Solubility of Straight-Chain and Branched Alkyl Barbiturates in Straight-Chain Alcohols

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Abstract □ The solubilities of a series of chemically related barbiturates, including some medically useful ones as well as phenobarbital, were determined at 25° in the straight-chain alcohols methanol through butanol. The solubility values are given in both milligrams per milliliter and the mole fraction notation. The solubility in methanol was the highest and decreased nonlinearly for the solubility in 1-butanol. In several cases, mole fraction solubility gave shouldering or peaking as a function of the carbon number of the solvent. This series of barbiturates was broken down into two subsets of straight-chain and branched alkyl barbiturates, and solubility ratios in these subsets were considered.

Keyphrases □ Barbiturates—straight-chain and branched alkyl substituents, solubility in straight-chain alcohols □ Alcohols, straight chain—solubility of 5,5-disubstituted barbiturates □ Solubility—5,5-disubstituted barbiturates in straight-chain alcohols

This study involved a basic approach to physical–chemical behavior. The approach utilized the experimental measurement of the solubility of a chemically related series of compounds in a chemically related series of solvents. This type of investigation allows for a delineation of the relationship between the magnitude of solubility and chemical differences.

The solubility of an important pharmacological class of sedative compounds—the 5,5-disubstituted barbituric acids with varying substituent groups—was studied. The compounds have both a straight-chain and branched series, allowing for a possible relationship for both the chain size and positional variations (1). Phenobarbital, a 5,5-disubstituted barbituric acid containing one phenyl ring in the 5-position, was included to observe the effect of an aromatic system on solubility as compared to the alkyl substituents of the other barbiturates. The magnitude of solubility was determined in straight-chain alcohols from methanol through butanol to allow for some definitive relationship for a particular solute in these related solvents.

EXPERIMENTAL

Materials—The following materials were used: 5,5-diethylbarbituric acid[1]; 5-ethyl-5-propylbarbituric acid[2]; 5-ethyl-5-isopropylbarbituric acid[3]; 5-butyl-5-ethylbarbituric acid[4]; 5-ethyl-5-pentylbarbituric acid[5]; 5-ethyl-5-(2-methylpropyl)barbituric acid[6]; 5-ethyl-5-(3-methylbutyl)barbituric acid[7]; 5-ethyl-5-(1-methylbutyl)barbituric acid[8]; 5-ethyl-5-(1-methylpropyl)barbituric acid[9]; 5-ethyl-5-phenylbarbituric acid[10]; methanol, anhydrous, spectrophotometric grade solvent[11]; ethanol (absolute alcohol), USP reagent quality[12]; 1-propanol[13]; 1-butanol, analytical reagent[14]; certified acetone, 99 mole % pure[15]; certified benzene, 99 mole % pure (thiophene free)[16]; sodium phosphate dibasic heptahydrate, analytical reagent[17]; sodium metal[18]; sodium hydroxide[19]; diethyl ethyl-*n*-propylmalonate[20]; diethyl ethyl-*n*-amylmalonate[21]; diethyl isobutylmalonate[22]; ethyl iodide certified[23]; sulfuric acid[24]; urea[25] USP; magnesium metal turnings[26]; and iodine crystals[27].

The purity of the alcohols was determined by measurements of physical constants. The refractive index[28] was determined at 25° using a standard with a known refractive index to check the accuracy of the instrument.

An oscillometer[29] was used in the measurements of dielectric constant values. Agreement with values in the literature was obtained.

For the synthesized barbiturates (II, IX, and X), purity and identification were evidenced by carbon, hydrogen, and nitrogen analysis and IR spectra. For all compounds studied, both IR and NMR spectra were determined. All solutes were recrystallized from ethanol and dried to constant weight, and their melting points[30] were determined. These values are shown in Table I, and there is excellent agreement between determined and literature values (3, 4). Table I also lists the chemical nomenclature, the chemical structure, and the common name of the barbiturate, if one exists.

