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A first estimation of the thermodynamic parameters of water/n-octanol partitioning of some tricyclic antidepressants: Similarities and differences with the values of other psychotropic drugs

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Summary

Thermometric titrimetry allows the determination of the thermodynamic parameters of transfer from water to *n*-octanol for tricyclic antidepressants. Their transfers are both entropy and enthalpy driven, whereas those of phenothiazinic neuroleptics are solely entropy driven. The hypothesis of the folding of the lateral chain upon the tricyclic nucleus in antidepressive drugs gives a satisfactory explanation of the results. Differences and analogies of behavior during the partitioning of antidepressants and phenothiazinic compounds are also underlined.

Introduction

Bente et al. (1964) put forward the hypothesis that among tricyclic psychotrope molecules those having the more planar geometry are neuroleptic while the more folded ones have thymoanaleptical properties. Wilhem (1974) studied in detail this hypothesis by considering the lateral chain positions with regard to that of the tricyclic nucleus. He has thoroughly analysed the model according to the folding of the lateral amino chain (a necessarily linear one containing three carbons) towards the tricyclic nucleus, in the shape of a closed curve looking like a cyclohexane cycle, which would be at the origin of the thymoanaleptical effect.

Our calorimetric studies on the determination of water/*n*-octanol transfer enthalpies, free enthalpies and entropies of some drugs (Burgot et al., 1989, 1990; Burgot and Burgot, 1990) have allowed us to define the enthalpic or entropic nature of the partitioning and to infer the most likely conformations of the solutes in the two solvents, especially in water (Burgot and Burgot, 1986). These determinations have revealed the

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folding of the unsaturated chain substituted in position 5 towards the pyrimidinetrione cycle in some barbiturates (Burgot et al., 1989).

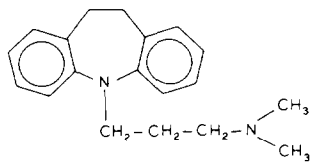
Therefore, it seemed interesting to us to determine the water/*n*-octanol transfer thermodynamic parameters of a series of tricyclic antidepressants, with the following objectives:

Firstly, to discover whether their thermodynamic behavior during the water/*n*-octanol partitioning differed from that of neuroleptic and not mainly neuroleptic derivatives (Burgot and Burgot, 1990).

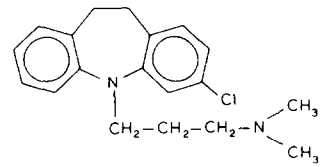
Secondly, to obtain data of a new type in order to discuss Wilhelm's hypothesis.

Materials and Methods

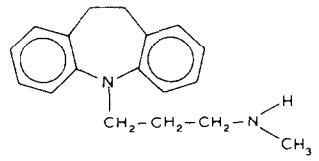
As in our previous studies (Burgot and Burgot, 1984), water/*n*-octanol partitioning enthalpies of



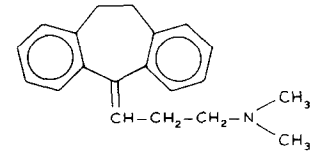
Imipramine



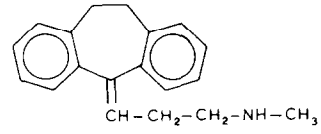
Clomipramine



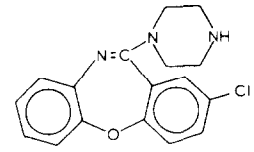
Desipramine



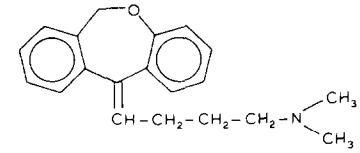
Amitriptyline



Nortriptyline



Amoxapine



Doxepine

Fig. 1. Structure of tricyclic antidepressants.

