DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 10(6), 861-871 (1984)

THERMODYNAMICS OF BUFFERED AQUEOUS SOLUTIONS OF VARIOUS BARBITURATES. II EFFECT OF BUFFERS, SUBSTITUENTS AND SOLUTE POLARITY

By

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ABSTRACT

Solution data of ten barbiturates at three temperatures in buffered systems was abtained at pH's of undissociated solute molecules and half-neutralized pH vlaues. From these results, various thermodynamic elements could be obtained. The solubility of these compounds showed an approximately linear relationship of mole fraction and carbon number. As the number of carbon atoms of various substituents increased, the aqueous buffered solubility decreased. Additionally, the solubility of linear carbon chains is greater than branched chain substituents with diminishing differences as the carbon number is increased. Finally, the solubility of these solutes, for the most part, were unaffected by the buffer componenets.

INTRODUCTION

Solubilities of a series of chemically related solutes were determined over a temperature range of fifteen degrees, 25°c to 40°c. Since data was obtained as a function of temperature, appropriate

0363-9045/84/1006-0861$3.50/0

plots of solubility would allow for the determination of various thermodynamic elements for slopes and intercepts. Specifically, various factors such as the enthalpy and entropy, including excess free energy could be obtained for these systems.

The compounds studied are all 5,5' - disubstituted barbiturates with one ethyl groups in the 5-position being held constant with various other substituents on the other 5-position (5'). In two cases, other molecular varients, such as N-1-methyl and 2-thio-substituents (metharbital and thiopental, respectively) of these malonyl urea compounds.

With these compounds, it would be possible to determine the net effect of various groups on the solubility in the two buffered solvent systems. There have been studies previously reported in the literature concerning the structure-activity relationships of these compounds (1-6). Some current work deals with partition coefficients (7) and a model of relative lipophilicity proposed by Hansch (8). Work on the solubility of these compounds are considered by other workers in water (9) in other solvents (10-12), in binary solvent mixtures (13-14) and in ternary solvents (15).

The experimental methodology is detail in the companion communication.

RESULTS AND DISCUSSION

In Table I, a summary of the mole fraction solubility data in the pKu and pKa buffered solvent systems are given in rank order of solubility as a function of temperature. The solubility was plotted versus temperature for several of the solutes as given in Figure 1. It can be seen that the solubility is a linear function of temperature for both the pKu and pKa buffered solvent systems.

The mole fraction data was utilized for plotting the ln of the mole fraction solubility versus reciprocal temperature for each solvent system and are shown in Figures 2-4. In all cases, a straight line relationship was observed with the slopes and intercepts being related to the enthalpy and entropy of solution. These slopes and intercepts were derived from a least squares method by the use of Hewlett-Packard Model 9810A Calculator and plotting system. The results, the enthalpy and entropy of solution were computer derived and are given in Table II and include the calculation of the excess free energy of these systems.

It should be noted here that it would have been somewhat better if a wider temperature range had been used and more individual

Table I: Summary of the mole fraction solubility of the solvents in two buffered solvent systems as a function of temperature.

Barbiturate	Temperature	Mole fraction x 104	
		pKu	pKa
Barbital	25	7.19	12.90
	33	8.48	15.26
	40	10.46	17.19
Butethal	25	3.32	6.21
	33	4.00	7.18
	40	4.52	8.13
Metharbital	25	1.95	3.83
	33	2.45	4.74
	40	3.11	5.45
Probarbital	25	1.58	2.55
	33	1.73	3.10
	40	2.19	3.83
Phenobarbital	25	0.94	1.79
	33	1.24	2.56
	40	1.71	3.11
Pentobarbital	25	0.79	1.51
	33	1.04	1.79
	40	1.19	2.40
Butabarbital	25	0.76	1.62
	33	1.04	2.21
	40	1.28	2.63
Vinbarbital	25	0.64	1.21
	33	0.88	2.01
	40	1.05	2.57
Amobarbital	25	0.48	0.96
	33	0.56	1.20
	40	0.72	1.58
Thiopental	25	0.045	0.082
	33	0.059	0.134
	40	0.074	0.179

