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Solubility of Various Barbiturates in Buffered Aqueous Solutions
I. Test of a Theoretical Equation

by

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ABSTRACT

The solubility of ten variously substituted barbiturates were determined in two pH buffered solvent systems at three temperatures. The buffer systems chosen were pH values at the pKa of these solutes and at about three pH units below the pKa, producing undissociated solute molecules and equimolar concentrations of the acid form and dissociated salt form, respectively.

The solubility values obtained experimentally were tested against a theoretical analytical expression that relates the solubility at pH values above the solubility of the undissociated form. There was seen to be some adherence to this equation with deviations that are considered in this communication.

INTRODUCTION

The solubility of compounds, such as these nonelectrolytes being considered, depends on the mixed physical chemical properties of each component and their relationship to such factors as temperature and pH. Solubility is defined in quantitiative terms as the concentration of solute in a saturated solution at a certain temperature; and in a qualitative way, it may be stated as the spontaneous interaction of two or more substances that form a homogenous molecular dispersion. In fact, solubility is a dynamic process that results from the making and breaking of adhesional

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and cohesional interactions at a given thermal equilibrium. The solubility of nonelectrolytes is usually represented by the fundamental thermodynamic relationships according to Van't Hoff's equation with appropriate assumptions. In the present study, the aqueous solubilities of ten barbiturares were determined. Since the magnitude of the solubility varies with pH and temperatures, two pH buffer systems were used here to provide a comparison between the charged and uncharged species. The equilibrium solubility of each solute in two buffered solvent systems was determined at several temperatures in order to evaluate adherence to the theoretical test equation. Work on the solubility of these compounds as a function of pH has been presented by various workers (1-3). Current work on cosolvent systems and alcohols has also been presented (4-6). These compounds act as weak acids in aqueous solutions (7) and possess pKa's in the range of about 7-9 (8, 9).

EXPERIMENTAL

Chemicals - The chemicals used in this study are as follows: 5,5' diethylbarbituric acid[1], 5-ethyl, 5-phenyl barbituric acid[2], 5-ethyl, 5-isoamyl barbituric acid[3], 5-ethyl, 5-(1-methylbutyl) barbituric acid[4], 5-ethyl, 5-butyl barbituric acid[5]. 5-ethyl, 5-isopropyl barbituric acid[6], 5-ethyl, 5(1-methyl propyl) barbituric acid[7], 5-ethyl, 5(1-methyl-butenyl) barbituric acid[8], 5,5-diethyl, 1-methyl barbituric acid[9], 5-ethyl, 5(1-methylbutyl) thiobarbituric acid[10], potassium chloride[11], boric acid[12], sodium carbonate[13], sodium hydroxide[14], and distilled water.

Equipment - The following were used: a rotating apparatus[15], a temperature controlling circulator[16], an analytical balance[17], pH meter[18], spectrophotometer[19], hypodermic adapter[20], drying oven[21], a melting point apparatus[22], computer[23], calculator plotter[24], glass aquarium[25] and a pH electrode[26].

Preparation of the Buffer Solution for the Solubility Study

In this study of the solubility of these barbiturates in water, two types of solvent systems were used: solutions buffered to pH values equal to the pKa values of the barbiturates and solu-

tions buffered to pH values equal to three pH units below the pKa value of the barbiturates.

Gifford's buffer solution system (10) was chosen, since this buffer system provides the required pH range within about three units for all of the barbiturates studied.

The buffer system consists of a stock acid solution and a stock alkaline solution. Combination of the former with the small quantities of the latter provide solutions of varying pH to meet any need in providing the appropriate pH values for each of the barbiturates (11, 8).

The stock acid solution was prepared with 12.4 grams of boric acid with 7.4 grams of potassium chloride dissolved and q.s. to 1000 milliliters of distilled water.

The stock alkaline solution was prepared with 21.2 grams of anhydrous sodium carbonate dissolved and q.s. to 1000 milliliters of distilled water.

Various pH buffer solutions were prepared volumetrically by these two stock solutions at room temperature. The pH of each buffer solution was determined by a Beckman Model SS-2 Expandomatic pH Meter and Benchmark pH electrode.