the studied tricyclic antidepressants were determined by titration calorimetry. We chose this procedure that we proposed for the determination of thermodynamic parameters of transfer in very weakly soluble solutes (Burgot and Burgot, 1989) because of the very low solubilities in water of the basic forms of tricyclic antidepressants. With this procedure, calorimetric data obtained by titration calorimetry allow the determination of transfer enthalpies (ΔH_T; see below). The standard transfer free enthalpy ($\Delta G°_T$) is computed using the well-known expression (Eqn 1) (Tremillon, 1971):

$$\Delta G°_T = -RT \ln P \quad (1)$$

where P is the thermodynamic partitioning coefficient. Once these two parameters known, the transfer entropy ΔS_T is computed using a second well-established formula (Eqn 2):

$$\Delta H_T = \Delta G°_T + T\Delta S_T \quad (2)$$

which can be applied for isobaric and isothermal physical and chemical processes. In our determinations, we assumed that it was only the basic (non-ionic) form which was transferred from water to *n*-octanol. This hypothesis is based on the low dielectric constant of *n*-octanol (= 10.3) (Veda et al., 1980). In other words, we assumed that the transfer of the acidic form as an ion pair was quite insignificant. As a result, the determined values were related to the partitioning of the basic, non-ionic, solutes. From a mere thermodynamical standpoint, the determined enthalpies could be considered as being the standard enthalpies of partitioning $\Delta H°_T$, given the very low concentrations of the basic solutes in water and their low concentrations in octanol after partitioning (Klotz, 1964). Therefore, the entropy computed using Eqn 2 was also the standard entropy of transfer $\Delta S°_T$.

To calculate the free enthalpies of partitioning using Eqn 1, we computed P values with the help of the fragmental method of Rekker and De Kort (1979). We chose to calculate the P values because the partioning coefficients of all the studied solutes had not yet been experimentally determined. Since, if the experimental and calculated log P values were mixed, the reliability of the results could be questioned. It is for the sake of homogeneity that we chose to compute log P values. The choice of the fragmental method of Rekker and De Kort is somewhat questionable since the advent of other methods of calculation of log P coefficients.

Of course, using the fragmental method which is essentially a statistical procedure and thus does not account for extraordinary unusual molecules in some cases, albeit seldom, may give somewhat spurious log P values. In any case, it is not a very significant point because our purpose in this work is solely to provide an estimate of the thermodynamic parameters of partitioning in order to establish some comparison trends among the different series of solutes.

Imipramine, clomipramine, desimipramine and nortriptyline of guaranteed purities were purchased as hydrochlorides and amitriptyline doxepine and amoxapine (also of guaranteed purities) as bases (Fig. 1).

The partitioning enthalpies $\Delta H°_T$ were determined from the thermal effects obtained during thermometric titration of the conjugate acids by sodium hydroxide solution in the aqueous phase in the presence of *n*-octanol (Burgot and Burgot, 1989). The thermal effects allow only the determination of the sum of the enthalpies of transfer $\Delta H°_T$ and of neutralization $\Delta H°_n$ of the acidic solutes. Fortunately, it is known from the literature data that aqueous neutralization enthalpies of organic acids can be estimated with reasonable accuracy once the structures of the groups located near the acid function are known (Christensen et al., 1967, 1969). Therefore, in our study we assumed that the neutralization enthalpies of all the solutes were very close to that of procaine hydrochloride ($\Delta H_N = -15.6$ kJ mol^{-1}) (Lobreaux, 1984). The only exception is amoxapine hydrochloride for which we adopted the neutralization enthalpy of piperazine ($\Delta H_N = -13.3$ kJ mol^{-1}) (Burgot and Burgot, 1991). We have already discussed the reasons for this approach in previous papers (Burgot and Burgot, 1989). The apparatus was the same as in our previous studies (Burgot et al., 1989). Our calorimetric data were obtained at 25°C. Fragmental constants used to

TABLE 1

Water / n-octanol thermodynamic parameters of some tricyclic antidepressants

	$\Delta H°_n$ (J mol^{-1})	log P [a]	$\Delta G°_T$ (J mol^{-1})	$\Delta H°_T$ (J mol^{-1})	$\Delta S°_T$ (J mol^{-1} K^{-1})
Imipramine	−15600	4.78	−27300	−270	91
		(4.42)	(−25215)	(271)	(83.70)
Clomipramine	−15600	5.71	−32600	1700	115
		(5.19)	(−29608)		(105.15)
Desimipramine	−15600	4.35	−24800	−6700	61
Amitriptyline	−15600	5.89	−33600	−560	111
		(5.04)	−28800		(94.60)
Nortriptyline	−15600	5.45	−21000	−6400	83
Doxepine	−15600	4.29	−24500	−3000	72
Amoxapine	−13300	1.89	−10800	+540	349

[a] Figures in parentheses are experimentally determined values (Burgot et al., 1989).

