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Thermodynamics of partitioning of β-blockers in the *n*-octanol-buffer and liposome systems

G.V. Betageri and J.A. Rogers

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alta (Canada)

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Summary

The thermodynamics of partitioning (K_m) of 10 β-adrenergic receptor blocking agents have been determined in the *n*-octanol-buffer and liposome-buffer systems at pH 7.4. Plots of log K_m vs $1/T$ were linear in the *n*-octanol-buffer system from 30 °C to 50 °C, but some drugs exhibited a lower than expected or a zero K_m at lower temperatures. Partitioning was generally greater in dimyristoylphosphatidylcholine liposomes than in the *n*-octanol-buffer system, but it was less below than above the T_c of the phospholipid. A K_m of nadolol in *n*-octanol-buffer was detected only at 50 °C, however, significant values were obtained in liposomes, but only above the T_c. A correlation between log K_m(*n*-octanol) and log K_m(liposome) ($r = 0.986$) was obtained at 30 °C for all β-blockers except acebutolol. Enthalpies and entropies of partitioning were positive in the *n*-octanol-buffer system and in liposomes above the T_c, but negative below the T_c. Hydrophobic substituent constants were 55% greater in liposomes overall and varied depending on the polarity of the substituent and its position on the aromatic ring structure. Enthalpy–entropy compensation was not observed in the *n*-octanol-buffer system or in liposomes below the T_c, but it was found in liposomes above the T_c. Thus, it is concluded that the liposome system is a more selective partitioning model than the *n*-octanol-buffer system.

Introduction

The distribution of drugs in membranes was first quantitatively described by Collander (1951) to be related to their partition coefficients in bulk oil-water systems. Among the many oils which have been investigated since then, semipolar solvents have been found to yield better correlations with the partitioning of solutes in model and biological membranes than non-polar solvents (Leo et al., 1971; Diamond and Katz, 1974). In particular, *n*-octanol has been shown to be a useful reference system for extrathermodynamic studies on a variety of systems (Hansch and Dunn, 1972).

Although the water-saturated *n*-octanol-water system presumably possesses structural characteristics as a result of the formation of water/*n*-octanol clusters (Smith et al., 1975), it has been suggested that the bulk oil lacks sufficient structural similarities to biological membranes to be expected to account for the role of steric influences of drug molecular structure on membrane partitioning, transport, drug-receptor interactions and, hence, biological activities (Rogers and Wong, 1980). Analysis by quantitative structural activity

Correspondence: J.A. Rogers, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alta, Canada T6G 2N8.

relationships with respect to several drug transport processes has revealed poor modelling by the *n*-octanol/water system (Martin, 1981). On the other hand, the liposome system has been shown to discriminate against branched solutes more than does a bulk solvent of similar semipolar character (Diamond and Katz, 1974) and liposome/saline hydrophobicities were found to correlate with the biological activities of chloramphenicol cogenors much better than the *n*-octanol/water system (Brown and Brown, 1984). The purpose of the present study was to compare the partitioning behavior of a series of β-blockers in the *n*-octanol/aqueous buffer and buffered liposome systems using a thermodynamic approach and from this, assess the relevance of each model as a selective distribution system for drugs.

A comparison of partitioning mechanisms of polar alkanol solutes in a bulk oil–water system vs a liposome system using a thermodynamic approach has been made by Katz and Diamond (1974). Their results pointed to a greater immobilization of solutes in bilayers than in bulk solvents. Enthalpies and entropies of partitioning of phenolic derivatives have also been shown to be positive in dimyristoylphosphatidylcholine (DMPC) liposomes below the phase transition temperature (T_c) (Rogers and Davis, 1980; Anderson et al., 1983) and in pure non-polar hydrocarbon–0.15 M NaCl systems (Anderson et al., 1983). However, in the *n*-octanol/water system (Rogers and Wong, 1980; Anderson et al., 1983) and above the T_c of DMPC liposomes (Rogers and Davis, 1980) negative enthalpies and entropies of partitioning were found. Recently, the thermodynamics of partitioning of phenothiazines in oil/water and liposome systems has been reported (Ahmed et al., 1985). At pH 6.0 using phosphate buffer, enthalpies and entropies were positive in cyclohexane, *n*-octanol, and liposome systems over the temperature range of 5–40 °C.

