International Journal of Pharmaceutics, 20 (1984) 209–211
Elsevier

IJP 00679

Short Communication

Octanol/water partition coefficients of 4-substituted benzylidene *t*-butylamine N-oxides

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(Received November 21st, 1983)
(Modified version received January 10th, 1984)
(Accepted January 17th, 1984)

Summary

Experimental octanol/water partition coefficients are reported for five 4-substituted benzylidene *t*-butylamine N-oxides at 25°C. The results of these measurements are used to calculate the aromatic fragment constants, $\pi_{HC=N(O)C(CH_3)_3}$ and $f_{HC=N(O)}$, for the group contribution methods of Hansch and Leo.

The partition coefficient of a drug is commonly recognized as a key parameter in determining its biological activity. Since this parameter cannot usually be determined in the biological system of interest, one must settle for data obtained by some in vitro partitioning experiment. Octanol/water is the most frequently used system for such studies and it has served as an adequate model for the correlation of biological activity.

The concept of predicting partition coefficients from group contribution was proposed initially by Hansch and coworkers (see Fujita et al., 1964; Leo et al., 1971; Hansch et al., 1972) who showed that:

$$\log PC_{RX} - \log PC_{RH} = \pi_X \tag{1}$$

where π_X is a constant which is characteristic for any given atom or group. More recently, Leo et al. (1975) suggested a slightly different group contribution method based on fragment f_X and factor F_X values

$$\log PC_{molecule} = \sum_i a_i f_i + \sum_j b_j F_j \tag{2}$$

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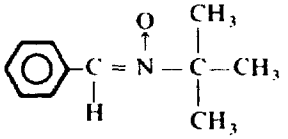
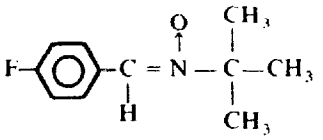
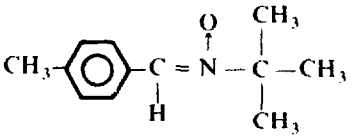
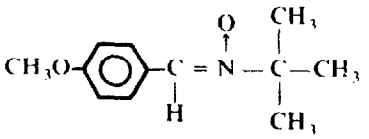
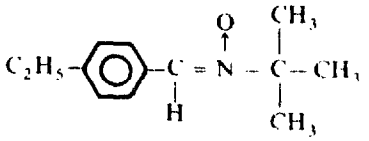
Eqns. 1 and 2 are ideally suited to the needs of the pharmaceutical industry as they enable one to estimate the partition coefficients of potential drug molecules, provided that all of the group parameters are known.

During the course of kinetic investigations in liquid crystalline solvents, it was necessary to measure the octanol/water partition coefficients of several 4-substituted benzylidene *t*-butylamine N-oxides. The compounds were prepared as reported previously (Bacon et al., 1983). Each member of the series was equilibrated with octanol/water solvent in a constant temperature shaker bath at 25.0°C for 24 h. The concentrations in each phase were determined spectrophotometrically at the following wave lengths: R = H 290, F 285, CH_3 294, C_2H_5 300, CH_3O 310 nm.

The experimental data (see Table 1) are reported in this short communication because the molecules do contain a function group not listed in either the Hansch π_X (the aromatic HC = N(O)C$(CH_3)_3$ group) or the Leo f_X (the aromatic HC = N(O) group) tabulations. Analysis of the partition coefficients of benzylidene *t*-butylamine

TABLE 1

OCTANOL/WATER PARTITION COEFFICIENTS OF 4-SUBSTITUTED BENZYLIDENE *t*-BUTYLAMINE N-OXIDES AT 25.0°C

Compound	log $PC_{molecule}$ [a]
	1.22 ± 0.04
	1.42 ± 0.04
	1.74 ± 0.04
	1.21 ± 0.05
	2.19 ± 0.06

[a] The partition coefficients are based on 8–10 determinations, with the 95% confidence limits denoted by the ± values. Attainment of equilibrium was verified in each case by repetitive measurements several days later.

N-oxide gives

$$\pi_{HC=N(O)C(CH_3)_3} = \log PC_{C_{11}H_{15}NO} - \log PC_{benzene}$$

$$= 1.22 - 2.13$$

$$= -0.91$$

for the aromatic $\pi_{HC=N(O)C(CH_3)_3}$ value and

$$f_{HC=N(O)} = \log PC_{C_{11}H_{15}NO} - f_{C_6H_5} - 4\,f_C - 9\,f_H - F_{gr\,br} + F_{ch\,br} - 4\,F_{bonds}$$

$$= 1.22 - 1.90 - 4\,(0.20) - 9\,(0.23) + 0.22 + 0.13 + 4\,(0.12)$$

$$= -2.72$$

for the aromatic $f_{HC=N(O)}$ value. Similar numerical values are obtained if the group parameters are calculated from the partition coefficients of the 4-substituted benzylidene *t*-butylamine N-oxides listed in Table 1.

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