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Notes

Thermodynamics of partitioning in the *n*-octanol/water system of some β-blockers

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Summary

It is possible to obtain by thermometric titrimetry the water/*n*-octanol transfer enthalpy of a series of β-blockers. The transfer entropy can be assessed by combining these results with the corresponding values of the partition coefficients determined independently. The results obtained are discussed according to the pharmacological properties of these substances.

The 1-octanol/water partition coefficient P is a widely used chemical described in studies of 'quantitative structure-activity relationships' (QSARS) of drugs. Since log P represents the difference in enthalpic and entropic contributions to phase transfer, one may believe that knowing more about these contributions might lead to greater knowledge of the solvation and desolvation which accompany the transfer as well as to new insights into qualitative and quantitative structure-activity relationships.

In the course of our studies concerning the partitioning of drugs (Burgot and Burgot, 1984, 1986, 1990; Burgot et al., 1989) we have estimated by titration calorimetry water/*n*-octanol partitioning enthalpies and entropies of some β-blockers (Table 1). According to Sundquist (1980), in these compounds, the lateral chain is responsible for the β-adrenergic activity and the rest of the molecule conditions their lipophilicity and thus their pharmacokinetics. The thermodynamics of the partitioning of some β-blockers in the *n*-octanol/buffer system has already been the subject of an initial study (Betageri and Rogers, 1987).

We have used exactly the same procedure as that described in our previous paper (Burgot and Burgot, 1990). For the two arylethanolamines (labetalol and sotalol) the common value of the ionization enthalpy we have adopted is that of sotalol which we determined directly by thermometric titrimetry (i.e. -33035 J mol^{-1}). For the aryloxypropanolamines, we have used that of atenolol which we evaluated directly in the same way (i.e. -47347 J mol^{-1}). All measurements were performed at 298 K. Partition coefficients, P, necessary to compute the Gibbs standard free energies of transfer, are those given by Recanatini

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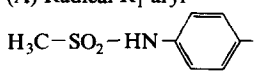
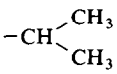
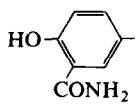
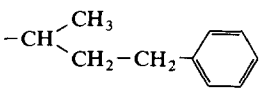
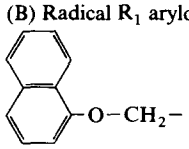
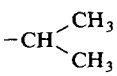
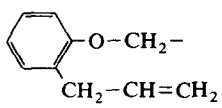
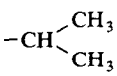
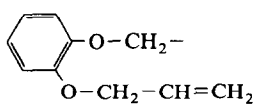
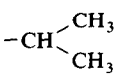
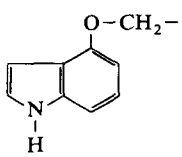
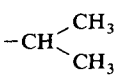
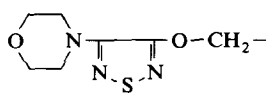
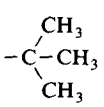
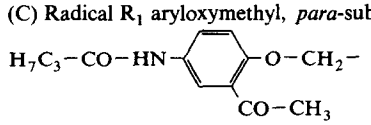
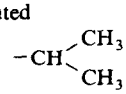
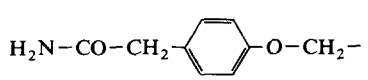
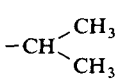
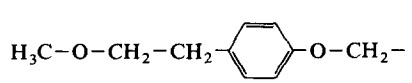
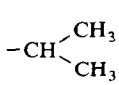
TABLE 1

Structures and water / n-octanol partitioning thermodynamic parameters of some β-blockers

R_1-CHOH-CH_2-NHR_2

R_1	R_2	Name	Log P	ΔG_T° (J mol^{-1})	ΔH_T° (J mol^{-1})	ΔS_T° (J K^{-1} mol^{-1})
(A) Radical R_1 aryl						
		Sotatol	0.24	−1370	−2215	−2.8
		Labetalol	3.09	−17637	−844	56.4
(B) Radical R_1 aryloxymethyl						
		Propranolol	3.37	−19236	4865	80.8
		Alprenolol	3.10	−17694	4782	75.4
		Oxprenolol	2.18	−12443	13284	86.3
		Pindolol	1.75	−9989	−1542	28.3
		Timolol	1.98	−11302	4786	53.9
(C) Radical R_1 aryloxymethyl, *para*-substituted						
		Acebutolol	1.77	−10103	11466	72.34
		Atenolol	0.16	−1313	690	6.7
		Metoprolol	1.80	−10274	2884	44

(1989). They are expressed on the mol l^{-1} concentration scale as is very often the case in pharmacochemistry. We consider (Burgot and Burgot, 1984) that, under the experimental conditions used, the enthalpies and entropies determined are the standard values: they express the changes in enthalpy and entropy when one molecule of solute passes from water to *n*-octanol, both at infinite dilution.

The first thing we immediately note is that our enthalpy values (and hence entropy values) are markedly lower than those obtained by Betageri and Rogers (1989). However, the hypothesis of an assumed value of the ionization enthalpies of these compounds (except, of course, those of sotalol and atenolol, vide supra) too far from the right cannot give a fully satisfactory explanation of these discrepancies.

For most of these compounds, the partitioning enthalpies and entropies are positive, as pointed out previously by Betageri and Rogers (1987). So, except for labetalol, sotalol and pindolol which we shall consider later, the partitioning process is entropy driven. This is in accordance with the results obtained in a number of investigations which show that antagonists bind with β-adrenergic receptors producing large increases in entropy (Miklavc et al., 1989). The magnitudes of transfer enthalpies and entropies can be roughly explained by the most common hydrophobic effect theory (Tanford, 1980) which can be summarised in terms of the structure of water around the apolar solute in the aqueous phase. When the solute is transferred into the octanol phase, destruction of the aggregates of water which were around it increases the entropy of the system and produces a slight endothermic effect. The highest values of transfer enthalpies obtained with oxprenolol and acebutolol (13284 and 11466 J mol^{-1}, respectively) cannot, as the values of entropic terms which do not differ significantly from those found for the other compounds show it to be explained solely by the hydrophobic effect. The case of labetolol and pindolol differ a little insofar as the transfer enthalpies are slightly negative. However, if enthalpies and entropies cooperate in the partitioning of these compounds, the process is still essentially entropy driven. The case of sotalol is very different. The process is enthalpy driven. This fact can be partly explained by the formation of an H-bond in the octanol phase between the polar substituents of the phenyl ring and the hydroxyl of the octanol molecule favoured by a weak polar medium. Interestingly, we note that sotalol and labetolol display fewer blocker properties than the derivatives of the aryloxypropanolamines (Palm, 1988).

According to Leffler and Grunwald (1963), the linear relationships of enthalpy - entropy plots suggest a single mechanism of transfer for a series of solutes. Hence, it appears that pindolol, metoprolol, timolol, acebutolol and oxprenolol have the same partitioning mechanism. Sotalol and atenolol, on the one hand, and propranolol and alprenolol, on the other, have two other transfer mechanisms. Thus, we found again the same three classes of β-blockers as those considered by Betageri and Rogers according the lipophilicities of these compounds.

Acknowledgment

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