Materials and Methods

Materials

The β-blockers used in this study were obtained as follows: propranolol hydrochloride, B.P. (PPL) (Ayerst Laboratories, Montreal, Canada); acebutolol hydrochloride (ABL) (May and Baker, Ltd., U.K.); atenolol (ATL) (ICI, U.K.); metoprolol hydrochloride (MPL) and oxprenolol hydrochloride (OPL) (Ciba-Geigy Canada, Ltd.); nadolol (NDL) (Squibb Canada, Inc.); pindolol (PDL) (Sandoz Canada, Ltd.); bupranolol hydrochloride (BPL) (Sanol Schwarz GmbH); toliprolol hydrochloride (TPL) (Boehringer-Ingelheim Canada, Ltd.); alprenolol hydrochloride (APL) (Hassle, Sweden). Molecular structures, molecular weights, pK_as and λ_{max} values of the β-blockers are given in Table I. Petroleum ether (Fisher Scientific Co., NJ), methanol (Caledon Lab, Canada) and *n*-octanol (BDH, Toronto, Canada) were all reagent grade. DMPC (Sigma Chemical Co., St. Louis, MO, 99%) was used as received.

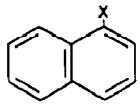
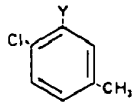
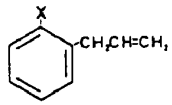
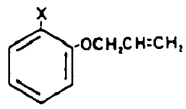
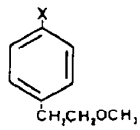
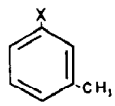
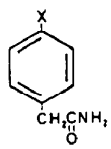
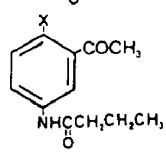
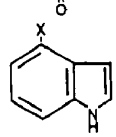
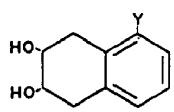
Methods

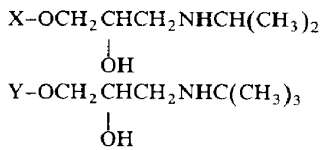
Distribution studies in n-octanol/buffer systems. Convenient volumes of aqueous phase (5 ml isotonic phosphate buffer, pH 7.4) containing the appropriate concentration of drug (0.2–1.4 mM) and *n*-octanol (0.5 ml) were weighed into 25-ml round-bottom flasks and equilibrated for 4 h at constant temperature (±0.5 °C) in a shaking water-bath (Dubnoff metabolic shaker bath). Both phases had been mutually pre-equilibrated. Concentrations of drug in the aqueous phase were determined by UV spectrophotometry (Pye Unicam SP6-550 spectrophotometer) at λ_{max} (see Table 1). The concentration of drug in the oil phase was determined by mass balance. The distribution of the drug was obtained from the average of duplicate determinations at each temperature over the range 10–50 °C.

Distribution studies in liposome systems. Phospholipid films were formed on the walls of 50-ml round-bottom flasks following rotary evaporation of 5-ml aliquots of a petroleum ether–methanol stock solution (10 mg/ml). The resulting dried films were dispersed in 5-ml aliquots of isotonic, aqueous, phosphate buffer solution (pH 7.4) at about 40 °C, to which a convenient concentration of drug (0.2–1.4 mM) had been added, by vortex mixing for 10 min. This resulted in the formation of multilamellar liposomes (MLVs). The distribution of the drug was determined in 24 h tempera-

TABLE 1

Chemical structures and physical properties of β-blockers

β-Blocker	Structure	Molecular weight	λ_{max}	pK_a
Propranolol (PPL)		259.3	288	9.45
Bupranolol (BPL)		271.8	274	9.6
Alprenolol (APL)		249.3	270	9.7
Oxprenolol (OPL)		265.3	272	9.5
Metoprolol (MPL)		267.4	277	9.7
Toliprolol (TPL)		223.3	270	9.6
Atenolol (ATL)		266.3	273	9.55
Acebutolol (ABL)		336.4	320	9.67
Pindolol (PDL)		248.3	263	8.8
Nadolol (NDL)		308.9	276	9.67



ture-equilibrated MLVs (3.5 ml) following centrifugation (143,000 *g*, 30 min) (Beckman L8-55 Ultracentrifuge) at the desired temperature from UV analysis and mass balance calculations over the range 10–41° C. Determinations were made in duplicate and the results averaged. Repeated analysis of stock solutions of the β-blockers confirmed their stabilities under experimental conditions.

