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SOLUBILITY FOR NORMAL AND BRANCHED CHAIN ALKYL BARBITURATES IN WATER. II. RELATIONSHIP WITH APPARENT MOLAR VOLUME

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INTRODUCTION

Aqueous solubility of solutes is considered to be dependent upon the ability and capacity to enter into the hydrogen bonded structure of water. The change in solubility of a chemically related series of compounds would be dependent upon the differences in the chemical groupings attached to a common molecular moiety. In this particular study, an extension of a previous communication deals with normal and branched chain barbiturates where substitutions in the C5 position were considered.

In the n-alkyl C5 substituents group, the effect of increasing chain length upon solubility in water at 25° was determined. These compounds were 5, 5' diethyl barbituric acid, 5-ethyl

5-propyl barbituric acid, 5-ethyl 5-butyl barbituric acid and 5-ethyl 5-pentyl barbituric acid and chosen since they represent a series where chain length increases in incremental steps by a methylene group. In another group of branched chain barbiturates the chain was also altered by the addition of a methylene group such that 5 compounds were studied. Included in this group were 5-ethyl 5-isopropyl barbituric acid, and 2 sets of positional variants with 5-ethyl 5-(1-methyl propyl) and 5-ethyl 5-(2-methyl propyl) barbituric acid and 5-ethyl 5-(1-methyl butyl) and 5 ethyl 5-(3-methyl butyl) barbituric acid. In this group, there were 3 branches composed of 3, 4, or 5 carbons.

Since all these substituents were the only chemical grouping that varied for each individual barbiturate, then it was possible that the magnitude of the aqueous solubility would be related to the volumetric occupation by these groups.

It was felt to be of interest if phenobarbital, 5-ethyl 5-phenyl barbituric acid were included in order to note the effect of the phenyl group with respect to the magnitude of solubility and its particular volume element with respect to the other chemical groupings.

EXPERIMENTAL

The experimental technique has been given in a prior communication for those compounds applicable in this study.

Values of dielectric constants for the alcohols were obtained from (1) and densities from various sources (2, 3).

RESULTS AND DISCUSSION

The barbiturates in this study, Compound I-X, (Table I, previous communication) were chemically related to one another except for the C5 substituent in a linear or branched chain configuration while the remainder of the molecule remained constant. The molar volumes of these compounds is not readily available nor could they be determined easily. It was felt that the common constant portion of this moiety in all the compounds studied would contribute the same value to the overall molar volume for each compound.

Since density values were available for the uncommon portions of these compounds as alcohols, phenol in the case of phenobarbital, the true molar volumes could be obtained for the uncommon C5 substituents and used directly.

Thus the molar volume for 5, 5 diethyl barbituric acid and 5-ethyl 5-propyl barbituric acid could be expressed as the molar volumes of ethanol and 1-propanol and referred to as the apparent molar volume.

It can be assumed that at the very low solubilities determined for this series of barbiturates, the magnitude of solubility would depend upon the ability and capacity of each solute to enter into the hydrogen bonded structure of water. This capacity would depend in a differential manner upon the bulkiness of the C5 substituent since the difference in solubility directly depends upon the difference in the sizes of these groups.

This would, of course, be true for the linear carbon chains such as the ethyl, n-propyl, n-butyl and n-pentyl in compounds I-IV. The branched chain solutes could be similarly considered as the variation in these compounds was the addition of a single carbon atom that branched from a linear carbon chain. In this series, it was found that the solubility for the 2 pairs of positional isomers were quite similar which would imply that the bulkiness or volume element occupied by these groups in the three dimentional structure of an aqueous matrix would be about the same. The true molar volume effect could then be ascribed to the uncommon C5 substituent as the contribution from the remaining portion of the molecule remained constant.

Phenobarbital, 5-ethyl 5-phenyl barbituric acid, because of its importance was also considered in a similar manner since its contribution to the overall bulkiness or volumetric occupation should be similar for the common portion of the molecule and depend directly upon the size or bulkiness of the phenyl group. It would be of interest to find the "effect" of the phenyl group with respect to its solubility compared to other members in this series.

The data on the various hydroxylated forms of the uncommon groups was available from the literature relative to the densities and as such the molar volumes could be easily obtained. The values used for the molar volumes are given in Table I.

On Figure 1, the solubility in mg/ml in water at 25^{o} is plotted as a function of the carbon number for compounds I-IV on the left hand side and the molar volume of the alcohols of the uncommon portion of the molecule on the right hand side.

