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The influence of cosolvents and substrate substituents on the sorption of benzoic acid derivatives by polyamides

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The sorption of some substituted benzoic acid derivatives by polyamides (nylons) from aqueous solution has been examined and the influence of their nature together with those of the cosolvent and polymer have been assessed. In all cases the sorption isotherms were linear and could be expressed by a simple distribution law, enabling the influence of cosolvent concentration to be predicted. The sorption of a series of *p*-substituted benzoic acids and some of their esters is related to their solubility except where the *p*-substituent is capable of hydrogen-bonding with the polymer. The extent of the interaction is also dependent upon the amide frequency of the polymer.

Problems may arise in the use of plastics materials as packaging media for liquid medicines due to the loss of drugs, preservatives and excipients by sorption into the plastics. In a previous report describing the influence of pH, temperature and ionic strength on the sorption of benzocaine from aqueous solution by a pure polyamide resin, nylon 6 (Richardson & Meakin, 1974), it was shown that the extent of sorption from aqueous potassium chloride solutions could be predicted from a knowledge of the drug's solubility. To see if the sorption-solubility relationship was more widely applicable, sorption studies with benzocaine and nylon 6 powder have been made from aqueous cosolvent mixtures and in addition, the sorption characteristics of a series of *p*-substituted benzoic acids and some of their ethyl esters having different solubilities in water, have been determined.

Many workers have concluded that the sorption of weak organic acids and bases by polyamides involves hydrogen bonding between the solute molecules and the polar amide groups in the polymer chain (Chipalkatti, Giles & Vallance, 1954; Kim & Autian, 1959; Guess, Worrell & Autian, 1962; Iijima & Sekeido, 1962; Kapadia, Guess & Autian, 1964; Rodell, Guess & Autian, 1964; Richardson & Meakin, 1974). The structure of simple linear polyamides, indicated below, shows that as the number of methylene groups in the chain decreases, the amide frequency increases and consequently, if hydrogen bonding is the principle mechanism involved, sorption should increase with the amide frequency of the nylon. To ascertain the influence of amide frequency, the sorption of benzocaine by films of nylon 6, 11, 12, 6:10 and 6/6:6 copolymer have been evaluated.

Polyamide copolymer $[(CH_2)_x\text{-CO-NH-}(CH_2)_y\text{-NH-CO}]_z$ e.g. Nylon 6:12 ($x = 10, y = 6$)

Polyamide homopolymer $[(CH_2)_a\text{-CO-NH}]_b$ e.g. Nylon 6 ($a = 5$)

MATERIALS AND METHODS

Materials. Benzocaine and nylon 6 powder were as described previously (Richardson & Meakin, 1974). Ethanol and polyethylene glycol 400 (PEG 400, BDH) were used as received. Nylon films (6, 11, 12, 6:10, 6/6:6) were a gift from Smith and Nephew Research Ltd. Other benzoic acid derivatives were either obtained commercially (reagent grade) or synthesized by standard methods. All compounds were recrystallized twice and stored under anhydrous conditions before use; (for full details of preparation and purification see Winterborn, 1972; Richardson, 1973). Water was freshly distilled from an all glass still.

Assay procedures. Aqueous cosolvent mixtures containing benzocaine were diluted as appropriate with water and assayed at 286 nm using a Unicam SP500 spectrophotometer. In all cases dilutions were sufficient to eliminate any cosolvent effect on the molar extinction coefficient of 16953. Other ethyl benzoates were similarly assayed at their wavelength of maximum absorption in 5% w/v ethanol. The benzoic acids were determined in 0·1N hydrochloric acid containing 5% w/v ethanol. Full details of the absorption maxima and extinction coefficients are available (Richardson, 1973).

Solubility measurements. Solubilities (Table 1) were determined as before (Richardson & Meakin, 1974). In all cases the solvents used ensured the compounds were in the unionized form. No detectable hydrolysis of the esters occurred during solubility determinations.

Sorption of benzocaine from aqueous cosolvent mixtures. Sorption isotherms for benzocaine on nylon 6 powder from aqueous ethanol and aqueous PEG 400 were determined at 30° by the standard procedure (Richardson & Meakin, 1974). All isotherms were linear and could therefore be characterized by their slopes (K values) which, together with their associated standard errors, are given in Table 2.