Determination of partition coefficients

The apparent molal partition coefficients, K'_m, were calculated from the distribution results by employing Eqn. 1:

$$K'_m = \frac{(C_T - C_w)w_1}{C_w w_2} \quad (1)$$

where C_T = the total initial concentration of drug (mg/ml) in the aqueous buffer phase before equilibration, C_w = final aqueous phase concentration of drug (mg/ml), w_1 = weight (g) of aqueous phase, and w_2 = weight (g) of phospholipid in the sample. Ion-corrected partition coefficients were calculated from

$$K_m = K'_m(1 + 10^{pK_a - 7.4}) \quad (2)$$

using published values of the pK_a of each β-blocker (Table 1).

The standard change in free energy, $\Delta G^0_{w\to L}$, due to partitioning is given by

$$\Delta G^0_{w\to L} = -2.3RT \log K_m \quad (3)$$

The temperature dependence of partitioning was employed to obtain data on the enthalpy of the process based on the relationship (Katz and Diamond, 1974)

$$\left(\delta H^0_{w\to L}/\delta T\right)_p = T\left(\delta S^0_{w\to L}/\delta T\right)_p \quad (4)$$

and the assumption is made that $\Delta H^0_{w\to L}$ and $\Delta S^0_{w\to L}$ are approximately independent of temperature over the range of interest (Cratin, 1968). Since

$$\log K_m = -\Delta H^0_{w\to L}/2.3RT + \Delta S^0_{w\to L}/2.3R \quad (5)$$

a linear plot of log K_m vs $1/T$ enables calculation of $\Delta H^0_{w\to L}$ from the slope and $\Delta S^0_{w\to L}$ from the intercept. However, the change in entropy of partitioning, $\Delta S^0_{w\to L}$, was conveniently obtained from

$$\Delta S^0_{w\to L} = \left(\Delta H^0_{w\to L} - \Delta G^0_{w\to L}\right)/T \quad (6)$$

$\Delta H^0_{w\to L}$ and $\Delta S^0_{w\to L}$ have the physical meaning of the change in enthalpy and entropy, respectively, when one mole of solute is transferred from water to lipid at infinite dilution (Katz and Diamond, 1974).

Results and Discussion

The dependence of the apparent partition coefficient, log K'_m, on increasing PPL concentrations is very low in either the *n*-octanol-buffer or liposome system over the concentration range studied (Fig. 1). A slight tendency towards decreasing values of log K'_m, which is somewhat more pronounced in liposomes, is in marked contrast to that observed for chlorpromazine in the *n*-octanol/phosphate buffer system at 37° C (Ahmed et al., 1985) and is indicative of the partitioning of a single species of PPL rather than an ion pair at pH 7.4 but not chlorpromazine under similar conditions. Also, the concentration dependence of log K'_m in liposomes does not exhibit a maximum as it did with chlorpromazine, suggesting that

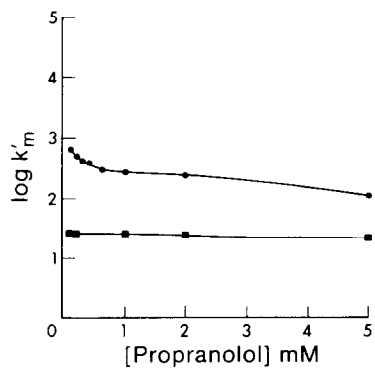


Fig. 1. Concentration dependence of the apparent molal partition coefficient of propranolol hydrochloride in the *n*-octanol buffer (■) and liposome (●) systems at pH 7.4 and 37° C.