Table I. Summary of the Molar Volumes for the noted substances obtained from $\bar{V}$ = M. W. /Density

Solvent	Molecular Weight	Density	Molar Volume ($\bar{V}$)
Ethanol	46.07	.7894	58.36
1-Propanol	60.10	.8036	74.79
1-Butanol	74.13	.8096	91.56
1-Pentanol	88.15	.8148	108.19
Phenol	84.11	1.0576	79.53
Isopropanol	60.10	.7851	76.55
1-methyl propanol	74.13	.8063	91.93
2-methyl propanol	74.13	.8020	92.43
1-methyl butanol	88.15	.8103	108.79
3-methyl butanol	88.15	.8092	108.94

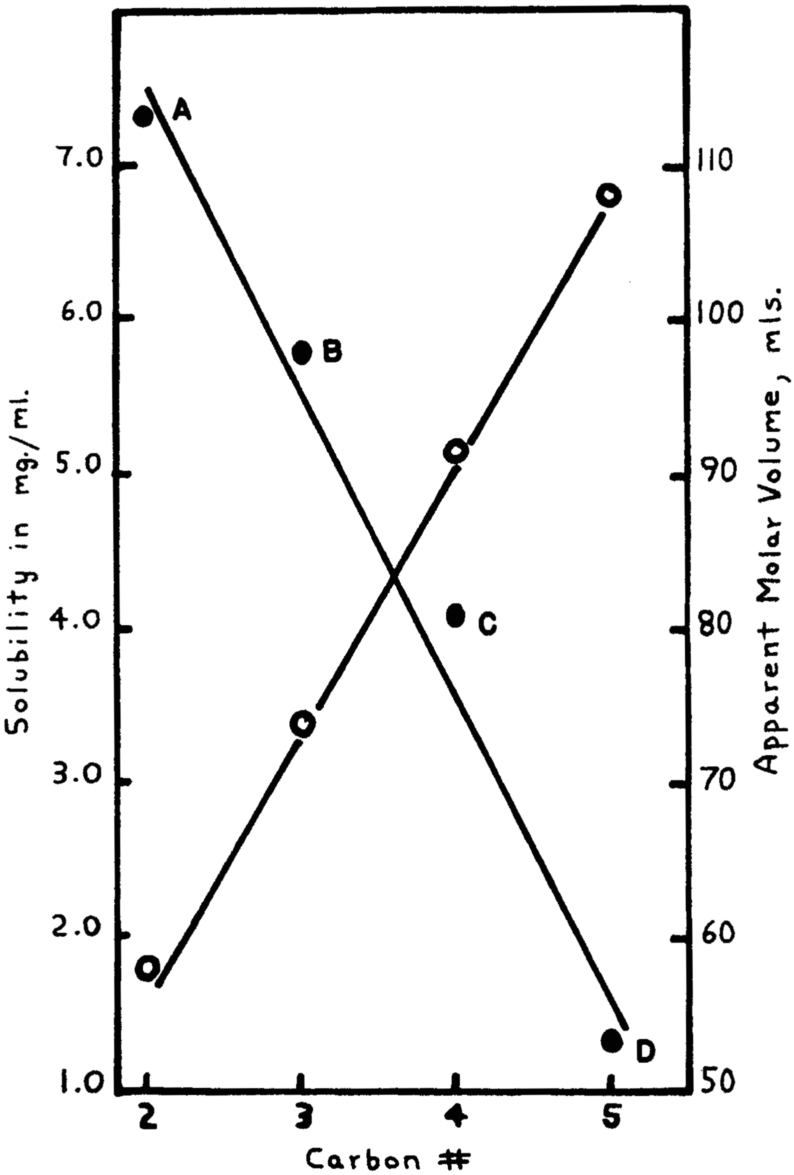

Figure 1. The solubility in mg/ml (●) and the apparent molar volume (o) as a function of the carbon number for A; Cpd. I, B; Cpd. II, C; Cpd. III, D; Cpd. IV.

It is apparent that as the solubility decreases, in an approximately linear fashion, the molar volume increases linearly as well. This would imply an inverse relationship of solubility and molar volume, that is, as the molar volume increases, the solubility decreases.