Table 1. *Data for the solubility of* p-*substituted benzoic acids and some of their ethyl esters in various solvents.*

Aqueous ethanol (30°)		*p*-Substituted benzoic acids in 0·1N hydrochloric acid containing 5% w/v ethanol (25°)	
Ethanol concentration (% w/v)	Benzocaine solubility (M × 10^3)	*p*-Substituent	Solubility (M × 10^3)
0	7·68	–H	28·00
		$-OCH_3$	1·50
10	12·18	$-NO_2$	1·28
		–F	4·21
20	22·89	–Br	0·17
		$-COCH_3$	1·80
30	59·59	–Cl	0·36
		–CN	2·49
40	160·47	–OH	49·97
Aqueous polyethylene glycol 400 (30°)		*p*-Substituted ethyl benzoates in 5% w/v ethanol (25°)	
PEG 400 concentration (% w/v)	Benzocaine solubility (M × 10^3)	*p*-Substituent	Solubility (M × 10^3)
0	7·68	$-COCH_3$	3·11
		$-NO_2$	1·21
10	15·00	–CN	4·25
20	30·08	$-N(CH_3)_2$	1·01
30	52·14	$-NH_2$	10·10
40	113·80	–OH	9·09

Table 2. *K values for the sorption of benzocaine from aqueous co-solvent mixtures by nylon 6 powder at 30°.*

Aqueous ethanol			Aqueous polyethylene glycol 400		
Ethanol concentration (w/v)	K (litre kg^{-1})	Standard error of K	PEG 400 concentration (% w/v)	K (litre kg^{-1})	Standard error of K
0	19·6	0·3	0	19·6	0·3
10	12·9	0·2	10	12·0	0·3
20	8·3	0·2	20	8·1	0·2
30	5·5	0·2	30	4·6	0·2
40	2·2	0·2	40	2·8	0·1

Sorption of p-*substituted ethyl benzoates and benzoic acids.* Sorption isotherms for *p*-substituted ethyl benzoates on nylon 6 powder were determined at 25° from 5% w/v ethanol to enhance the solubility of the less water soluble compounds. No detectable hydrolysis occurred during equilibration. Isotherms were determined for *p*-substituted benzoic acids from 0·1N hydrochloric acid containing 5% w/v ethanol. The sorption data for the isotherms, all of which were linear are given in Table 3.

Sorption of benzocaine by nylon films. The films were cut into strips, washed with distilled water and dried to constant weight at 60° under vacuum. 0·2 g of dried film was shaken with 10 ml of the appropriate benzocaine solution in water at 30° until

Table 3. *K values for the sorption of* p-*substituted benzoic acids and some of their ethyl esters from 5% w/v ethanol at 25°.*

Benzoic acid derivatives in 0·1N hydrochloric acid			Ethyl benzoate derivatives		
p-Substituent	K (litre kg^{-1})	Standard error of K	*p*-Substituent	K (litre kg^{-1})	Standard error of K
–H	15·5	0·6	$-COCH_3$	14·2	0·4
$-OCH_3$	23·8	0·4	$-NO_2$	21·4	0·8
$-NO_2$	26·6	0·5	–OH	40·5	0·7
$-COCH_3$	22·0	0·1	$-N(CH_3)_2$	47·2	0·4
–CN	20·5	0·2			
–Cl	50·3	1·3	$-NH_2$	14·9	0·3
–OH	38·5	0·4			
–Br	48·2	0·3	–CN	12·0	0·2
–F	16·5	0·4			

Table 4. *K values for the sorption of benzocaine from aqueous solution by various nylon films at 30°.*

Nylon type	K (litre kg^{-1})	Standard error of K
6 (powder)	19·6	0·3
6 (75 μm thick)	24·0	0·4
6 (30 μm thick)	24·8	0·6
6/6:6 copolymer	25·1	0·2
6:10	6·9	0·2
11	5·2	0·2
12	8·6	0·3

equilibrium was obtained. The sorption process was much slower for the films than for nylon 6 powder and the equilibration time for each film type was determined for the most concentrated benzocaine solution used, before the sorption experiment. Sorption isotherms were again linear and the K values are shown in Table 4.

DISCUSSION

All sorption isotherms were found to be linear, with correlation coefficients $>0{\cdot}99$ ($n_{min} = 5$) except for sorption from 40% w/v ethanol where $r = 0{\cdot}98$; all intercepts spanned zero within $\pm$ two standard deviations. Such C-type partition behaviour (Giles & others, 1960) can be described by a generalized distribution law which holds up to saturation if the system behaves ideally (equation 1).

$$K = \frac{C_p}{C_s} = \frac{S_p}{S_s} \qquad (1)$$

K is the slope of the isotherm and is equivalent to the partition or solubility coefficient of the solute molecule in the polymer and C_p, S_p and C_s, S_s are the equilibrium solute concentrations below saturation and solubilities of solute, in the polymer and solution respectively. Equation 1 predicts that as the drug solubility in the solution phase of the system increases the extent of sorption will decrease, and a plot of log K against log solubility should be linear with a slope of -1.