TABLE 2

The thermodynamics of partitioning of β-blockers in the n-octanol/phosphate buffer system at pH 7.4 and 30°C

β-Blocker	Log K_m	$\Delta G^0_{w\to L}$ (KJmol^{-1})	$\Delta H^0_{w\to L}$ (KJmol^{-1})	$\Delta S^0_{w\to L}$ (Jmol^{-1}K^{-1})
PPL	3.37	−19.6	33.2	174
APL	3.34	−19.4	42.5	204
BPL	3.25	−18.9	38.3	189
OPL	2.62	−15.2	35.1	166
TPL	2.57	−14.9	39.8	180
ABL	2.43	−14.1	52.6	220
MPL	2.28	−13.2	44.1	189
ATL	1.95	−11.3	19.3	101
PDL	1.56	−9.1	11.1	66.6
NDL	0	0	0	0

adsorption of PPL at liposome surfaces is negligible.

n-Octanol/buffer partitioning

The temperature dependence of log K_m of the β-blockers in the *n*-octanol buffer system and the associated thermodynamic parameters are given in Fig. 2 and Table 2, respectively. The values of log K_m increased uniformly with temperature for all the β-blockers except at low temperatures.

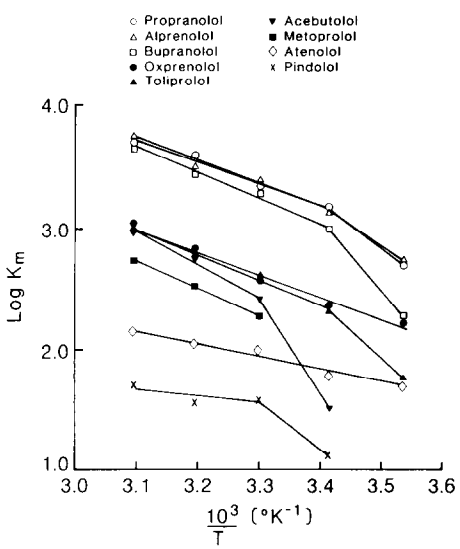


Fig. 2. Van't Hoff plots of the partition coefficient of β-blockers in the *n*-octanol/phosphate buffer system at pH 7.4.

Depending on the chemical nature of the drug, some had lower log K_m values than expected at 10°C (PPL, BPL, APL, TPL) while for others a K_m could not be detected at 10°C (ABL, MPL, PDL) or 20°C (MPL). Nadolol did not yield a measurable K_m from 10–40°C but the log K'_m at 50°C was −1.22 in the *n*-octanol/buffer system. The exceptions to this type of behavior were OPL and ATL which yielded linear plots over the entire temperature range. The relative lipophilicities of the β-blockers fall into approximately 3 groups: PPL, BPL, APL (I); OPL, TPL, ABL, MPL (II); and ATL, PDL (III) were the rank orders of lipophilicities is I > II > III. The magnitudes of $\Delta G^0_{w\to L}$ are indicative of the spontaneity of the partition process and for the various β-blockers (Table 2) these are seen to be proportional to the degree of lipophilicity (lower $\Delta G^0_{w\to L}$) or hydrophilicity (higher $\Delta G^0_{w\to L}$). Both $\Delta H^0_{w\to L}$ and $\Delta S^0_{w\to L}$ values are positive and, except for ATL and PDL, each is approximately of equal magnitude among the drugs. Also, positive enthalpies and entropies of partitioning have been found in the phenol/cyclohexane (Anderson et al., 1983) and the phenothiazine/*n*-octanol/aqueous phase system (Ahmed et al., 1985). In contrast, negative enthalpies of partitioning of phenols in the *n*-octanol/0.15 M NaCl system have been observed (Rogers and Wong, 1980) indicating the presence of significant hydrogen bonding between molecules of phenol and *n*-octanol. Although many of the β-blockers are phenolic derivatives, their behavior does not resemble that of the phenols because of the absence of the phenolic OH group.

