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Thermochemical Aspects of Water/*n*-Octanol Partitioning of Some Local Anaesthetic Agents

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The water/*n*-octanol partitioning thermodynamic parameters of some local anaesthesic agents are determined through a calorimetric estimation of the enthalpies of transfer. Partitionings are entropy-driven. Although no single mechanism of transfer can be ascribed, the mechanisms seem identical for each subfamily of the same kind of structure.

Keywords partition property; hydrophobicity; enthalpy, entropy; 1-octanol/water; local anaesthetic agent; thermometric titrimetry

The determination of water/*n*-octanol partitioning thermodynamics is the logical consequence of the equivalence: log *P*–standard free enthalpy of transfer of the solute from water to *n*-octanol ΔG_T°.[1] Given the numerous quantitative structure–activity relationship (QSAR) where log *P* is engaged, this equivalence calls inevitably for the knowledge of the enthalpy, ΔH_T, and the entropy, ΔS_T, of the partitioning process. From the very deep significance of enthalpy and entropy, one may believe that knowing their contributions to the standard free enthalpy of transfer might lead to greater knowledge of the solvation and desolvation processes which accompany the transfer.[2] Moreover, new types of QSAR implicating the enthalpy, ΔH_T, and entropy, ΔS_T, of transfer can be established.[3-5] We report here an estimation of the water/*n*-octanol thermodynamic parameters of some local anaesthetic agents (Chart 1), determined during the course of our previous research in the field.[6-8]

Standard enthalpies of water/*n*-octanol transfer, ΔH_T°, have been determined by titration calorimetry according to our previously described method for compounds with very low solubility in water.[9,10] This method is derived from our general procedure to determine simultaneously ΔG_T°, ΔH_T° and hence ΔS_T°.[10,11] Titration of hydrochlorides by a solution of sodium hydroxide of C_t concentration in the presence of *n*-octanol allows the determination of the enthalpy difference:

$$\Delta H_n - \Delta H_T^\circ$$

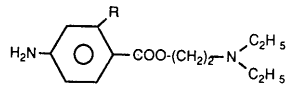
where ΔH_n is the enthalpy of neutralization of the solute according to

$$BH^+aq + OH^-aq \rightarrow B\ aq + H_2O \text{ (where B stands for the base[12])}$$

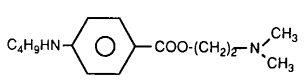
A drawback of our procedure is that it gives only the difference $(\Delta H_n - \Delta H_T^\circ)$. If the aqueous solubility of the basic form B is sufficient, ΔH_n can be determined directly by an independent calorimetric method. If not, ΔH_n can fortunately be estimated, with acceptable accuracy, from the values of the tables.[13] The main advantage is that it gives directly the enthalpy of transfer by a calorimetric method (which is fundamentally, of course, the most judicious way to obtain an enthalpy). Besides, the indirect determination of transfer enthalpies through the Van't Hoff relation raises a number of difficulties[14] and has been a matter of criticism.[15-17] Our standard transfer free enthalpies ΔG_T° have been computed using the well-known equation

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

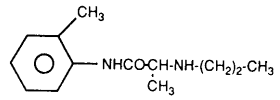
We intentionally used *P* values calculated according to the methods of Leo[18] and Rekker[19] for the sake of homogeneity because the experimental values that we could have used had not been determined in the same experimental conditions as the enthalpies. Otherwise, since the Π and f constants used to calculate log *P* values were obtained statistically from experiments performed at room temperature, the ΔG_T° values can be considered as insignificantly different from those which would be obtained at 25 °C. Therefore, since transfer enthalpies,



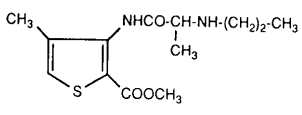
procaine(1) : R=H
ravocaine(2) : R=OC_3H_7



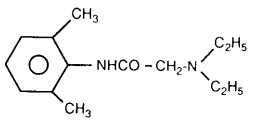
tetracaine(3)



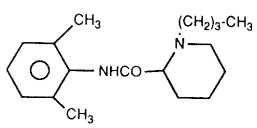
prilocaine(4)



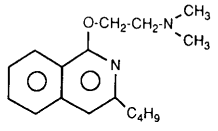
articaine(5)



lidocaine(6)



bupivacaine(7)



quinisocaine(8)