Tables 1 and 2 show that increasing concentrations of both ethanol and PEG 400 increase the solubility of benzocaine and decrease the extent of its sorption by nylon 6 powder. Log K varies linearly with log solubility for both cosolvents and the data can be represented by a single line whose slope is $-0{\cdot}7$ ($r = 0{\cdot}992$, $n = 9$). The low value of this slope compared to that predicted from equation 1 suggests the systems are not behaving ideally and that the linearity of the double log plot is fortuitous, depending upon the mathematical nature of the logarithm and the fact that the data only cover approximately one decade of K values. Similar non-ideal behaviour occurs for the sorption of benzocaine from aqueous potassium chloride solutions (Richardson & Meakin, 1974).

For non-ideal behaviour, another parameter, the activity coefficient of the solute in solution, must be introduced into equation 1 and the value for this will differ for each electrolyte and cosolvent concentration. This activity effect was eliminated for sorption from potassium chloride solutions by combining equation 1 with the Setchènow relationship, which exponentially relates the solubility of a neutral organic molecule in water with the concentration of neutral electrolyte present (Harned & Owen, 1958). Similar exponential relationships (equation 2) have been reported for the effect of cosolvents on the solubility of neutral drugs in water (Higuchi, Gupta & Busse, 1953; Yalkowsky, Flynn & Amidon, 1972).

$$\log S_c = \log S_o + m\,C_o \qquad (2)$$

S_c and S_o represent the solubilities of the drug in the aqueous cosolvent mixture and water respectively, C_o is the cosolvent concentration and m is an empirical constant. Combination of equations 1 and 2 eliminates activity terms and leads to equation 3.

$$\log K = \log \frac{S_p}{S_o} - m\,C_o \qquad (3)$$

Fig. 1 shows plots of log K against cosolvent concentration for benzocaine. The linear relation predicted by equation 3 holds over the whole concentration range investigated for PEG 400 ($r = 0{\cdot}999$ $n = 5$) and up to 30% w/v for ethanol. ($r = 0{\cdot}999$ $n = 4$). The values of S_p, the apparent solubility of benzocaine in the polymer at 30°, were calculated from the intercepts and found to be 0·15 mol kg^{-1} for both solvents which correlates well with that calculated for sorption from aqueous potassium chloride solutions (0·15 mol kg^{-1}) and that determined experimentally at saturation of the aqueous phase (0·16 mol kg^{-1}), previously reported, which does suggest this type of plot is the best way of expressing the sorption-solubility relationship. The deviation from linearity at ethanol concentrations above 30% w/v cosolvent was not unexpected as the data in Table 1 show that the solubility of benzocaine in ethanol does not fit equation 2 well, in contrast to PEG 400. Similar anomalous behaviour in ethanol–water mixtures, in contrast to many other cosolvent–water mixtures, has been reported for other neutral organic solutes and is attributed to the marked non-ideal character of the ethanol–water systems (Higuchi & others, 1953).

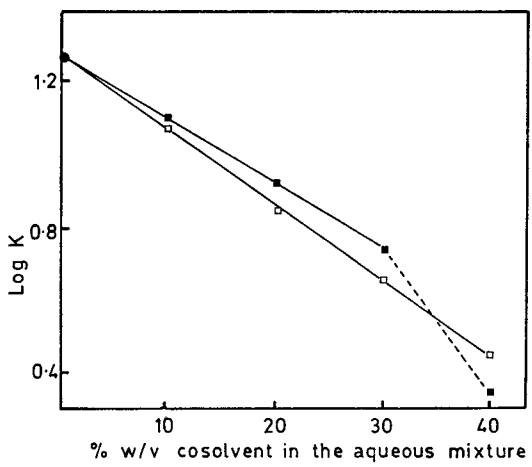

FIG. 1. Relation between K and cosolvent concentration for the sorption of benzocaine by nylon 6 powder from aqueous cosolvent mixtures at 30°. ■ Ethanol–water, □ PEG 400–water.