Liposome buffer partitioning

The temperature dependence of log K_m of the β-blockers in the DMPC-buffer system and the associated thermodynamic parameters are given in Fig. 3 and Table 3, respectively. It can be seen that the β-blockers partitioned in liposomes even at low temperatures (except NDL) in contrast to the *n*-octanol/buffer system. The curves show a discontinuity between the low- and high-temperature ranges occurring in the vicinity of the T_c of DMPC dispersions (23°C). Also, slopes of the curves decrease with increase in lipophilicity $< T_c$ and $> T_c$ although their inclinations are generally

TABLE 3

The thermodynamics of partitioning of β-blockers below T_c (15 °C) and above T_c (30 °C) in DMPC liposomes

β-Blocker	Log K_m	Below T_c(15 °C)			Log K_m	Above T_c(30 °C)		
		$\Delta G^0_{w\to L}$ (KJmol^{-1})	$\Delta H^0_{w\to L}$ (KJmol^{-1})	$\Delta S^0_{w\to L}$ (Jmol^{-1}K^{-1})		$\Delta G^0_{w\to L}$ (KJmol^{-1})	$\Delta H^0_{w\to L}$ (KJmol^{-1})	$\Delta S^0_{w\to L}$ (Jmol^{-1}K^{-1})
PPL	4.16	−22.8	−11.2	40.8	4.73	−27.4	−6.6	68.6
APL	4.11	−22.7	4.9	95.8	4.47	−25.9	1.9	91.7
BPL	4.22	−23.3	−6.4	58.8	4.69	−27.2	8.3	117
OPL	3.20	−17.2	−30.1	−44.8	3.61	−21.0	10.6	104
TPL	3.30	−18.0	−49.3	−109	3.69	−21.4	9.9	103
ABL	1.92	−10.6	−172	−562	2.93	−17.0	13.4	100
MPL	3.17	−17.2	28.6	−39.6	3.43	−20.0	28.9	161
ATL	2.29	−12.6	−207	−675	3.18	−18.4	19.6	126
PDL	2.57	−14.2	−9.5	16.2	2.82	−16.4	21.3	124
NDL	0	0	0	0	3.22	−18.7	−78.0	−196

opposite. The obvious exception to this pattern of behavior is NDL which displays a reciprocal dependence of log K_m with temperature $> T_c$ but its partitioning in liposomes $< T_c$ was not detectable. Liposomes exist in a gel crystalline state $< T_c$ which requires a greater energy for partitioning of solute molecules (hence, a lower value of log K_m) than in the liquid crystalline state $> T_c$. In the region of the T_c, chain melting occurs which gradually allows greater uptake of some drugs. Partitioning studies do not represent a sensitive means of detecting the T_c of a phospholipid but the results in Fig. 3 suggest the following: PPL, APL, BPL, TPL, OPL do not change the T_c of DMPC; MPL, ATL, ABL, PDL decrease the T_c of DMPC. Also, the greater the decrease in the T_c by the solute (e.g. ATL, ABL), the more unfavorable is the environment for partitioning in the region of the T_c. Hence, a K_m could not be measured for ATL and ABL at 20 °C.

The free energies of partitioning in liposomes ($\Delta G^0_{w\to L}$) as shown in Table 3 are slightly lower $< T_c$ than $> T_c$ of the phospholipid but the respective contributions of $\Delta H^0_{w\to L}$ and $\Delta S^0_{w\to L}$ are opposite. In the liquid crystalline state of the liposomes, enthalpies and entropies are positive (except NDL) whereas $< T_c$ they are generally negative. Nadolol partitions under strong enthalpy control only in fluid liposomes, probably arising through polar group interactions between NDL and the bilayer. This behavior is in contrast to that of a series of phenols (Rogers and Davis, 1980; Anderson et al., 1983) which are generally unionized at neutral pH. Below the T_c of DMPC liposomes, $\Delta H^0_{w\to L}$ and $\Delta S^0_{w\to L}$ are positive whereas $> T_c$ they are negative. Since it is generally understood that the compensating changes in enthalpy and entropy can be attributed to changes in liposome structure as well as the actual transfer of the solute (Anderson et al., 1983), the difference in the partitioning behavior of phenols and β-blockers may be due to the greater hydrogen bonding ability of the phenols with the phospholipid molecules compared with the β-blockers. In addition, enthalpies and entropies of partitioning of ionized phenothiazines in DMPC liposomes were found to be positive both $> T_c$ and $< T_c$ (Ahmed et al., 1985). However, chlorpromazine was also found to be strongly adsorbed at liposome surfaces, which was not the case with the β-blockers, and could account for the loss of order in the system through its surface interaction with the bilayer. It would appear that the phospholipid bilayer molecules are less available for interaction with the β-blockers when the bilayer is in the gel state $< T_c$.