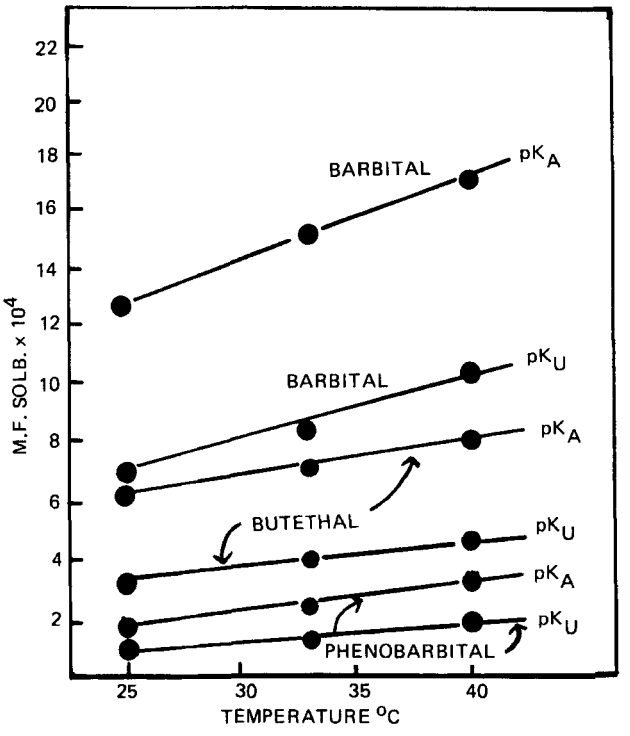

FIGURE 1: Solubility of several barbiturates expressed in mole fraction as a function of temperature.

temperature points determined. In determining thermodynamic elements from these plots, the assumption is that three points will define a straight line and that each temperature deviates minimally from the slope. While the data indicated good (>.97) coorelation coefficients, it is felt that the thermodynamic values reported in Table II may vary by as much as 10% in accuracy. However, the excellant reproducibility of replicate samples would lead to an error of about 5% in terms of precision. Thus, the values reported in this communication are considered to be fairly accurate. The thermodynamic data derived from these plato for each solute in the pKu and pKa systems are given in Table II.

It can be seen from this data that the excess free energy for the pKu and pKa solvent systems are relatively large values which would indicate the highly non-ideal nature of these solutions. Except for pentabarbutal, referred to latter, the excess free energy in the pKu system is larger than the pKa systems. This would be indicative that these solutions are energetically unfavorable in the pKu system but somewhat less so in the pKa solvent system where the solubility is

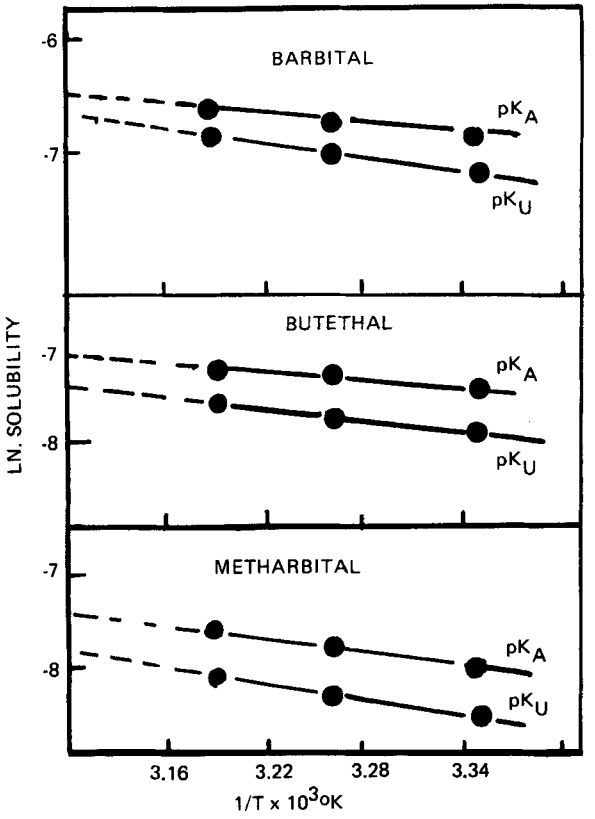

FIGURE 2: Solubilty of the noted barbiturates expressed as ln. mole fraction solubility versus reciprocal temperature.

Table II: Summary of the Solution Thermodynamic Value for the noted solutes in the pKu and pKa buffered solvent systems.

