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Short Communication

1-Octanol–water partition coefficients of the anionic and zwitterionic species of diprotic zwitterionic cephalosporin antibiotics

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The 1-octanol–water partition coefficient is a widely employed chemical descriptor in studies of 'quantitative structure–activity relationships' (Q-SARs) of drugs, and the phenomenon of partitioning anions is occasionally involved (La Rotonda et al., 1985; Irwin et al., 1987). The apparent partition coefficient P, at equilibrium, is defined in Eqn. 1:

$$P = [\text{Drug}]_{\text{1-octanol}}/[\text{Drug}]_{\text{water}} \quad (1)$$

The diprotic zwitterionic β-lactam antibiotics, ampicillin, cephalexin and cephaloglycin, have been reported by Purich et al. (1973) to possess pH-dependent P values which increase to a maximum value of about 0.25 with decreasing hydrogen ion concentration above pH 5, indicating that anions are the predominant partitioning species in this pH region. However, Carney and Hurwitz (1977) subsequently reported that ampicillin has a pH-independent P value of about 0.007 within the pH range 3.0–7.9.

We have determined the partition coefficients of 3 diprotic zwitterionic cephalosporins, cephalexin, cephaloglycin and cephradine, at 37 °C and ionic strength μ of 0.2 M, using a shaker-flask method (Hansch and Leo, 1979). Solutions of cephalosporin in aqueous buffer (2 ml) at an initial antibiotic concentration of 5×10^{-5} M were agitated with 1-octanol (2 ml), the solvents having been mutually presaturated. Fluorimetric assay Ju et al. (1977) of the aqueous phases at equilibrium yielded pH–P profiles (Table 1, Fig. 1) similar to those reported by Purich et al. (1973), but with lower values of P. From the results of the present work it is possible, using graphical-regression techniques, to apply Eqn. 2 to the experimental P data of each compound at pH > 5 to determine the true partition coefficients of the zwitterionic and anionic species, P_{zw} and P_{an}, respectively.

$$P(1 + a_{H^+}/K_{a^2}) = P_{an} + P_{zw}(a_{H^+}/K_{a^2}) \quad (2)$$

Eqn. 2 is derived by direct analogy with the derivation of the equation reported by Tsuji et al. (1977) which allows the calculation of the $P_{\text{unionised}}$ and P_{ionised} values of monobasic acids. K_{a^2} in Eqn. 2 is the macrodissociation constant for side-chain–NH_3^+ dissociation. A plot of $P(1 + a_{H^+}/K_{a^2})$ as a function of (a_{H^+}/K_{a^2}) is linear with a slope of P_{zw} and an intercept with the $P(1 + a_{H^+}/K_{a^2})$ axis of P_{an} (Table 1).

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TABLE 1

1-Octanol–water partition coefficients of three diprotic zwitterionic cephalosporins

Compound	pK_{a^2}*	*P* at pH:				P_{zw}	P_{an}	Statistics of the fit of Eqn.2		
		5.00	7.10	7.40	8.00			*n*	*r*	*s*
Cephalexin	6.88	0.02	0.04	0.08	0.09	0.017	0.274	4	0.929	0.308
Cephaloglycin	6.90	0.01	0.08	0.09	0.13	0.009	0.127	4	1.000	0.012
Cephradine	7.30	0.01	0.05	0.07	0.11	0.009	0.121	4	1.000	0.008

* pK_{a^2} values from Jamana and Tsuji (1976).

Eqn. 2 is applicable to the *P* values at pH > 5 of the 3 compounds studied because the concentration of cationic species is not significant in this pH region and the concentration of unionised molecules is negligible at any pH (Streng, 1978). The relationship may be applied to the *P* data for any diprotic zwitterionic compound which undergoes anionic partitioning and which has a difference between pK_{a^1} (carboxylate dissociation) and pK_{a^2} values of sufficient magnitude to satisfy the requirements for negligible concentrations of cationic and unionised species in the pH region where anions predominate.

The monoprotic zwitterionic cephalosporin cephaloridine (pK_a = 1.19, this research) was found to have a 1-octanol–water partition coefficient of 0.02, the value of which was independent of pH in the range 2.70–7.40. A *P* value (1-butanol–water) of 0.03 was previously reported for this antibiotic (Koprivc and Polla, 1977).

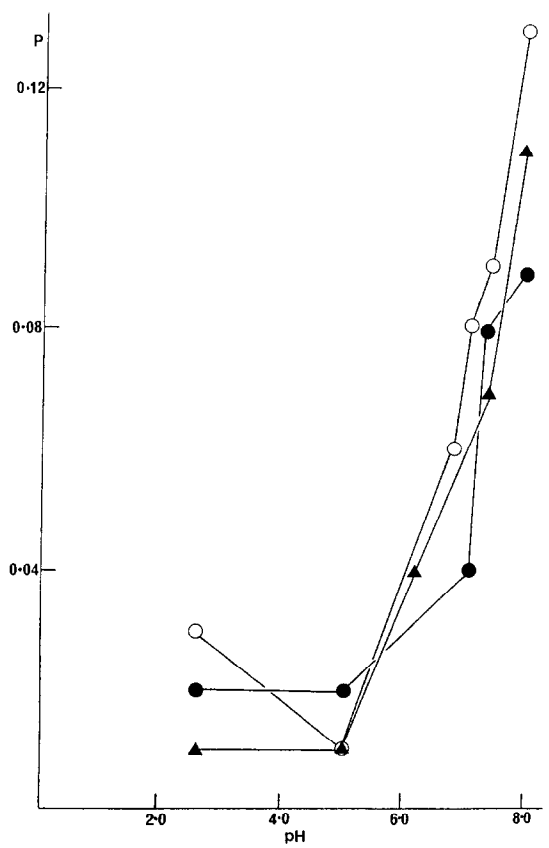

Fig. 1. pH–partition coefficient relationships of 3 diprotic zwitterionic cephalosporins. ▲, cephradine; ●, cephalexin; ○, cephaloglycin.

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