The pH values for the buffered systems used in this study varied from 5.0 to 8.6 and provided two buffer systems for each barbiturate. However, it should be noted that the final experimental values of pH for the barbiturate solutions varied from 4.8 - 4.85 at the pKu end and from 8.7 - 8.8 at the pKa end. The lowering of the pH may be due to the effect of dissolved carbonic acid by carbon dioxide incorporation during the solubility runs. The higher pH's of the experimental solutions especially noted with the 40°C solutions may be due to slight losses of carbon dioxide at the higher temperatures and the variation of pKw with temperature.

In both these cases, very small amounts of carbonic acid, i.e., 10^{-8} molar could cause these small changes. While these solutions should effectively resist changes in pH, the pKa of carbonic acid is 6.37 which is within the range of these buffers and may add more protons and thereby lower the pH. In addition to the

above, there is also experimental error in the pH determinations and would be of the order of about ± 0.05 pH units.

The lowest pH required in this study was 4.4; however, the lowest attained pH was 4.8, then

$$pH = pKa + \log \frac{(salt)}{(acid)} \qquad \text{equation 1}$$

For phenobarbital and thiopental, the pKa's are 7.4. The use of an experimentally buffered solution at a pH = 4.8; the relative concentration of the acid and salt species would be

$$4.8 = 7.4 + \log \frac{(salt)}{(acid)}$$

$$-2.6 = \log \frac{(salt)}{(acid)}$$

then the salt concentration is

$$(salt) = .0025\ (acid)$$

This would mean that 99.75% is in the undissociated acid form and 0.25% in the dissociated salt form, and thus was considered sufficient in terms of the number of undissociated molecules.

The drugs investigated are tabulated in Table I. This table comprises ten different 5,5-disubstituted barbiturates with the corresponding physical chemical properties.

Dissolution Process

The determination of the solubility of the various barbiturates in two different solvents was based essentially on the procedures given by Paruta et al (12). A slight excess of solute was placed in a glass vial and a quantity of solvent added. The vials, sealed by means of plastic caps with teflon liners, were placed on a rotating apparatus in a temperature-controlled water bath for a period of twenty-four hours, a time which was found to be sufficient for equilibrium. The temperature, maintained by a Porta-Temp circulator, was observed to vary not more than ± 0.1° C at each of the temperature settings of 25°, 33° and 40°C.

After the sample had reached equilibrium, the rotating apparatus was stopped. Each of the three samples was removed from the temperature bath. The vial was quickly dried and the cap was care-

TABLE I: A SUMMARY OF THE PHYSICAL-CHEMICAL PROPERTIES OF BARBITURATES USED IN THIS STUDY

	BARBITURATES	pKa#	MOLECULAR+ WEIGHTS	MELTING* POINTS
1	BARBITAL	7.90	184	188-190
2	BUTETHAL	7.92	212	126-128
3	METHARBITAL	8.30	198	151-155
4	PROBARBITAL	7.98	198	202-203
5	PHENOBARBITAL	7.40	232	156-157
6	PENTOBARBITAL	8.07	226	127-130
7	BUTABARBITAL	8.00	212	165-166
8	VINBARBITAL	7.99	224	160-163
9	AMOBARBITAL	7.92	226	156-158
10	THIOPENTAL	7.40	242	156-158

*From A. N. Paruta and T. L. Breon, Drug Development Communication, 2 (6) 521 (1976) [reference (13)]

+From Merck Index, seventh edition, Merck & Co., Inc. (1960) [reference (14)]

#From M. E. Krable, J. Phys. Chem. 44, 449 (1940) [reference (8)]. T. D. Doyle and J. B. Proctor, J. Am. Offi. Anal. Chem. 56, 864 (1973). [reference(9)]

fully unscrewed to prevent water contamination. The contents were immediately filtered, utilizing a hypodermic syringe fitting with a Swinny adaptor, into a second vial. An aliquot of the filtrate was then removed by a pipette to a volumetric flask, and a suitable dilution with the approriate buffer solution was prepared. The hypodermic syringe, Swinny adaptors, pipettes and transfer vials were warmed in a Telco drying oven prior to use to prevent thermal precipitation. Then these prepared sample solutions were subjected to

a spectrophotometric assay. Prior to the assay, the sample solutions were again diluted with 1 N NaOH solution to maintain the pH at about 13, a pH which was found to have a consistent maximum absorption for all of these barbiturates throughout the study. At least three spectrophotometric determinations were made. The equilibrium solubility analysis was determined utilizing an IBM 370/60 Digital Computer; the reported results of solubility are thus at saturation. Each solubility reported represents the average values from at least 3 runs of triplicate samples of the two-solvent system for each of 10 barbiturates at 3 different temperature settings.