The attempt to correlate sorption and liquid phase solubility for a series of related solutes was only partially successful. Fig. 2 shows that for the *p*-substituted benzoic acid series -Cl, -Br, $-NO_2$, $-OCH_3$, $-COCH_3$, -CN, -F, there is a reasonable linear relationship between log K and log solubility in 0·1N hydrochloric acid containing 5% w/v ethanol ($r = 0{\cdot}974$ $n = 7$). However, both benzoic acid itself and *p*-hydroxybenzoic acid had much greater affinities for nylon 6 powder than would be predicted from their solubilities, by factors of 5·4 and 1·7 respectively. No satisfactory linear relationship could be established for the *p*-substituted ethyl benzoates from 5% ethanol but the data do indicate that the K value for the *p*-hydroxy ester and probably for the *p*-amino ester (benzocaine) are higher than expected from solubility considerations. A similar linear relation between sorption and solubility which also showed some anomalies has been described for the sorption of a series of substituted anilines on nylon 6:6 (Ward & Upchurch, 1965), who suggested that the deviations resulted from steric hindrance retarding polymer penetration. Such an explanation is not

satisfactory for our results, with the possible exception of benzoic acid, which lacks a *p*-substituent and could therefore be perhaps expected to penetrate more readily. A more feasible suggestion for the strong sorption characteristics shown by the *p*-hydroxy derivatives is that the substituent itself is readily capable of hydrogen bond formation, in addition to that formed at the other end of the molecule; a similar argument can be advanced for benzocaine.

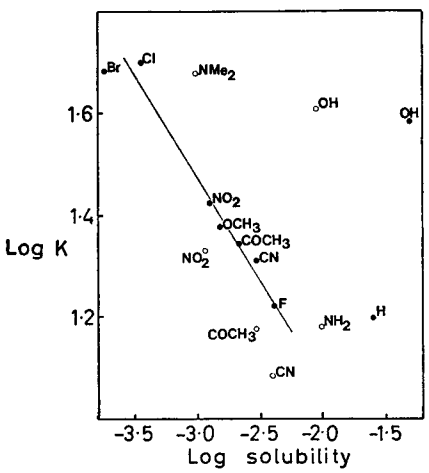

FIG. 2. Relation between K and solubility for the sorption of *p*-substituted benzoic acids (●) from 0·1N hydrochloric acid containing 5% w/v ethanol and *p*-substituted ethyl benzoates (○) from 5% w/v ethanol by nylon 6 powder at 25°.

The sorption data for the different nylon films are shown in Table 4. Equilibration times ranged from 1 to 5 h, the time increasing with film thickness and the number of methylene groups between the amide links. The K values for nylon 6 films were essentially independent of film thickness as expected from a partition model, but higher than for nylon 6 powder which probably reflects the different sources of the materials and consequent variation in such properties as polymer crystallinity. The K value for nylon 6/6:6 copolymer was close to that for the nylon 6 which has a similar amide frequency, but the more hydrophobic 6:10, 11 and 12 films showed a much lower degree of interaction with benzocaine. Fig. 3 shows that the effect of amide frequency on benzocaine sorption parallels that for water sorption (Mark & Gaylord, 1969). Puffr & Sebenda (1967) explain the marked increase in water absorption for nylon 6 and below, in terms of the number of water molecules bound per two amide groups in the polymer. In nylons 8 to 12 only one water molecule is bound per two amide groups whereas in nylon 6 and below there are three per two amide groups. The sorption mechanisms of benzocaine from aqueous solution could therefore be explained in terms of an increase in swelling of the nylon 6 by water resulting in an increased penetration of drug. Nylons 6:10, 11 and 12 would not be swollen to the same extent and so penetration of the benzocaine would be less.

It is thus apparent that for an individual compound such as benzocaine, the interaction with nylon 6 can be predicted from its solubility in the liquid phase of the system. The affinities of a neutral drug series capable of hydrogen bonding with the polymer appear to be closely related to their solubilities except where more than one

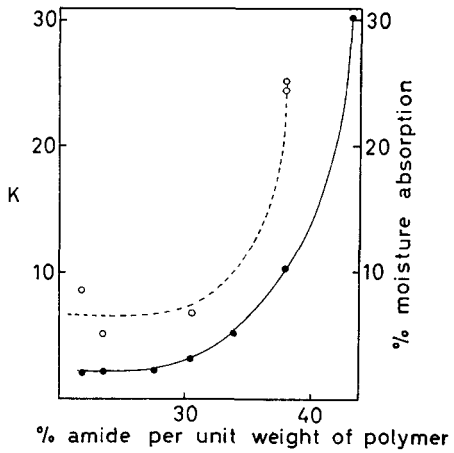

FIG. 3. Effect of amide frequency on the equilibrium moisture sorption* at 20° 100% R.H. (●) and the K values for benzocaine from aqueous solution at 30° (○) for nylons of varying structure. (* taken from Mark & Gaylord, 1969).

hydrogen bonding group is present, when the sorption is enhanced. The extent of sorption is also markedly dependent upon the hydrophilic character of the polymer and is probably related to the water sorption properties of the material.

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