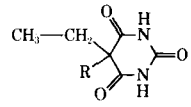
Procedure—The solubilities of the various barbiturates in the various alcohols were determined by a procedure given previously (5). Screw-capped[31] bottles with an excess of a barbiturate in each solvent were rotated for 24 hr in a constant-temperature bath set at 25 ± 0.1°. Samples were withdrawn through a pledget of glass wool into a pipet, which was wiped clean and allowed to drain into a tared volumetric flask. The flasks were reweighed to determine the weight of the sample.

A pH 10.9 buffer solution was prepared by dissolving 134 g of sodium phosphate dibasic heptahydrate in 2 liters of distilled water and adjusting to pH 10.9 with 1 *M* sodium hydroxide. Suitable dilutions were made with this buffer, and the concentration of the solute was determined spectrophotometrically. Each solubility determination represents the average values for at least four runs of the 10 barbiturates in each solvent. The variation in the results of the solubility study was 2–4%.

Assay Procedure—A spectrophotometric assay[32] was used for the quantitative determination of each barbiturate. UV spectra of each compound were obtained to determine the wavelength at which maximum absorbance occurred. The maxima for all these barbiturates were between 239 and 240 nm. A linear relationship

[1] Lot 5115, Merck and Co.
[2] Compound II; synthesized in this laboratory (2).
[3] Lot SQ3540, E. R. Squibb and Sons.
[4] Lot 20-4441-01, Abbott Laboratories.
[5] Compound IX; synthesized in this laboratory.
[6] Compound X; synthesized in this laboratory.
[7] Lot 3180, Ruger Chemical Co.
[8] Lot 776-7548, Abbott Laboratories.
[9] Lot 5086, McNeil Laboratories.
[10] Lot MPY, Mallinckrodt Chemical Works.
[11] Lot VMN, Mallinckrodt Chemical Works.
[12] U.S. Industrial Chemical Co.
[13] Lot 35592, Baker Analyzed, J. T. Baker Chemical Co.
[14] Lot +DY, Mallinckrodt Chemical Works.
[15] Lot 792702, Fisher Scientific Co.
[16] Lot 793859, Fisher Scientific Co.
[17] Lot WTKL, Mallinckrodt Chemical Works.
[18] Lot 71046, J. T. Baker Chemical Co.
[19] Lot W183J, Allied Chemical.
[20] Lot 26294, K & K Laboratories.
[21] Lot 20929, K & K Laboratories.
[22] Lot 11008, K & K Laboratories.
[23] Lot 794939, Fisher Scientific Co.
[24] Lot D610153, Allied Chemical.
[25] Lot 701909, Fisher Scientific Co.
[26] Lot 55053, Fisher Scientific Co.
[27] Lot 772803, Fisher Scientific Co.
[28] Abbe-3L refractometer.
[29] Model V Sargent Chemical oscillometer.
[30] Hoover melting-point apparatus.
[31] Lined with Teflon.
[32] Beckman DU model spectrophotometer.

Table I—Summary of the Compound Number, Chemical Name, Alkyl Substituent Group Structure, and Melting Point of Solutes Used in This Study



Compound	Chemical Name	R Group	Common Name	Melting Point	
				Determined	Literature (Refs. 3 and 6)
I	5,5-Diethylbarbituric acid	CH_3CH_2—	Barbital	188–190°	188–192°
II	5-Ethyl-5-propylbarbituric acid	$CH_3CH_2CH_2$—	—	146–147°	146–147°
III	5-Butyl-5-ethylbarbituric acid	$CH_3CH_2CH_2CH_2$—	Butethal	126–128°	124–127°
IV	5-Ethyl-5-pentylbarbituric acid	$CH_3CH_2CH_2CH_2CH_2$—	—	135–136°	135–136°
V	5-Ethyl-5-phenylbarbituric acid		Phenobarbital	156–157°	156–157°
VI	5-Ethyl-5-isopropylbarbituric acid	$(CH_3)_2CH$—	Probarbital	202–203°	203°
VII	5-Ethyl-5-(1-methylpropyl)-barbituric acid	$CH_3CH_2(CH_3)CH$—	Butabarbital	165–166°	165–168°
VIII	5-Ethyl-5-(2-methylpropyl)-barbituric acid	$(CH_3)_2CHCH_2$—	—	174–175°	174–176°
IX	5-Ethyl-5-(1-methylbutyl)-barbituric acid	$CH_3CH_2CH_2(CH_3)CH$—	Pentobarbital	129–130°	130°
X	5-Ethyl-5-(3-methylbutyl)-barbituric acid	$(CH_3)_2CHCH_2CH_2$—	Amobarbital	156–158°	156–158°

existed in all cases, indicating that the Beer–Lambert relationship was operative within the concentration ranges studied.