Chart 1

TABLE I. Water/*n*-Octanol Thermodynamic Parameters of Transfer of Some Local Anaesthetic Compounds

	log *P*	ΔG_T° [d]	ΔH_T° [d),23]	ΔS_T° [e]
Procaine (**1**)	2.41[a]	−13760	4230	61
	2.00[b),21]	−11420	(3600)[f),25]	53
	1.92[c),22]			
Ravocaine (**2**)	3.90[a]	−22260	10203	109
	3.82[b]	−21803		107
Tetracaine (**3**)	3.52[a]	−20090	−405	61
	3.40[b),21]	−19410		65
Prilocaine (**4**)	2.06[a]	−11760	11330	77
	1.78[b),21]	−10160		72
Articaine (**5**)	1.90[a]	−10850	10255	71
	1.88[b]	−10730		70
Lidocaine (**6**)	2.51[a]	−14330	26460	137
	2.76[b),21]	−15750	(2890)[f),25]	142
	2.26[c),24]			
Bupivacaine (**7**)	4.25[a]	−24260	1907	145
	4.33[b),21]	−24710		147
Quinisocaine (**8**)	3.88[a]	−22150	2350	82
	4.55[b]	−25400		93

a, b) Calculated according to Rekker's and Leo's methods respectively. *c*) Experimental. *d*) $J \cdot mol^{-1}$. *e*) $J \cdot mol^{-1} K^{-1}$. *f*) In brackets, values found in literature.

ΔH_T°, are determined calorimetrically at 25 °C, the thermodynamic parameters obtained are also values at 25 °C. Anyway, these points are not very significant, because our purpose in this work is solely to provide an estimate of the thermodynamic parameters of partitioning in order to establish whether some trends exist among the different chemical structures. Finally, standard entropies of transfer are calculated from the well known relation[20]

$$\Delta H_T^{\circ} = \Delta G_T^{\circ} + T\Delta S_T^{\circ}$$

It can be inferred from the values of Table I that the transfer processes are only entropy-driven since the enthalpies are positive except for tetracaine, the enthalpy value of which is nearly null. The fact that we failed to find a single satisfactory linear relationship of compensation $\Delta G_T^{\circ}/\Delta H_T^{\circ}$, by plotting on the same graph the values (in our case, truly independent values from one group to the other[27]) of these two parameters, for all the solutes is an indication of the multiplicity of partitioning mechanisms.[28] However, it appears that some similarities of behavior can be found for solutes with the same kind of structure.

Procaine **1** and ravocaine **2** exhibit nearly the same ratios ($\Delta G_T^{\circ}/T\Delta S_T^{\circ} \approx 0.70$). This may indicate a similar partitioning mechanism. Values obtained for ΔH_T° and ΔS_T° can be explained by hydrophobic interactions.[29] The greater values of ΔS_T° and ΔG_T° of ravocaine **2** originate in its propyl chain which, in water, increases the number of structured water molecules. Due to the transfer, more water is released. This increases the disorder of the whole system and the partitioning is more endothermic than with procaine (the structuration of water around the solute being slightly exothermic). These hydrophobic interactions do not preclude the existence of polar H-bonds between the aromatic and aliphatic primary amino groups, carbonyl groups with water as well as *n*-octanol, which is an H-donor or acceptor.

Given the value of the ratio ($\Delta G_T^{\circ}/T\Delta S_T^{\circ} \approx 0.50$), prilocaine **4**, articaine **5** and bupivacaïne **7** probably have the same behavior of partitioning. If we compare their values ΔH_T° and ΔS_t° to those of procaine **1**) which has a $\Delta G_T^{\circ}(\log P)$ of the same order of magnitude) it appears that these values are markedly greater. This can be accounted for by the greater solvation of the acetamido group in water than in octanol, attributable to a torsion of this group between the N–C bond in the first solvent due to the presence of the σ-methylphenyl.[30] However, closely related compounds from the structural stand-point, lidocaïne **6** and bupivacaïne **7**, have different partitioning parameters. The high values of ΔH_T° and ΔS_T° of lidocaine **6** compared with those of bupivacaine **7** which themselves are proportionally higher than those of ravocaine **2**, the log *P* of which is of the same order of magnitude.[31] are particularly noticeable. Undoubtedly, these high values are accounted for by the presence of the di σ-o′ methyl substituents of the acetanilido group, which induces a rotation of the gross acetanilido group (around the aryl-N bound) in water with a greater solvation in this solvent.[30,32] Other explanations for abnormal *f*-values of the Ar–NHCO–CH_2–N group have been given.[33] The difference of behavior between lidocaine **6** and bupivacaine **7** can be explained by the fact that the last molecule is proportionally more compact than the first. This effect has been named a desolvation effect.[30]

Finally, a surprising analogous behavior, with a particularly weak enthalpy effect, of tetracaine **3** and quinisocaine **8** is found. It is tempting to attribute this analogy to the presence of the 2-dimethylaminoethoxy group. In any case, a possible explanation for this markedly less endothermic partitioning is the occurrence of bonds between *n*-octanol and the solutes, which did not exist in water.

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