	(Cal/mole) Entholpy		(Cal/deg.-mole) Entropy		(col/mole) Excess Free Energy	
Barbiturate	pKu	pKa	pKu	pKa	pKu	pKa
Barbital	4627	3534	1.53	1.80	4154	2978
Butethal	3718	3314	0.79	1.79	3474	2761
Metharbital	5743	4361	0.44	1.00	5607	4052
Probarbital	5240	5004	0.40	0.80	5116	4754
Phenobarbital	7388	6667	0.34	0.63	7282	6463
Pentobarbital	5038	5664	0.19	0.49	4978	5513
Butabarbital	6764	6038	0.21	0.45	6671	5899
Vinbarbital	6089	5843	0.94	0.61	5799	5654
Amobarbital	4987	3479	1.27	0.95	4595	3186
Thiopental	6173	4976	0.16	0.39	6124	4856

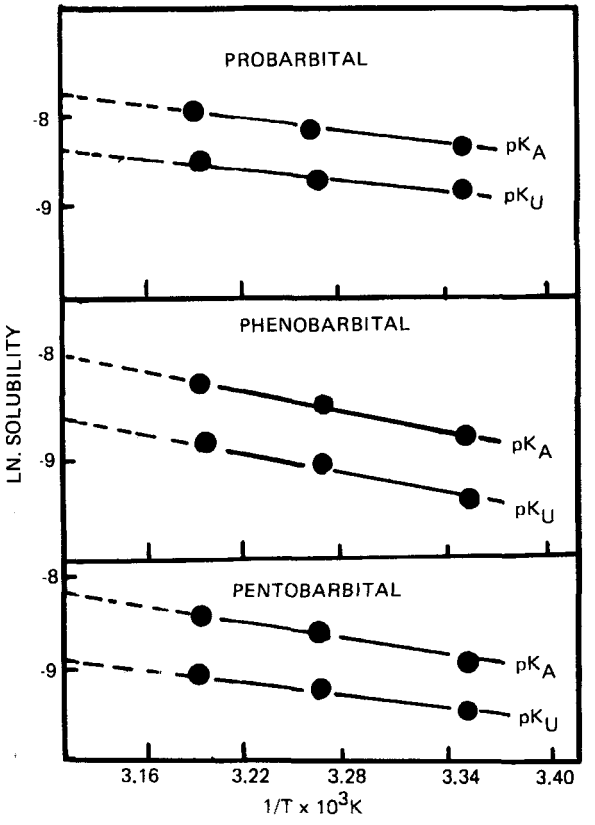

FIGURE 3: Solubility of the noted barbiturates expressed as mole fraction solubility as a function of reciprocal temperature(ln.S)

enhanced by the prescence of a water soluble species. There does not seem to be any coorelation of these thermodynamic values with structure, straight chain, branched chain or polarity of these molecules.

Effect of Buffer Components

Since this study involved the determination of solubility of these solutes in a buffer pH that guaranteed the existance of only the acid form of these solutes, it would be instructive to compare their solubilities in water to the present work.

The aquesus solubility of these compounds has previously been determined (16), then there could a possibility of detecting the effect of buffer components in the present study. These values are given in Table III.

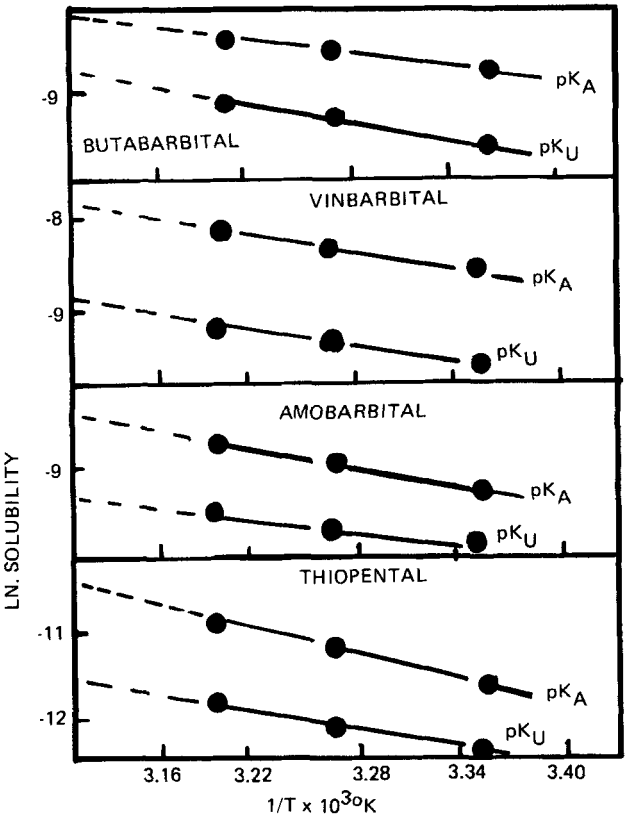

FIGURE 4: Solubility of the noted barbiturates expressed as mole fraction solubility as function of reciprocal temperature (ln.S)

Table III: Summary of the solubilities of the noted barbiturates in water (Sw) and buffer (SB) expressed in moles/liter and the ratio of Sw and SB.