RESULTS AND DISCUSSION

All compounds studied were 5,5-disubstituted barbituric acid derivatives where one substituent was an ethyl group. The chemical variation in these compounds was the other group at the 5-position; differences in physicochemical behavior were due to the differences in the functional group at this position. Thus, the solubility of 5-ethyl-5-butylbarbituric acid when compared with the solubility of 5-ethyl-5-amylbarbituric acid was due to the relative influences of the amyl and butyl groups. The effect of positional changes in branching also could be deduced by comparing 5-ethyl-5-(1-methylbutyl)barbituric acid and 5-ethyl-5-(3-methylbutyl)-barbituric acid.

From the compounds listed in Table I, two subsets of derivatives can be considered, those possessing a linear arrangement of a carbon chain and those with a branched carbon chain. Phenobarbital, the only aromatic substituted barbiturate, was grouped with the *n*-alkyl set since a phenyl group is considered to correspond in effect to an *n*-propyl group. The ensuing discussion is based on a comparative effect for the particular substituent in a set or series of compounds.

The magnitudes of solubilities were experimentally determined for a series of barbituric acid derivatives at 25°. The solubility values for these compounds in straight-chain alcohols are given in Table II, where solubilities are expressed as milligrams per milliliter and mole fraction. Previous studies (1, 4, 6–9) of barbiturate solubility dealt with solubility maxima, solubility parameters, and dielectric constant relationships.

In Fig. 1, the solubilities of the barbiturates noted are plotted in milligrams per milliliter at 25° *versus* the carbon number of the alcohols. Nonlinear solubility curves were evidenced for all barbiturates studied; they were plotted as two derivative subsets including linear derivatives (and aromatic phenyl) and branched derivatives.

From inspection of Table II, the following rank-order solubilities were noted regardless of solvent for the linear substituted

Table II—Barbiturate Solubilities at 25° in Straight-Chain Alcohols

Compound	Melting Point	Solubility[a], mg/ml			
		Methanol	Ethanol	1-Propanol	1-Butanol
I	189°	166 (4.1)	95 (3.2)	58 (2.4)	41 (2.1)
II	147°	325 (8.3)	195 (6.4)	123 (4.2)	78 (3.8)
III	127°	530 (17.1)	392 (14.3)	341 (14.3)	278 (13.4)
IV	136°	553 (20.6)	444 (16.9)	377 (17.1)	324 (16.6)
V	157°	252 (5.8)	127 (3.7)	71 (2.9)	54 (2.4)
VI	203°	129 (3.1)	65 (2.1)	21 (0.8)	13 (0.6)
VII	166°	132 (2.8)	80 (2.3)	42 (1.5)	28 (1.2)
VIII	175°	123 (2.6)	72 (2.1)	35 (1.3)	28 (1.3)
IX	130°	313 (7.5)	235 (7.4)	201 (7.7)	151 (6.8)
X	157°	293 (7.4)	215 (6.2)	177 (6.5)	134 (6.0)

[a] Mole fraction solubilities × 10^2 are given in parentheses.