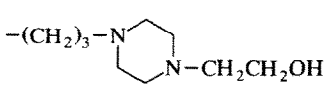
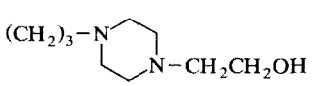
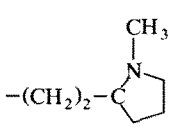
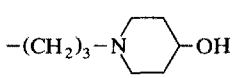
calculate log P values were obtained from experiments performed at room temperature. Therefore, ΔG_T values can be considered as insignificantly different from those which would be obtained at 25°C. Since the ΔH_T values were obtained at this temperature, the ΔS_T values therefore correspond to values at 25°C. As in all the other methods of computation of log P values used in pharmacochemistry, fragmental constants are expressed in terms of concentrations based on the molar concentration scale (Klotz, 1964).

Results and Discussion

The values obtained are listed in Table 1. For the sake of facilitating the discussion of results, the partitioning values obtained in the same way

TABLE 2

Water / n-octanol thermodynamic parameters of some phenothiazines (Burgot and Burgot, 1990)

	R_2	R_1	ΔG^0_T (J mol^{-1})	ΔH^0_T (J mol^{-1})	ΔS^0_T (J mol^{-1} K^{-1})
Chlorpromazine	Cl	$(CH_2)_3-N-(CH_3)_2$	−30900	3800	116
Fluphenazine	CF_3		−32300	2700	118
Perphenazine	Cl		−30200	4400	116
Thioridazine	SCH_3		−37200	3200	135
Propericiazine	CN		−22300	3200	86
Levomepromazine	OCH_3	$CH_2-CH(CH_3)-CH_2-N(CH_3)_2$	−30000	780	103
Alimémazine	H	$-CH_2-CH(CH_3)-CH_2-N(CH_3)_2$	−28600	1500	101
Chlorproethazine	Cl	$-(CH_2)_3-N-(C_2H_5)_2$	−36900	−1300	119
Diethazine	Cl	$-(CH_2)_2-N-(C_2H_5)_2$	−33900	440	116

with some phenothiazines, which are closely related to the tricyclic antidepressants from a chemical standpoint, are recalled in Table 2(Burgot and Burgot, 1989, 1990).

(i) It can be seen that:

The partitioning of the tricyclic antidepressants is both entropically and energetically driven. The two exceptions are clomipramine and amoxapine, the partitioning of which is solely entropy driven since their transfer enthalpies are unfavorable. However, these enthalpies are only weakly endothermic.

The partitioning of the neuroleptic phenothiazines (chlorpromazine, fluphenazine, perphenazine, thioridazine, propericiazine; Table 2) is only entropically driven since their transfer enthalpies are markedly endothermic.

The partitioning of the phenothiazinic compounds which are not mainly neuroleptic (levomepromazine, alimemazine, chlorproethazine, diethazine; Table 2) displays behavior which is similar to that of the antidepressants under study.

(ii) It can also be seen that the differences exhibited by the three types of compounds lie in the values of their transfer enthalpies. Indeed, for the three types, the transfer entropies are favorable. Moreover, at first glance, they are of the same order of magnitude. In contrast, the enthalpies of partitioning are exothermic for the antidepressants (two of which are weakly endothermic), markedly endothermic for the neuroleptics, and weakly endothermic for the other phenothiazines.

(iii) Therefore, it appears that tricyclic antidepressants and neuroleptic phenothiazines do not follow the same partitioning mechanism. It also appears that the transfer of other phenothiazines is similar to that of tricyclic antidepressants. The multiplicity of transfer mechanisms is confirmed by the failure to find a single satisfactory linear relationship of compensation enthalpy/entropy on plotting on the same graph the values of these two parameters for all the solutes of the three types. According to some authors (Leffler and Grunwald, 1963), the discovery of such a relation (or a similar free enthalpy/entropy relation, all these parameters being possible activation parameters) should represent strong support for a single-mechanism process. All these results indicate the interest, in pharmacochemistry, of improving the determination of log P (transfer free enthalpy) through a knowledge of the transfer enthalpy and entropy). There are some examples in the literature (Goffredi and Turcoliveri, 1982) of linear relationships between log P and the length of a carbon chain suggesting a single mechanism of partitioning, whereas this is actually not the case (Beezer and Hunter, 1983).