Variation in solubility was found to be within ± 5% range for each barbiturate studied.

Assay Procedure

A spectrophotometric assay using a Hitachi Model 200 UV-VIS Spectrophotometer was developed for the quantitative determination of these barbiturates.

The barbiturates as a group are of interest spectrophotometrically because they only exhibit ultraviolet absorption in alkaline solution, the wavelength, itnensity, and stability of which is dependent on pH. In acid solution, practically no absorption is noted; at about pH 10, all barbiturates show absorption with maximum at 240 nm, and above this pH level, the absorption shifts to a maximum of about 255 nm in 1 N NaOH, except for the N-substituted compound, metharbital, whose maximum absorption rarely exceeds 244 nm.

The use of 1 N NaOH in the sample solutions of these barbiturates was to insure that maximum absorption peaks were consistent throughout the study. The maximum absorption for most of these barbiturates was found to be about 255 nm.

A minimum of seven dilutions for each compound was made, the absorption determined, and a plot of absorption versus concentration was drawn.

RESULTS AND DISCUSSION

In this study, the solubilities of ten variously substituted barbiturates were determined at the pK_a's and three pH units below

the pKa (pKu) at three temperatures. At the pK_a values, these solutes would exist as one half the total concentration in the acid form and the salt form. For those systems buffered to three units below the pK_a, referred to as the pKu solvent system, the concentration of the solute would express the solubility of the acid form or undissociated barbiturate. In Table II, a summary of the compound, number, chemical name, structure, substituent groups and common name of the barbiturates used in this study are given. The duration of action (14) of these substances are also given in this table. Since these compounds are given in rank order of aqueous solubility, the duration of action is seen to approximately decrease with increasing lipophilicty which confirms an earlier study (5).

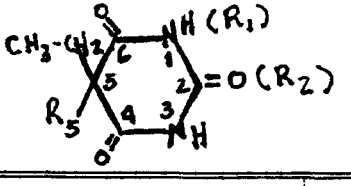
In Table III and IV, the determined solubilities of these solutes in mg/ml. and moles/liter at the three temperatures and two pH buffered systems are given. These solubilities have been rank listed with respect to the solubility for the undissociated species or the pKu solvent system. It can be observed that in all cases, the solubility, as expected, increased with temperature and increasing pH, and the solubility at the pKa values was greater than that at the pKu values. In the pKa buffered solvent system, the overall concentration of the solute would be expressed by one half in the acid form and one half in the salt form. The salt form of any of the solutes would be water soluble and would increase the overall concentration of the barbiturate in solution and be limited only by the pH of the buffering system.

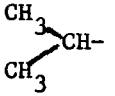
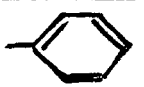
Additionally, the ratio of the pKa solubility to the pKu solubility in terms of M/L is given in the final column of Table IV.

In Figure 1, the solubility in mg./ml. for barbital, butethal and phenobarbital in the pKa solvent and pKu solvent systems are plotted versus temperature.

In these typical plots, the solubility of the solute in the pKa solvent system is always greater than the solubility of the pKu solvent. The solubility for these solutes is seen to increase linearily with increasing temperature in both the pKu and pKa sol-

TABLE II. A SUMMARY OF THE COMPOUND NUMBER, CHEMICAL NAME AND SUBSTITUENT GROUPS, COMMON NAMES AND DURATION OF ACTION OF COMPOUNDS USED IN THIS STUDY