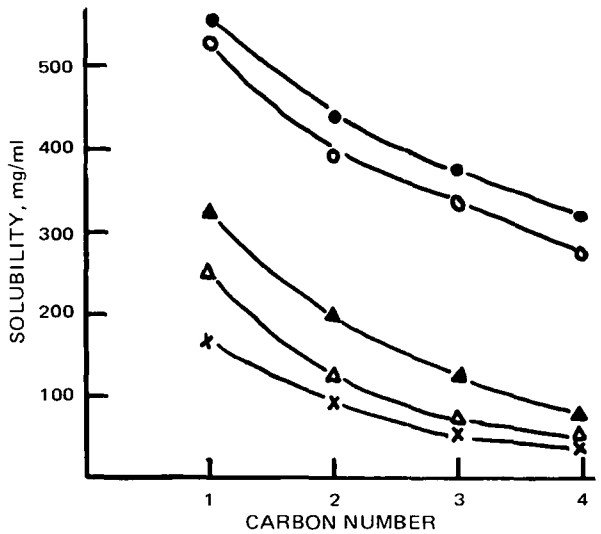


Figure 1—*Solubility at 25° of various* n*-alkyl barbiturates as a function of the carbon number of the alcohol solvents. Key:* ●, *IV;* ○, *III;* ▲, *II;* △, *V; and* ×, *I. See Table I.*

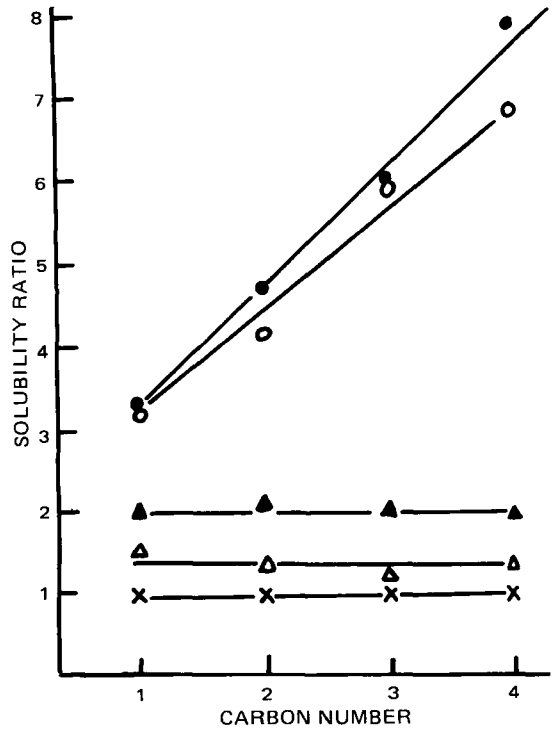


Figure 2—*Ratio of solubility of the various* n*-alkyl barbiturates to that of ethyl barbiturate as a function of the carbon number of the alcohol solvents: Key:* ●, *IV;* ○, *III;* ▲, *II;* △, *V; and* ×, *I. See Table I.*

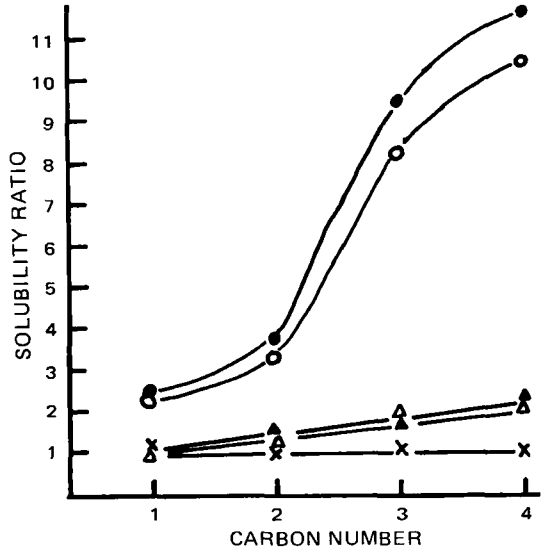


Figure 3—*Ratio of solubility of the various branched-chain barbiturates to that of 1-propyl barbiturate as a function of the carbon number of the alcohol solvents. Key:* ●, *IX;* ○, *X;* △, *VIII;* ▲, *VII; and* ×, *VI. See Table I.*

groups (I–V): amyl > butyl > propyl > ethyl; the effect of the phenyl group on solubility was intermediate between the ethyl and propyl groups. Moreover, solubilities expressed in milligrams per milliliter decreased for each solute as the alkyl chain length of the solvent was increased from one to four. When the data were expressed in the mole fraction notation, however, IV (amyl) and III (butyl) gave solubility profiles that showed shouldering or peaking effects in ethanol and 1-propanol.

