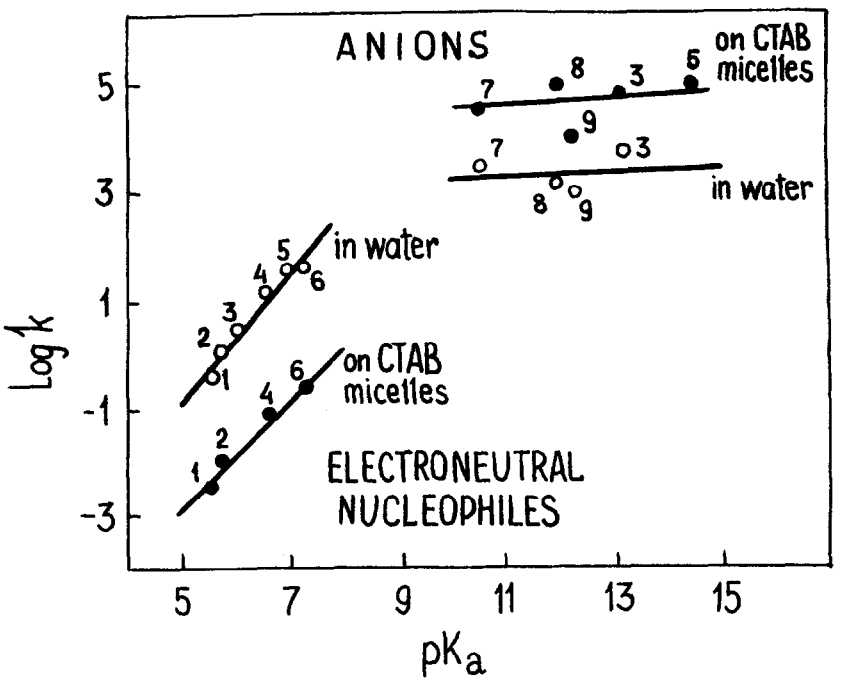

Figure True second order rate constants ($M^{-1}min^{-1}$) for acylation of a series of imidazole derivatives by p-nitrophenylheptanoate versus pK_a values for the nucleophiles. Compounds: (1) N-methylbenzimidazole, (2) N-phenylimidazole, (3) 4(5)-phenylimidazole, (4) N-benzylimidazole, (5) N-benzoyl-L-histidine, (6) N-heptylimidazole, (7) 5(6)-nitrobenzimidazole, (8) 4(5)-bromoimidazole, (9) benzimidazole.

Conditions: 30°, 0.2 M KNO_3, 1 vol. % of dimethylsulphoxide, 0.02 M borate or phosphate buffer; CTAB concentration was varied from 0 to 10^{-2}M. The pK_a values were determined by spectrophotometric titration [8,9] in the absence of the surfactant.

The experimental results are presented in terms of the Brønsted relationship, see the figure. One may see that the linear Brønsted dependence both in water and in the micelles has the same slope (approximately equal to unity in the reaction of electroneutral nucleophiles and almost zero for anions). This should be interpreted as indicating that the micellar environment produces no specific effect on the structure (polarity) of the transition states of these reactions.

Another observation seems to be more important,i.e. that for electroneutral nucleophiles the true reaction rate constant in the micelles (see the figure) is by two orders of magnitude lower than in water. This seems to be due to the fact that the low dielectric permeability and weak solvating ability of the micellar medium (see ref's 2-4) produce an unfavourable effect on the formation of the polar transition state of the reaction (possibly close to a tetrahedral complex).

On the contrary, a micellar medium produces a favourable effect on the reaction of imidazole anions. Their reactivity increases by more than one order of magnitude on their being transferred from an aqueous to a micellar medium (see the figure). This evidently happens because, as a result of sorbtion, the anion on the micelle becomes (at least in part) desolvated.

These results are of great importance for the understanding of the structure of CTAB micelles and the properties of their surface layer. Moreover, they may help explain some polymer and protein effects in reactions involving imidazole. These aspects are described in detail in ref's 7,8.

1 W.P.Jencks, in "Chemical Reactivity and Biological Role of Functional groups in Enzymes" (R.M.S.Smellie, ed.), Acad.Press, London-New York, 1970.

2 E.Fendler and J.Fendler, Adv.Phys.Org.Chem., 8, 271 (1970).

3 E.H.Cordes and C.Gitler, in "Progress in Bioorganic Chemistry" (E.T.Kaiser, and F.J.Kezdy, eds.), v. 2, J.Wiley a.S.Inc., N.Y.-Toronto, 1973.

4 I.V.Berezin, K.Martinek and A.K.Yatsimirski, Uspekhi Khimiyi (Russ.) 42, 1729 (1973); Wissenschaft.Zeitsch., 15, 338 (1973).

5 A.K.Yatsimirski, K.Martinek and I.V.Berezin, Tetrahedron, 27, 2855 (1971).

6 K.Martinek, A.K.Yatsimirski, A.P.Osipov and I.V.Berezin, Tetrahedron, 29, 963 (1973).

7 K.Martinek, A.P.Osipov, A.K.Yatsimirski and I.V.Berezin, Tetrahedron, in press.

8 K.Martinek, A.P.Osipov, A.K.Yatsimirski and I.V.Berezin, Bioorg.Khim. (Russ.), 1, No. 3 (1975).

9 A.K.Yatsimirski, A.P.Osipov, K.Martinek and I.V.Berezin, Kolloid Zhurn. (Russ.),37, No. 3 (1975).