The enthalpies and entropies of partitioning are greater in the *n*-octanol/buffer system than in liposomes $> T_c$ for 7 β-blockers listed in Tables 2 and 3. For example, the ratio of $\Delta H^0_{w\to L}$(*n*-octanol): $\Delta H^0_{w\to L}$(liposome) is approximately 4:1 (on average), the same as was found for pheno-

thiazines (Ahmed et al., 1985). In contrast, this same ratio is 80 : 1 $< T_c$ of DMPC which compares with 1.3 : 1 for phenothiazines (Ahmed et al., 1985). These results suggest a different mechanism of interaction of β-blockers with model membranes than the phenothiazines which have considerable surface activity (Seeman and Bialy, 1963; Zografi and Auslander, 1965). In a membrane existing in a fluid state, such as occurs $> T_c$ of DMPC, interaction is mainly by hydrophobically controlled partitioning (i.e. entropy-dominated). On the other hand, in a membrane of a more rigid structure ($< T_c$) interaction through polar group association on the membrane surfaces is predominant for the β-blockers which have low surface activity and partitioning becomes enthalpy-dominated.

Functional group contributions

Hydrophobic substituent constants have been derived from

$$\pi_x = \log K_{mx} - \log K_{mH} \quad (7)$$

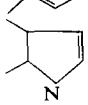
in order to compare the relative affinities of the various functional groups for *n*-octanol and DMPC liposomes. These values as shown in Table 4 were obtained from the values of K_m of the β-blockers (x) and the parent compound, pre-prenalterol (*H*). In every case π_x(liposome) is greater than π_x(*n*-octanol) and on average, it is 55% greater. Furthermore, the more polar the functional group the smaller is π_x in either partitioning system, but the increase of π_x in liposomes compared to the *n*-octanol buffer system becomes larger with polar group addition indicating a greater sensitivity of the liposome system as a model membrane for quantifying the interaction of more polar solutes.

Correlations

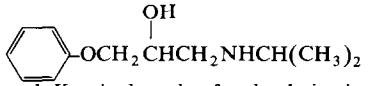
A plot of log K_m(*n*-octanol buffer) vs log K_m(liposome) is given in Fig. 4 and shows generally that the hydrophobicities of the β-blockers are correlated in the *n*-octanol-buffer and liposome systems ($r = 0.946$, $n = 9$). However, ABL does not correlate as well as the others ($r = 0.986$, $n = 8$). Correlations of this type have been found

TABLE 4

Hydrophobic substituent constants of functional groups on the aromatic ring structure of β-blockers at pH 7.4, 30 °C

Functional group	Liposomes > T_c		*n*-Octanol/buffer	
	Log K_{mx}	π_x	Log K_{mx}	π_x
–	3.05(H)	–	2.11(H)	–
$-CH_3$(meta)(TPL)	3.69	0.64	2.57	0.46
$-CH_2CH{=}CH_2$(ortho)(APL)	4.47	1.42	3.34	1.23
$-OCH_2CH{=}CH_2$(ortho)(OPL)	3.61	0.56	2.62	0.51
$-CH_2CH_2OCH_3$(para)(MPL)	3.43	0.38	2.28	0.17
$-CH_2\overset{O}{\overset{\|}{C}}NH_2$(para)(ATL)	3.18	0.13	1.95	−0.16
 (PPL)	4.73	1.68	3.37	1.26
 (PDL)	2.82	−0.23	1.56	−0.55

[a] The constants are determined from $\pi_x = \log K_{mx} - \log K_{mH}$ where K_{mH} is the partition coefficient of preprenalterol



and K_{mx} is the value for the derivative.