CPD. NO.	CHEMICAL NAME	R_5 GROUP	R_1 GROUP	R_2 GROUP	COMMON NAME DURATION OF ACTION
I	5,5-Diethyl	CH_3-CH_2-	H	O	BARBITAL (LONG)
II	5-Ethyl-5-butyl	$CH_3-CH_2-CH_2-CH_2-$	H	O	BUTETHAL (LONG)
III	5,5-diethyl, 1-methyl barbituric acid	CH_3-CH_2-	CH_3	O	METHARBITAL (LONG)
IV	5-Ethyl-5-isopropyl barbituric acid		H	O	PROBARBITAL
V	5-Ethyl-5-phenyl barbituric acid		H	O	PHENOBARBITAL (LONG)

VI	5-Ethyl-5-(1-methylbutyl)-barbituric acid	$CH_3-CH_2-CH_2-CH(CH_3)-$	H	O	PENTOBARBITAL (SHORT TO INTERMEDIATE)
VII	5-Ethyl-5-(1-methylpropyl)-barbituric acid	$CH_3-CH_2-CH(CH_3)-$	H	O	BUTABARBITAL (INTERMEDIATE)
VIII	5-Ethyl-5-(1-methyl-1-butenyl barbituric acid	$CH_3-CH_2-CH=C(CH_3)-$	H	O	VINBARBITAL (INTERMEDIATE)
IX	5-Ethyl-5-(3-methylbutyl)-barbituric acid	$CH_3-CH(CH_3)-CH_2-CH_2-$	H	O	AMOBARBITAL (SHORT TO INTERMEDIATE)
X	5-Ethyl-5-(1-methylbutyl)-2-thio barbituric acid	$CH_3-CH_2-CH_2-CH(CH_3)-$	H	S	THIOPENTAL (ULTRA-SHORT)

Table III: A summary of the solubility of the solutes expressed in mg./ml. in two buffered aqueous systems at three temperatures.

N	Barbiturate	Temperature	Buffer System pKu	pKa
I	Barbital	25	7.3	13.0
		33	8.6	15.4
		40	10.6	17.3
II	Butethal	25	3.9	7.3
		33	4.7	8.4
		40	5.3	9.5
III	Metharbital	25	2.1	4.2
		33	2.7	5.2
		40	3.4	6.0
IV	Probarbital	25	1.6	2.8
		33	1.9	3.4
		40	2.4	4.2
V	Phenobarbital	25	1.2	2.3
		33	1.6	3.3
		40	2.2	4.0
VI	Pentobarbital	25	1.0	1.9
		33	1.3	2.5
		40	1.5	3.0
VII	Butabarbital	25	0.9	1.9
		33	1.2	2.6
		40	1.5	3.1
VIII	Vinbarbital	25	0.8	1.5
		33	1.1	2.5
		40	1.3	3.2
IX	Amobarbital	25	0.6	1.2
		33	0.7	1.5
		40	0.9	2.0
X	Thiopental	25	0.06	0.11
		33	0.08	0.18
		40	0.10	0.24

Table IV: Summary of the solubility in mole/liter for the solutes at three temperatures and the solubility ratio S(pKa/S(pKu).

No.	Barbiturate	Temperature	Buffer System M/L pKu	pKa	S(pKa) S(pKu)
I	Barbital	25	.0397	.0706	1.78
		33	.0467	.0837	1.79
		40	.0576	.0940	1.63
II	Butethal	25	.0184	.0344	1.87
		33	.0222	.0396	1.78
		40	.0250	.0448	1.79
III	Metharbital	25	.0106	.0212	2.00
		33	.0136	.0283	2.08
		40	.0172	.0303	1.76
IV	Probarbital	25	.0081	.0141	1.74
		33	.0096	.0172	1.79
		40	.0121	.0212	1.75
V	Phenobarbital	25	.0052	.0099	1.95
		33	.0069	.0142	2.05
		40	.0095	.0172	1.81
VI	Pentobarbital	25	.0044	.0084	1.91
		33	.0058	.0111	1.91
		40	.0066	.0133	2.02
VII	Butabarbital	25	.0042	.0090	2.14
		33	.0057	.0123	2.15
		40	.0071	.0146	2.06
VIII	Vinbarbital	25	.0036	.0067	1.86
		33	.0049	.0117	2.39
		40	.0058	.0143	2.46
IX	Amobarbital	25	.0027	.0053	1.97
		33	.0031	.0066	2.13
		40	.0040	.0088	2.20
X	Thiopental	25	.00025	.00045	1.80
		33	.00033	.00074	2.24
		40	.00041	.00041	2.41

Table V: Variation of Solubility Ratio in Equation 2 as a function of small pH changes.