	Solubility M/L		
Barbiturate	Water (Sw)	Buffer (SB)	Sw/SB
Barbital	.0397	.0397	1.0
Butethal	.0193	.0184	1.05
Metharbital	.0104	.0106	1.02
Probarbital	.0061	.0081	0.75
Phenobarbital	.0052	.0052	1.0
Pentobarbital	.0022	.0044	0.5
Butabarbutal	.0042	.0042	1.0
Vinbarbital	.0031	.0036	0.86
Amobarbital	.0027	.0027	1.0
Thiopeutal	.00033	.00025	1.32

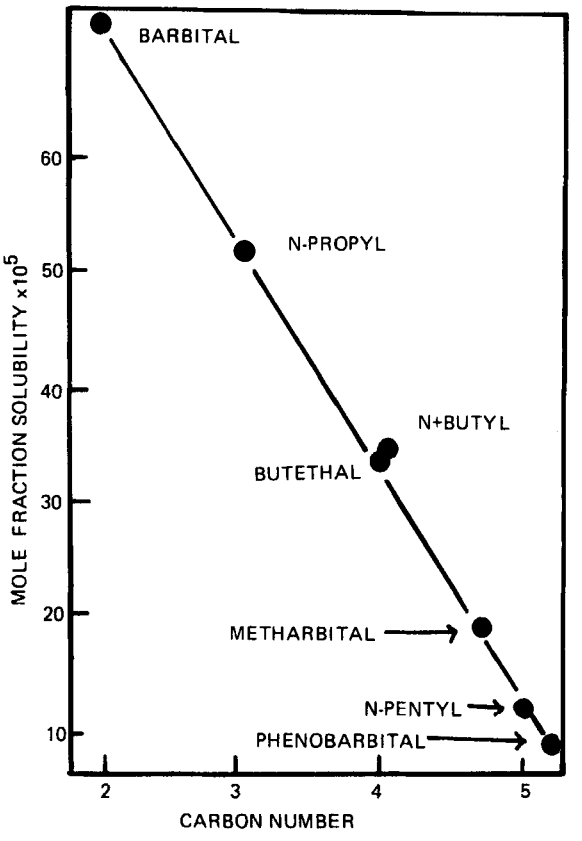

FIGURE 5: The mole fraction solubility in the pK_u buffer system of c-5 position substituted barbiturates as 25 C as a function of the carbon number.

In comparing these results, by means of the ratio, (SW/SB), solubility in water compare to solubility in buffer, six of the ten solutes were very close in magnitude as evidenced by a ratio of values close to unity. However, three of the remaining solutes, probarbital, vinbarbital, and thiopental, the solubility values in distilled water versus the buffer systems varied from 14-32%. It is difficult, in these three cases to discern whether the differences noted are due to the buffer components or experimental error in solubility in either one of these studies. Only one of these solutes varied significantly from each other, that bring the case of pentobarbital where there is a two fold change. There is no doubt that this is due to experimental error in either one of these solubility and should be carefully redetermined.

In general, the effect of the buffering components on the solubility of these compounds is slight. These observations would need to be substantiated by further work of solubility determinations by variation of