For the branched solutes (VI–X), the rank-order solubilities were 1-methylbutyl > 3-methylbutyl > 1-methylpropyl > 2-methylpropyl > isopropyl. The solubilities of the last three compounds were quite similar to one another. For these solutes, the melting points, as expected from preferred configurational interactions, would at best be approximately correlatable with solubilities and this was found to be the case. Compounds VI–VIII, possessing similar solubilities, had high melting points whereas the lower melting compounds possessed significantly higher solubilities. In the mole fraction notation given in Table II, it can be discerned that VI and VII produced shouldering in methanol, whereas IX and X produced peaks in 1-propanol in the solubility profiles as a function of the carbon number of the alcohol solvent.

Inspection of the data reveals the following relationships among the derivatives studied. Solubility expressed in the pharmaceutical notation showed that each derivative had the highest solubility in methanol and decreased nonlinearly in each successive alcohol up to and including 1-butanol. The solubility increased with increasing chain length in both the linear and branched subsets of 5,5-disubstituted barbituric acids studied. The solubility isotherm of phenobarbital resided between the two and three linear carbon chain of the alkyl barbiturate. In all cases, the linear three, four, and five carbon chains (II–V) were more soluble in the alcohols than the branched three, four, and five carbon chains (VI–X).

Positional variations such as the 5-ethyl-5-(1-methylpropyl)barbituric acid and 5-ethyl-5-(2-methylpropyl)barbituric acid (VII and VIII) and the 5-ethyl-5-(1-methylbutyl)barbituric acid and the 5-ethyl-5-(3-methylbutyl)barbituric acid (IX and X) did not cause very large shifts in the magnitude of solubility of the solutes. However, these solubility shifts were greater for the larger branched chains (IX and X) than for the smaller branched chains (VII and VIII).

Another parameter of interest would be the relative magnitudes of solubility in the alcohol solvent series as the variable groups changed. Thus, the magnitudes could be compared between 5,5-diethylbarbituric acid and 5-ethyl-5-propylbarbituric acid or any other set of compounds. If the ratios of solubility were similar for the alcohol series, then the solubility profiles would be parallel, indicating that the solubility increased proportionately and invariantly in the linear alcohol series. If the ratios were not parallel (or/and linear), this finding would indicate a disproportionate relative effect in the alcohol series. In Figs. 2 and 3, the ratios of the solubilities in straight-chain alcohols are plotted for both the *n*-alkyl and branched alkyl barbiturate series utilizing 5,5-diethylbarbituric acid and 5-ethyl-5-isopropylbarbituric acid as unity, respectively.

The solubility ratios are given in Tables III and IV, and the data are plotted in Fig. 2 as a function of carbon number. There was a direct proportionality between 5-ethyl-5-propyl- and 5,5-diethylbarbituric acid such that the effect of the propyl group compared to the ethyl group was constant. Furthermore, the solubility of 5-ethyl-5-propylbarbituric acid was about twice as large in all alcohols studied. The other *n*-alkyl groups, butyl (III) and amyl (IV), showed ratios of about threefold in methanol rising to seven- or eightfold in 1-butanol. This finding indicates that the solubility of 5,5-diethylbarbituric acid in these alcohols decreased at a more rapid rate than the solubility of 5-ethyl-5-butyl- or 5-ethyl-5-amylbarbituric acids.

Table III—Ratios of Barbiturate Solubilities to Ethyl Barbiturate Solubility

Compound	Methanol	Ethanol	1-Propanol	1-Butanol
I	1.0	1.0	1.0	1.0
II	2.0	2.1	2.0	1.9
III	3.2	4.1	5.9	6.8
IV	3.3	4.7	6.5	7.9
V	1.5	1.3	1.2	1.3

Table IV—Ratios of Barbiturate Solubilities to 5-Ethyl-5-isopropylbarbituric Acid Solubility

Compound	Methanol	Ethanol	1-Propanol	1-Butanol
VI	1.0	1.0	1.0	1.0
VII	1.0	1.2	2.0	2.2
VIII	1.0	1.1	1.7	2.2
IX	2.4	3.7	9.5	11.6
X	2.3	3.2	8.2	10.3

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Determination of Methyl Methacrylate in Surgical Acrylic Cement

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Abstract □ A methyl methacrylate cement used in hip surgery as well as in dentistry was identified and quantitatively analyzed for its monomer content in starting materials and in the finished cement by proton magnetic resonance spectroscopy. IR data indicated that the monomer continued to escape from the product after it had hardened. The presence of 21% methyl methacrylate monomer relative to the polymer was demonstrated at the time the cement normally would be inserted into the body.