ΔpH (Ka-$[H^+]$)	S_T
+0.20	$2.58S_0$
+0.15	$2.40S_0$
+0.10	$2.25S_0$
0.00	$2.00S_0$
-0.10	$1.79S_0$
-0.15	$1.70S_0$
-0.20	$1.63S_0$

vent systems. This linearity would indicate a constant dissolution mechanism in each of these solvent systems.

It was recognized that the pKw of water varies slightly over this narrow temperature range, and this effect upon the pH of these solvent systems would make a difference of about 0.1 pH units. It is possible that this slight difference in pH did contribute to the experimentally determined solubilities and the variance from the theoretically calculated solubility.

The solubility of these solutes should follow the theoretical equation:

$$S_T = S_o + \frac{S_o K_a}{[H^+]} \qquad \text{Equation 2}$$

where S_T is the total solubility, Ka and $[H^+]$, the acid dissociation constant and hydrogen ion concentration, respectively. S_o represents the solubility of the undissociated solute. When K_a and $[H^+]$ are equal to each other, i.e., pH = pKa, then the solubility at the pKa values should be

$$S_T = S_o + S_o = 2\,S_o \qquad \text{Equation 3}$$

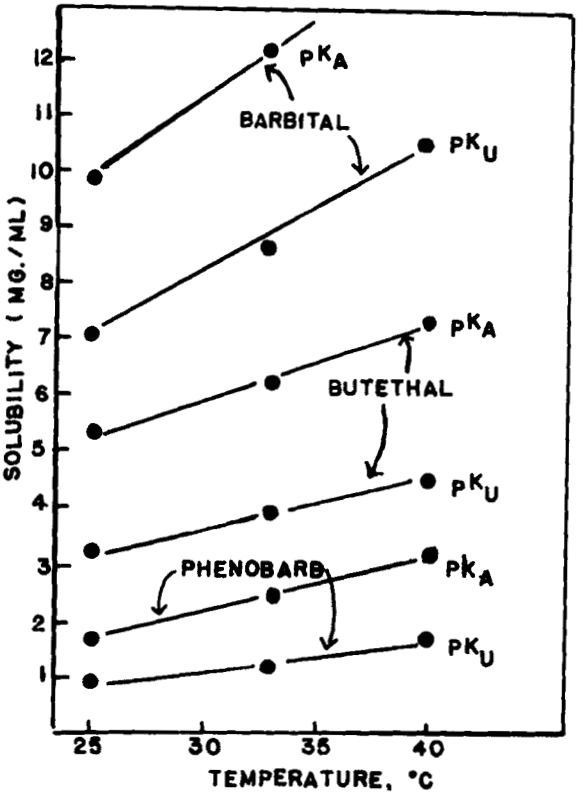


FIGURE 1. The solubility in mg/ml for the noted barbiturates in the pK_a and pK_u solvent systems as a function of temperature.

or

$$S(pKa) = 2S\ (pKu)$$

that is, the solubility at the pKa value is twice the solubility at the pKu value. As given in Table IV, it can be seen that the theoretical ratios of two were not followed exactly but varied from a low of 1.63 to a high of 2.46. It would be instructive at this point to determine the relationship of equation 2 and its varience by small changes in pH. These values have been calculated and are given in Table V. These calculations can be illustrated by the following example. For barbital, the pKa is 7.9, so the Ka = 1.26×10^{-8}; and if the pH of the solution were exactly 7.9 - it would lead to unity in the ratio $Ka/[H^+]$ and then S(pKa) = 2S (pKu).