(iv) The values of the parameters of transfer can be rationalized in terms of different solvation of solutes in water and in octanol. In these processes of solvation, hydrophobic interactions play a role of utmost importance (Tanford, 1980). During the transfer from water to n-octanol, breaking up of the structured water which surrounds the solute molecule in the aqueous phase occurs. The release of some water molecules increases the disorder of the whole system. At the same time there is a slight endothermic effect, since the formation of the structured water around the solute is slightly exothermic.

On comparison of the values obtained with chlorpromazine and clomipramine and assuming that the two molecules are identically solvated in octanol, one may envisage that, in the aqueous phase, the masking of the tricyclic nucleus by the lateral chain is greater in the latter molecule than in the former.

The resulting screen would decrease the solvation of the antidepressant with a lower endothermic transfer enthalpy. This hypothesis is not necessarily inconsistent with the fact that the entropies of transfer of the two compounds have the same values, which probably means that during the partitioning the same number of water molecules is released. Indeed, it is quite conceivable that the solvation in the aqueous phase of the ethano-bridge is slightly more important than that of the sulfur atom. We encountered the same screening effect during a study of the partitioning of some barbiturates (Burgot et al., 1989). In these compounds, when the chain substituted in position 5 possesses one or more unsaturated sites, it folds towards the pyrimidine trione cycle as a result of the interactions between the π-electrons and the carbonyl groups of the cycle. This

explains why, for example, the entropy transfer is weaker and the enthalpy less endothermic (even exothermic in the case of phenobarbital) than with other saturated barbiturates. Hansch and Anderson (1967) had already noted that phenobarbital was actually more soluble in water than was expected. The folding of the lateral chain towards the tricyclic nucleus of antidepressants is in conformity with Wilhelm's hypothesis (1974). As concerns the folding of the lateral chain, which is more important with clomipramine than with chlorpromazine, it can undoubtedly be ascribed to the different geometries of the two central tricyclic nuclei.

The values of the thermodynamic parameters of partitioning obtained with imipramine and amitriptiline suggest similar folding of the lateral chain. It is interesting to note that the replacement of a C-N bond by a C-C bond has very little effect on the partitioning parameters. Such replacement slightly increases the entropy, as shown by the values obtained with the two pairs imipramine/amitriptyline and desimipramine/nortriptyline. It is also interesting to note that replacing the H atom in position-3 in the tricyclic nucleus by a Cl atom results in an endothermic effect with an increase in the entropy linked to the increase in the hydrophobic interactions. However, it has been reported that the replacement of an H atom by a Cl atom on an aromatic nucleus can sometimes be the source of a decrease in entropy (Dearden and Bremen, 1981).

In the antidepressant series, desimipramine and nortriptyline exhibit closely similar partitioning values. They differ markedly from those obtained with the other thymoanaleptical compounds. The former exhibit a weaker transfer entropy and a much greater exothermic effect. Both these results can be explained on the basis of the occurrence of an H bond between the secondary amino group and the hydroxyl of octanol, thus resulting in a somewhat unusual structured final state (entropy effect) with the corresponding enthalpic effect. The behavior of desimipramine and of nortriptyline, which differs from that of the other tricyclic antidepressants, supports the hypothesis that two families of serotonic receptors exist (Pepe et al., 1989), however, this proposal has been refuted (Andrews et al., 1987). Nevertheless, it is a well-known fact that secondary monomethylated amines are more psychotonic than tertiary dimethylated amines which are more sedative. These molecules (desimipramine, nortriptyline) would inhibit primarily noradrenaline recapture whereas other antidepressants would be more effective at recapturing serotonin (Loo et al., 1987, 1988). It is interesting to note that the differences in transfer enthalpies and entropies between imipramine and desimipramine, on the one hand, and between amitriptyline and nortriptyline, on the other, are nearly identical. This fact once again demonstrates, on thermodynamical grounds, the structural analogies between these two pairs of compounds.

Doxepine also has a partitioning enthalpy which is markedly less positive than that of imipramine in addition to a plainly exothermic transfer enthalpy. The latter result can be explained by the formation, in the organic phase, of an H bond with the octanolic hydroxyl. The former result can be accounted for by an increase in the rigidity of the central nucleus with concomitantly less effective solvation in water. The rigidity of this compound and of other closely related species has been studied in different solvents using NMR (Munro et al., 1986). Amoxapine is structurally too different from the other antidepressants for a meaningful comparison between them.