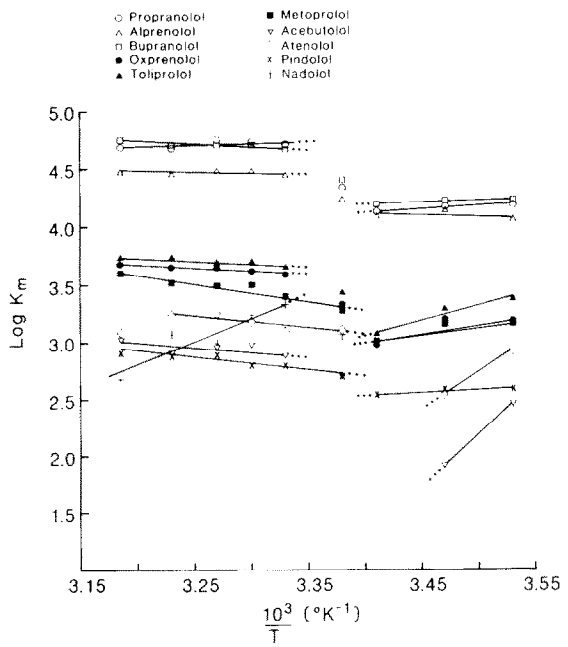


Fig. 3. Van't Hoff plots of the partition coefficient of β-blockers in the liposome-phosphate buffer system at pH 7.4.

with other solutes (Diamond and Katz, 1974; Rogers and Davis, 1980), but this does not necessarily mean that the two systems behave similarly thermodynamically (Anderson et al., 1983).

Linear relationships obtained from enthalpy–entropy compensation plots suggest a single mechanism of transfer for a series of solutes or solvents (Leffler and Grunwald, 1963). However, in the *n*-octanol–0.15 M NaCl solution system, no linear relationship between ΔG and ΔH for phenolic solutes was observed (Anderson et al., 1983). Likewise, a poor correlation between $\Delta G^0_{w\to L}$ and $\Delta H^0_{w\to L}$ was obtained for the β-blockers in the *n*-octanol buffer system ($r = -0.543$) and in DMPC liposome $< T_c$ ($r = -0.493$). However, a positive correlation was obtained in DMPC liposomes $> T_c$ ($r = 0.767$) as shown in Fig. 5. This is not a strong indication that all of the β-blockers interact with phospholipid bilayer molecules in exactly the same manner but it does suggest that there are no major structural alterations in the lipid environment over the temperature range of the study, whereas this may be the case in *n*-octanol because of the existence of structures of water-centered aggregates (Smith et al., 1975). In addition, preliminary observations in the use of liposomes of varying composition have indicated that improved correlations are possible. Although either model system is able to differentiate this series of β-blockers on the basis of their relative hydrophobicities, the thermodynamic approach shows how structural organization and rigidity of the lipid phase might account for the selectivity of molecules through the interactive behavior of certain functional groups. Thus, acebutolol and

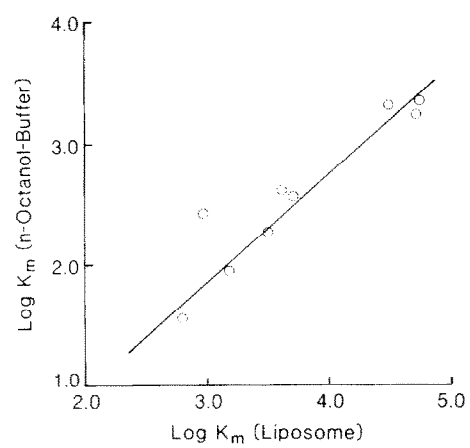


Fig. 4. Correlation of the partition coefficients of β-blockers in the *n*-octanol-buffer and liposome-buffer system at pH 7.4 and 30 °C.

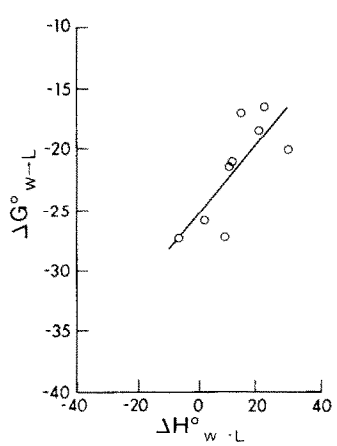


Fig. 5. Enthalpy–entropy compensation of β-blockers in DMPC liposomes above the T_c ($r = 0.767$).

nadolol were found to be selected by one system but not the other.

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