This relationship would be valid since the true overall molar volume of the compounds would be the values shown plus a constant value for the remaining portion of the molecule. The solubility is seen to decrease linearily with a slope of about 3 mg/carbon atom while the molar volume increased linearily with a slope of about 16.6 ml/carbon atom. The molar volume change is obviously due to the additional methylene group, CH_2 to each of the alcohols in this series. The molecular weight change is 14 grams/mole whereas the volumetric change for this methylene group is 16.6 ml/mole.

This would indicate that as the linear chain is lengthened by a methylene group, the solubility decreases by an approximately constant amount which is directly related to the increased volume of that group. The capacity of these compounds to interact within the structure of an aqueous environment progressively decreased as the chain lengthens probably due to the increased potential for dispersion force interactions when these linear chains are in a configurationally favorable position.

These interactions would progressively increase with chain length and fewer molecules would be found "in solution" with respect to those molecules "out of solution" since solubility is an equilibrium process.

In Figure 2, the solubility in mg/ml in water at 25° is shown for the branched chain barbiturates used in this study as a function of carbon number, the scale is given at the left hand side of the figure. The molar volumes of the alcohols of the same groups are also shown with the scale on the right hand side of the figures. The solubility is seen to decrease in an approximately linear fashion while the molar volume increases in a linear fashion as well.

The solubility of phenobarbital is also shown in this figure and it possesses a solubility about the same as the isopropyl derivative and interestingly, the volume element occupation for the phenyl and isopropyl groups are strikingly similar. The molar volumes of the two pairs of positional isomers, 1-methyl and 2-methyl propyl and 1-methyl and 3-methyl butyl are, of course, constant; the solubilities of these pairs were also about the same. If the rate of change of solubility is considered versus the total number of carbons in the chain a negative linear slope of about 0.34 mg/carbon atom is obtained while the molar volume increases linearily with a slope of

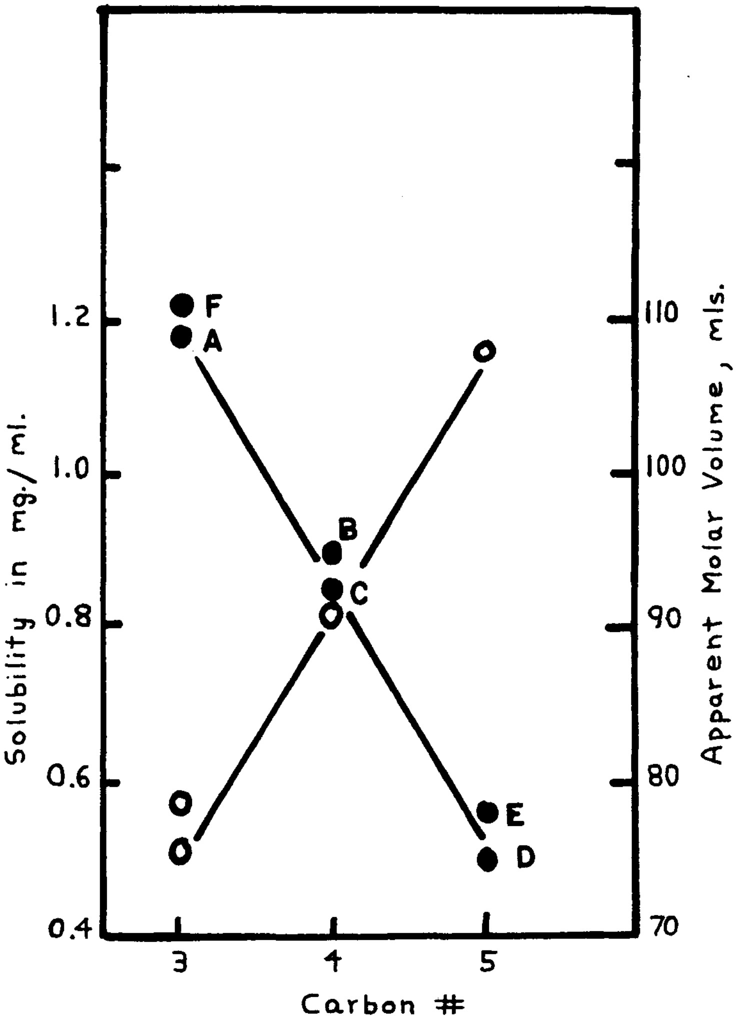

Figure 2. The solubility in mg/ml (●) and apparent molar volume (o) as a function of carbon number for A; Cpd. VI, B; Cpd. VII, C; Cpd. VIII, D; Cpd. IX, E; Cpd. X, F, Cpd. V.