Keyphrases □ Methyl methacrylate—PMR analysis, ratio of monomer to polymer content, surgical acrylic cement □ Cement, surgical—PMR analysis of methyl methacrylate monomer relative to polymer content □ PMR spectroscopy—analysis, methyl methacrylate in surgical acrylic cement

The biomedical applications of polymers have increased rapidly in recent years (1, 2). One of the more widely used polymeric materials is methyl methacrylate bone cement. This polymer has been used extensively in dentistry and was approved for use in the United States for hip replacement and knee replacement operations. It is also used in skull surgery. Some deaths reported in 1971 during surgery prompted the examination of the material.

BACKGROUND

The methyl methacrylate cement is supplied as a kit made up of a sterile ampul of liquid and a sterile package of powder. The liquid consists of methyl methacrylate monomer, *N,N*-dimethyl-*p*-toluidine (polymerization initiator), and hydroquinone (polymerization inhibitor). The powder consists of polymethyl methacrylate–styrene copolymer (83.3%) and polymethyl methacrylate (16.7%) with benzoyl peroxide added as an initiator; preparations are available with or without barium sulfate (10%).

In the surgical application of the product, the liquid is mixed intimately with the powder until a putty is formed. This soft, workable putty is generally made into a ball and kept until just before being placed around the metal prosthesis. In this form, the prosthesis is placed in the body of the patient where the putty continues to harden.

Under normal surgical procedures, some monomer can diffuse out of the cement and into the body. It has been detected in the breath of patients undergoing this type of surgery. The high lipid solubility of the monomer aids its distribution throughout the body and makes hepatotoxicity a real possibility. This toxicity has been demonstrated in mice (3). In addition, extensive studies on dogs have shown large drops in blood pressure, decreases in heart rate, increased respiration, and changes in the ECG (4).

Sensitization to the monomer in humans has been reported (5–8); some investigators also suggested that it is responsible for, or a contributory factor in, observed cases of hypotensive states and cardiac arrest (4). In 1970, the British literature reported nine cases of cardiac arrest following the use of methyl methacrylate cement, and at least one fatality was reported in 1971 in this country (9).

There have been no definitive reports on the concentration of the potentially toxic monomer in the putty stage of the cement during the 4–5-min period after mixing when the putty is placed into the body of the patient. It was estimated that there may be up to 10% residual monomer in the curing mass after 1 hr (10). In a related study using a GLC method, Bechtel *et al.* (11), using the same product as that analyzed in the authors' laboratories, determined the amount of monomer leaching out of acrylic bone cements into tissues during polymerization. At 2 min after mixing, the monomer killed varying amounts of the surrounding tissue cells. However, the putty was placed in contact with the tissues earlier than the instructions indicated for the material used in that work. The monomer concentration in the putty at any time was unknown.

In 1971, Smith (12) reported the approximate composition of very similar acrylic cements used for dental applications, using an assay method based on the bromination of the double bond (13), and obtained 1.9 and 3.5% monomer content in acrylic cements used in hip replacement surgery. In these cases, the earliest reported analysis was obtained 1 hr after the kit contents were mixed. Methods based on IR spectrophotometry (14) and on polarography (15) have been used to determine the monomer content in bone cements sampled 1 hr or more after mixing.

The purpose of this investigation was to determine the amount of monomer, relative to the polymer, present in the putty at the recommended time of insertion into the body. Proton magnetic resonance (PMR) spectroscopy was used; this method requires no internal standard nor weighing of the sample, since the ratio of monomer to polymer is determined from the ratio of the vinyl to methoxyl signals.