The behavior of the neuroleptical phenothiazines is more normal than that of the antidepressants with respect to the hydrophobic effect, since the thermal effect is more endothermic. The solvation of the neuroleptic phenothiazines in the aqueous phase is probably more important than that of the antidepressants. According to our model, the endothermic effect and the increase in entropy should both be greater than in the cases of fluphenazine, perphenazine and propericiazine. The difference probably results from an H bond between the octanolic hydroxyl and the hydroxyl moieties of these compounds. The value of the transfer enthalpy found with thioridazine, which is not an alcohol, provides contrariwise proof of this hypothesis.

Finally, the values determined with the phenothiazines which are not mainly neuroleptical (Table 1, 2nd part) are of the same order of magnitude as those found with antidepressants, except for desimipramine and nortriptyline, and can be explained similarly. All these compounds have carbon fragments which are more important in their lateral chains. The central nucleus is screened to a greater extent by these supplementary fragments than by the lateral chains of neuroleptical compounds. As shown by the values of their transfer enthalpies, the supplementary screening effect developed by the 2-methyl group in the lateral chain (alimemazine and levomepromazine) is slightly less extensive than that developed by the methyls of the diethylamino function, in agreement with simple geometrical considerations.

Conclusion

The results on the partitioning between water and *n*-octanol enthalpies and entropies of some tricyclic antidepressants, as estimated by thermometric titrimetry, lead to the following conclusions:

Their transfers are both entropically and energetically driven (except for clomipramine and amoxapine). The results found with both of these products provide support for this finding, since their partitioning enthalpies are only very weakly unfavorable.

The thermodynamical transfer behavior of dibenzoazepines and that of dibenzocycloheptadiene are nearly identical. This phenomenon involves analogous solvation of the two series of compounds which itself involves the same conformations.

The values determined with desimipramine and nortriptyline are perfectly analogous. However, they differ markedly from those found with the other antidepressants.

The values found with the antidepressants differ substantially from those observed with neuroleptical phenothiazines, the partitioning of which is systematically and solely entropically driven.

The behavior of the tricyclic antidepressants can be explained by a folding of the lateral chain towards the central tricyclic nucleus. Their solvation is therefore less effective than when there is no folding, which is the case for neuroleptical phenothiazines, for instance. Similar values of partitioning obtained with both tricyclic antidepressants and phenothiazines which are not mainly neuroleptical can be also rationalized on the basis of folding of the lateral chain in the latter compounds.

Nevertheless, such an analogy appears to lack significance, since the lateral chains of the two series differ.

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References

Andrews, P.R., Craik, D.K. and Munro, S.L., A pharmacophore hypothesis for antidepressant activity. *Quant. Struct. Act. Relat.*, 6 (1987) 97–103.

Beezer, A.E. and Hunter, W.H., Oscillation in some linear free energy relationship derived from partition coefficients of phenols between octanol and water. *J. Med. Chem.*, 26 (1983) 757–759.

Bente, D., Hippius, H., Poldinger, W. and Stach, K., Chemische Konstitution und klinische Wirkung von Antidepressiven Pharmaka. *Arzneimittel-Forsch.*, 14 (1964) 486–490.

Burgot, G. and Burgot, J.L., Détermination simultanée de l'enthalpie, de l'enthalpie libre via le coefficient de partage et de l'entropie de transfert eau/*n*-octanol de l'éphédrine par titrimétrie thermométrique. *Thermochim. Acta*, 81 (1984) 147–156.

Burgot, G. and Burgot, J.L., Comaparaison des parameètres thermodynamiques de transfert eau/*n*-octanol de la D-(−)-éphédrine et de la D-(−)-pseudoéphédrine. *Ann. Pharm. Fr.*, 44 (1986) 313–316.

Burgot, G. and Burgot, J.L., Principe de l'estimation par titrimétrie thermométrique de l'enthalpie et de l'entropie de transfert eau/*n*-octanol de solutés très lipophiles. *Thermochim. Acta*, 152 (1989) 463–468.

Burgot, G. and Burgot, J.L., Water/*n*-octanol thermodynamic parameters of some phenothiazines. *Int. J. Pharm.*, 62 (1990) R5–R7.

Burgot, G., Huet, J. and Burgot, J.L., Détermination des paramètres themrodynamiques de transfert eau/*n*-octanol de barbituriques: application aux relations quantitatives. *Eur. J. Mec. Chem.*, 24 (1989) 15–21.