16 ml/carbon atom. This again is the effect of the addition of a methylene group to the progressive increase in the size of

the branches. For these branched chain barbiturates the change in solubility is about one-tenth the effect of the linear chains previous considered.

It should be pointed out, however, that the apparent molar volume of several of the linear C5 alkyl barbiturates were quite similar to the apparent molar volumes of the C5 branched chain barbiturates. For example, the apparent molar volume of the n-butyl group is 92 ml/mole and the molar volume of the 1-methyl propyl and 2-methyl propyl groups are also around 92 ml/mole, but the solubilities are vastly different. The n-butyl derivative is 6-7 times more soluble than the branched chains of similar molar volume.

This would indicate that while the apparent volumes are similar, the number of molecules (magnitude of solubility) entering the structure of the aqueous environment for the branched chains are substantially reduced. This could indicate that the branched chain compounds enter the aqueous environment in a particular conformation where the entropy factor (increased disarray) contributes to the diminished solubility.

There are several well known rules governing the melting points and boiling points of n-alkyl and branched chain compounds such as the increase in melting point with chain length and the decrease due to branching since less compact molecular assays exist in the solid state with the same number of carbon atoms.

It can also be pointed out that the melting points of the various barbiturates used in this study offer no reasonable ranking in the discernment of the aqueous solubility trends or even the apparent molar volume relationship.

Diminished solubility with chain length probably resides in the fact of increasing potential for dispersion forces interactions leading to increased cohesional or self-association possibilities, obviously causing diminished solubility. This is valid for the four members of the n-alkyl series of barbiturates. The branched chain barbiturates could be considered in a similar vein and would seem to depend upon cohesional London interactions based upon configurationally complementary orientation in order to promote self-association again leading to diminished solubility. Measurement a priori of these potential interactions would be difficult indeed. Another approach to a ranking within series of these cohesive energy densities would be via a consideration of the energies of vaporization of these groups as their alcohols.

The energies of vaporization for these alcohols can be computed from the following consideration. The solubility parameter (δ) can be obtained from dielectric constants (E) (1) according to the following relationship (4).

$$\delta = 7.5 + 0.2E \qquad \text{Eq. 1}$$

The solubility parameter can be expressed in terms of the energy of vaporization (Ev) and molar volume ($\bar{V}$) thusly

$$\delta = \left(\frac{Ev}{\bar{V}}\right)^{1/2} \qquad \text{Eq. 2}$$

Squaring both sides of Eq. 2 and multiplying through by the molar volume $\bar{V}$, one obtains

$$(\delta)^2 \bar{V} = Ev \qquad \text{Eq. 3}$$

Since solubility parameter values were available from Eq. 1 and the molar volumes $\bar{V}$ were computed from literature values, the energy of vaporization could be obtained.

In Table II, the energies of vaporiziation for the alcoholic form of the C5 substituent is shown in rank order with solubility expressed in mg/ml. There is seen to exist a rank order correlation of energy of vaporization and the magnitudes of solubility for both the linear and branched chain series. This is taken as evidence that the cohesive energies of these alcohols increase within a series with an increase in carbon number irrespective of position and supports the contention of generally increasing dispersion forces with the addition of a methylene group.

Table II. Summary of the magnitudes of the solubility for the noted compounds and the energy of vaporization of the alcoholic form of the uncommon portion of the barbiturate moiety

Compound	Uncommon group alcohol	Ev cal/mole	Solb. mg/ml
I	ethanol	8775	7.31
II	n-propanol	9922	5.81
III	n-butanol	11334	4.13
IV	n-pentanol	11458	1.33
VI	iso-propanol	9363	1.18
VII	1-methyl propanol	10534	0.90
VIII	3-methyl propanol	11335	0.84
X	3-methyl butanol	11912	0.56
IX	1-methyl butanol	12366	0.50

REFERENCES

1. Maryott, A. A. and Smith, E. B., N.B.S. Circular 514, Department of Commerce, Washington, D. C., 1951.

2. "Merck Index" 8th Ed., Merck & Co., Inc., Rahway, NJ, 1968.

3. "Handbook of Chemistry and Physics" 49th Ed., The Chemical Rubber Co., 1968-69.

4. Paruta, A. N., Sciarrone, B. J. and Lardi, N. G., Jour. Pharm. Sci. 51, 704 (1962).