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Water/*n*-octanol thermodynamic parameters of some phenothiazines

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Summary

Thermometric titrimetry allows the determination of the water/*n*-octanol transfer enthalpies of a series of phenothiazines. By combining these results with the corresponding average values of the partition coefficient determined independently, their transfer entropies can be assessed. The transfer enthalpies of the series studied are significantly more endothermic for the compounds endowed with major neuroleptic activity.

The phenothiazines (**1**) exhibit different pharmacological properties according to the nature of the R_1 and R_2 substituents. In the series we studied the compounds **1a**–**1f** which display essentially neuroleptic properties along with more or less sedative characteristics while compounds **1h**, **1i** and **1j** are, respectively, antihistaminic, neuromuscular myorelaxant and antiparkinsonian, rather than neuroleptic derivatives (Costentin et al., 1987).

The determination of water/*n*-octanol transfer enthalpies and entropies of these compounds falls within the field of our broader work on the determination of water/*n*-octanol partitioning thermodynamics of drugs (Burgot and Burgot, 1984, 1986, 1989; Burgot et al., 1989, 1990). Our main aim is to determine the precise enthalpic or entropic nature of the transfer which cannot be inferred from the simple value of log *P* (a parameter so widely used in Q.S.A.R. studies!) which expresses only the value of the Gibbs free energy of transfer (Tremillon, 1971). Another of our objectives is to establish new types of structure-activity relationships as determined only on thermodynamic bases.

Values for the partitioning of compounds **1a**–**1i** have been determined by titration calorimetry according to our previously described method for compounds of very low solubilities (Burgot and Burgot, 1989). This procedure implies that the solute should have basic or acidic properties in water. If so, the calorimetric measure gives only the sum of the transfer ΔH_T and ionization ΔH_i enthalpies of the solute. The latter, in view of the poor solubility, cannot be determined directly in water. Fortunately, they can be estimated with fair accuracy from the values of the tables (Christensen et al., 1969). Therefore, on having chosen a model compound, the structure of which is very

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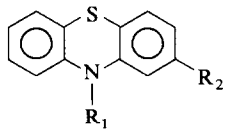
TABLE 1

Structures and water / n-octanol partitioning thermodynamic parameters of phenothiazines

General structure: 

Compound no.	Chemical name	R_1	R_2	Log P	G_T° (J mol^{-1})	H_T° (J mol^{-1})	S_T° (J mol^{-1} K^{-1})
1a	Chlorpromazine	Cl	$(CH_2)_3-N-(CH_3)_2$	5.41	−30 890	3812	116.44
1b	Levomepromazine	OCH_3	$CH_2-CH(CH_3)-CH_2-N(CH_3)_2$	5.26	−30 040	782	103.42
1c	Fluphenazine	CF_3	$-(CH_2)_3-N$ piperazine $-CH_2CH_2OH$	5.67	−32 380	2670	117.62
1d	Perphenazine	Cl	$-(CH_2)_3-N$ piperazine(CH_3) $-CH_2CH_2OH$	5.28	−30 150	4340	115.74
1e	Thioridazine	SCH_3	$-(CH_2)_2-C$ piperidine	6.51	−37 160	3150	135.27
1f	Propericiazine	CN	$-(CH_2)_3-N$ piperidine $-OH$	3.90	−22 270	3230	85.57
1h	Alimemazine	H	$-CH_2-CH(CH_3)-CH_2-N(CH_3)_2$	5.01	−28 610	1490	101
1i	Chlorproethazine	Cl	$-(CH_2)_3-N-(C_2H_5)_2$	6.46	−36 880	−1319	119.33
1j	Diethazine	Cl	$-(CH_2)_2-N-(C_2H_5)_2$	5.94	−33 920	440	115.30

similar to that of the compound under study, the ionization enthalpy can be used for the compound studied. For compounds **1a, 1b, 1h, 1i** and **1j**, the model compound was procaine hydrochloride ($\Delta H_i = -40.13$ kJ mol^{-1} (Lobreaux, 1985)). For **1c, 1d** and **1e, 1f**, the model compounds chosen were piperazine and triethylamine (-42.51 and -43.13 kJ mol^{-1}, respectively). The entropy of transfer can finally be obtained by use of the general thermodynamic relation

$$\Delta H = \Delta G + T\Delta S$$

The standard Gibbs free enthalpies of transfer ΔG_T° were calculated from the partition coefficient P using the relation:

$$\Delta G_T^\circ = -RT \ln P$$

For the sake of consistency, we used log P values calculated according to the method of Rekker and De Kort (1979), since experimental values are determined using a variety of techniques under different conditions.

We noted that transfers were only entropy driven except for chlorproethazine (**1i**) of which the transfer was entropy and enthalpy cooperative. Two series of compounds can be readily distinguished:

The first of our series, **1a, 1c–1f**, contains compounds that have approximately equal magnitudes for the enthalpy of transfer. Interestingly, these compounds behave mainly as neuroleptics. The values obtained for their parameters of transfer are consistent with hydrophobic interactions which can be summarised in terms of the structure of

'frozen' water around the apolar (or weakly polar) solute in the aqueous phase (Tanford, 1980). On solute transfer into the octanol phase, destruction of its surrounding aggregates of water increases the entropy of the system and produces a slight endothermic effect.

In the second series, **1b**, **1h** and **1j**, the transfers are less endothermic and in one case (**1i**) even slightly exothermic. These compounds do not behave mainly as neuroleptics. Both types of transfer can probably be rationalized in terms of different conformations of the solutes in either the aqueous or octanol phase, with the result that the enthalpies of solvation can differ somewhat. We have previously encountered a case similar to that of the phenothiazines during a study of the partitioning of some barbiturics (Burgot et al., 1989). In order to explain the shift in the enthalpies of transfer towards less endothermic values and, in one case, even toward a weakly exothermic value, we postulated the folding of the unsaturated 5 branch chain on the pyrimidine trione cycle.

Thus, fewer water molecules were frozen around the solute in the aqueous phase while the interactions in the octanol phase were identical for both folded and unfolded compounds. Support for this explanation was provided by measurements of log *P* for these compounds (Hansch et al. 1967).

The folding in the aqueous phase of the lateral aminoalkyl chain on the phenothiazine nucleus is quite possible. Numerous conformations of phenothiazines in solutions have been envisaged and for some of them the folding of the lateral chain on the phenothiazine tricycle or even between the two phenyl nuclei has been postulated (Wilhelm, 1974; Barbe, 1978; Fronza et al., 1981).

Of course, the task of establishing the different conformations of phenothiazines in solution is difficult to accomplish and our last explanation is clearly conjectural. Nevertheless, the present data demonstrate that with relatively slight modifications in structure of the molecules, new conformations do occur. Moreover, they allow us to put forward the hypothesis that the water/*n*-octanol transfers of the phenothiazines which are mainly neuroleptic compounds are endowed with the most endothermic transfers.

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