Burgot, G., Serrand, P. and Burgot, J.L., Thermodynamics of partitioning in the n = octanol/water systems of some β-blockers. *Int. J. Pharm.*, 62 (1990) R1–R4.

Burgot, G. and Burgot, J.L., Détermination simultanée de l'enthalpie, du coefficient de partage et de l'entropie de transfert eau/*n*-octanol de l'éphédrine par titrimétrie thermométrique: aspects cinétiques. *Thermochim. Acta*, 180 (1991) 49–59.

Christensen, J., Izatt, R.M. and Hansen, L.D., Thermodynamics of proton ionization in dilute aqueous solution: VII. $H°$ and $S°$ values for proton ionization from carboxylic acids at 25°C. *J. Am. Chem. Soc.*, 89 (1967) 2, 213–223.

Christensen, J., Izatt, R.M., Wrathall, D.R. and Hansen, L.D., Thermodynamics of proton ionization in dilute aqueous solution: XI. pK, $H°$ and $S°$ values for proton ionization from protonated amines at 25°C. *J. Chem. Soc.*, A (1969) 1212–1223.

Dearden, J.C. and Bresnen, G.M., Thermodynamics of partitioning. some considerations of intra molecular bonding and steric effects. *J. Pharm. Pharmacol.*, 33 (1981) 107 P.

Goffredi, M. and Turco Liveri, V., Thermodynamic transfer functions of non ionic solutes between unmiscible liquid phases – Transfer of some secondary alcohols from *n*-octane to water at 298.15 K. *J. Phys. Chem.*, 86 (1982) 2455–2458.

Hansch, C. and Anderson, S.M., The structure-activity relationship in barbiturates and its similarity to that in other narcotics. *J. Med. Chem.*, 10 (1967) 745–753.

Hansch, C., Bjorkroth, J.P. and Leo, A., Hydrophobicity and central nervous system agents. On the principle of minimal hydrophobicity in drug design. *J. Pharm. Sci.*, 76 (1987) 663–686.

Klotz, I.M., The dilute solution: Non-electrolytes. In *Chemical Thermodynamics*, Benjamin, New York, 1964, pp. 335–345.

Leffler, J.E. and Grunwald, E., Extrathermodynamic free energy relationships. In *Rates and Equilibria of Organic Reactions*, Wiley, New York, 1963, pp. 128–314.

Lobreaux, J., Détermination par titrimétrie thermométrique de l'enthalpie, de l'enthalphie libre et de l'entropie de transfert eau/*n*-octanol de la procaïne. *Mémoire de D.E.A.*, Université de Rennes (1985).

Loo, H., Caillard, V. and Zarifian, E., Antidépresseurs *Encycl. Med. Chir, Psychiatr.*, 10, 25420 B50 (1988) 1–14.

Loo, H., Davy, J.P. and Zarifian, E., Les antidépressurs *Encycl. Med. Chir. Psychiatr.*, 12, 37860 B70 (1987) 1–27.

Munro, S.L., Andrews, P.R., Craik, D.J. and Gale, D.J., ^{13}C NMR studies of the molecular flexibility of antidepressants. *J. Pharm. Sci.*, 75 (1986) 133–141.

Pepe, G., Reboul, J.P. and Oddon Y., Relation between psychotonic or sedative activity of tricyclic antidepressant drugs and noradrenaline and serotonin receptive characteristics from conformational and molecular electrostatic potential analysis. *Eur. J. Med. Chem.*, 24 (1989) 1–13.

Rekker, R. and De Kort, H., The hydrophobic fragmental constant; an extension to a 1000 data point set. *Eur. J. Med. Chem.*, 14 (1979) 479–488.

Tanford, C., Origin of the hydrophobic effect. *The Hydrophobic effect. Formation of Micelles and Biological Membranes*, 2nd Edn, Wiley, New York, 1980, pp. 1–4.

Tremillon, B., Correlation entre les propriétés dans des solvants differents. In *La chimie en solvants non aqueux*, Coll. Sup., Presses Universitaires de France, Paris, 1971, pp. 167–231.

Veda, I., Yasuhara, Smiem, Lin M.C., Lin S.M. and Eyring H., In *Progress in Anesthesiology*, Vol. 2, Raven Press, New York, 1980.

Wilhelm, M., La chimie des psychotropes polycycliques, jeu de hasard ou systématique? *Actual. Chim. Ther.*, 2^{e} Ser. (1974) 33–45.