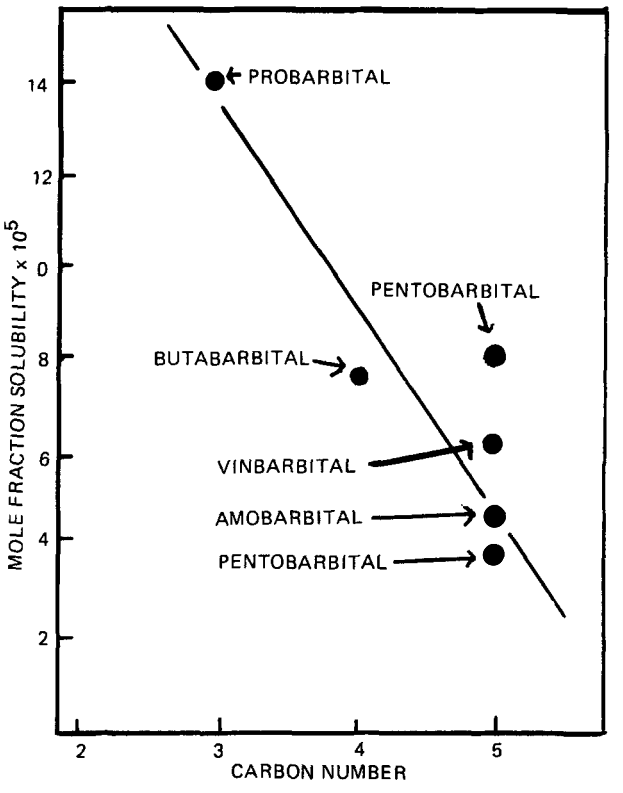

FIGURE 6: The mole fraction solubility in the pK_u buffer system of the c-5 position branched chain substituent barbiturates at 25 C as a function of the carbon number.

Table IV: Comparison and difference of the pH variation for various barbiturates in distilled water and aqueous buffer systems.

	pH		
Barbiturate	(A) Water[a]	[b]Buffer (B)	pH=(A)-(B)
Barbital	4.7	4.8	-0.1
Butethal	4.8	4.8	-
Metharbital	5.1	5.2	-0.1
Probarbital	5.1	4.9	+0.2
Pentobarbital	5.4	5.1	+0.3
Butabarbital	5.2	5.1	+0.1
Vinbarbital	5.3	5.1	+0.2
Amobarbital	5.2	5.1	+0.1
Thiopental	5.4	5.1	+0.3

a= calculted from pH=pKa/2 - log c/2

b= the final value of pH in the pKu buffer

buffer capacity. A partial explanation, however, can be considered by the pH variation in the two sets of data. In Table IV, the pH of the system for the Breon data was calculated and compared with the final experimentally determined pH of the buffer system, both being studies at at temperature of 25 c. It can be seen from these results in Table IV that the ratios of solubility are close to unity when the difference in pH of the distilled water and the pKu buffered solvent system varied by about 0.1 pH units.

Deviations in the ratios of solubility, for example, probarbital, pentsbarbital, reinbarbital and thiopental occurr when the pH varies by 0.2 - 0.3 pH units.

Effect of Substituents and Solute Polarity

The effect of various substituents on the aqueous or buffer solution solubility can be observed by comparing the magnitude of solubility expressed in mole fraction versus the number of carbons in that substituent group.

In Figure 5, the mole fraction solubility in the pKu solvents at 25°c of the linear C-5 position substituents are plotted which also include the data from a previous study (16). A straight line relationship is observed with a slope of about 20 x 10^{-5} in terms of mole fraction. In general, there is observed to be a decrease in solubility with an increase in carbon number or molecular size. When the solubility of phenobarbital is plotted on this line, its value exists at greater than a linear 5-carbon chain with respect to the phenyl group since the remainder of the compound is constant. Thus, the phenyl group effectively acts between a 5 and 6 linear chain carbon. When the solubility of metharbital, is plotted on this line, the N-methyl substitution is seen to effect a decrease in solubility about equal to 2.8 linear carbon atoms.

For the branched chain barbiturates the mole fraction solubilities are shown in Figure 6. An approximate straight line relationship is also found for these derivatives with only pentobarbital deviating significantly from this line. As indicated earlier, the solubility values of pentobarbital in the two studies varied significantly and both points are shown in this figure. However, the actual value of pentobabital must be reconciled by redetermination of values. It would seem from this figure that the previous value in distilled water was a better value. The slope of this line is approximately 3 x 10^{-5} in terms of mole fraction. It can be observed that the solubility decreases with an increase in the number of carbons or molecular size.

Thipental, 5-ethyl-5-(1-methyl butyl)-2-thiobarbituric acid can be directly compared to pentobarbital, 5-ethyl, 5-(1-methyl butyl) barbituric

acid and here the effect of the sulfur atom in position 2 causes about a twentyfold decrease in solubility.

Overall, the solubility of linear carbon chains is greater than branched chain with diminishing difference as the carbon number is increased. In general, solubility decreases with an increase in carbon number. A thio substituent in the 2 position causes a dramatic decrease in aqueous solubility and this ultrashort babriturate possesses greater lipophilicity than the other barbiturates used in this study.

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