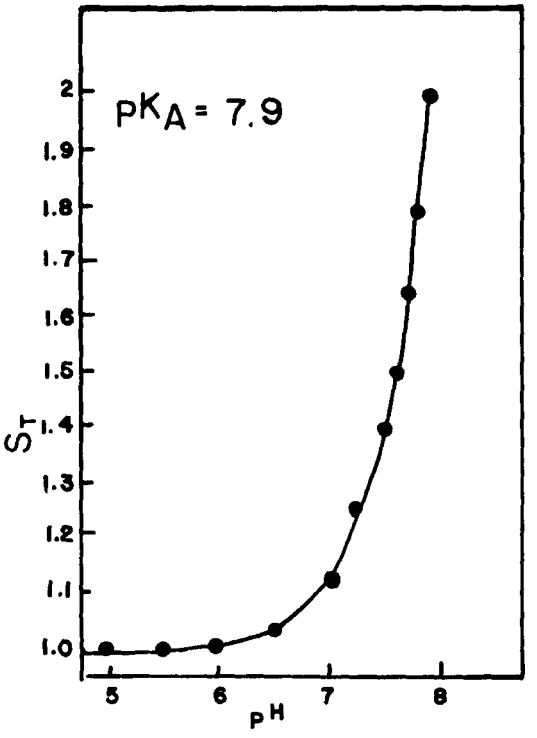


FIGURE 2. The solubility of Barbital as a function of pH, where the pK_a=7.9

If the pH is decreased by 0.1 units, the Ka remains the same at 1.26 x 10^{-8} and the $[H+]$ concentration would be 1.58 x 10^{-8} and the (pH = 7.8) and the ratio of $Ka/[H+]$ would be 0.79 and then S(pH = 7.8) = 1.79 S(pKu)

From table V, it can easily be seen that very minor changes in the pH values of ± 0.1-0.2 units would cause dramatic shifts in these rations with values of 1.63 So to 2.58 So. Additionally these ratios determine experimentally varied by the same magnitude in terms of these ratios. These obtained values indicated that the experimental initial and final pH's varied only slightly yet producingresults that are not in accord with the theoretical equation.

From pKw values at various temperatures, the pH at 40°C. should be decreased by o.1 pH units and ratios greater than 2 would indicate a positive shift (higher pHO to a total of about 0.3 pH units. It

has been noted that these shifts in the ratios may be due to several factors.

There is the experimental variation in the solubility determinations, temperature and pH variation, absorption or loss of carbon dioxide (carbonic acid) to and from the air spaces in the solubility vials and the pKw of water at the above ambient temperatures at 33° and 40°C.

The magnitude of solubility would also have to be considered as several of the solutes possessed very low aqueous solubilities and a slight error in accuracy could cause a large change in the the theoretical ratio.

While the results obtained in this study were considered adequate, there would be a need in studies of this type to carefully control the pH of the system, nitrogen purging of solubility vials, using solutes with higher solubilities and more accurate determination of the solubility value itself.

The effect of buffers, solute polarity, temperature and aqueous thermodynamics is duscussed in a companion communication.

FOOTNOTES

[1]Lot 10-TT-113, Ganes Chem. Works, Carlstadt, NJ

[2]Lot 6588, Mallinkrodt Chem. Works, NY, NY

[3]Lot DUC-44 Eli Lilly and Col, Indianapolis, Ind.

[4]Lot 776-7548 Abbott Labs., Chicago, IL

[5]Lot 20-4441-01 Abbott Labs., Chicago, IL

[6]Lot C-40398 E. R. Squibb & Sons, Inc., New Brunswick, NJ

[7]Lot 5086, McNeil Labs, Fort Washington, PA

[8]Lot L578, 303-1-4, Merck, Sharp & Dohme, Rahway, NJ

[9]Lot 685-7608, Abbott Labs, Chicago, IL

[10]Lot 760-7657, Abbott Labs, Chicago, IL

[11]Lot C316B313, Allied Chemical, Morristown, NJ

[12]Lot C611549, Allied Chemical, Morristown, NJ

[13]Lot 3602, Anhydrous, J. T. Baker, Chem. Co., Philipsburgh, NJ

[14]Lot W183JL, Allied Chemical, Morristown, NJ

[15]Menold Apparatus, SA7-2424, E. D. Menold, Lester, PA

[16]Porta-Temp, Precision Scientific Co., Chicago, IL

[17]Mettler Type H6T, Mettler Instr. Corp., Hightstown, NJ

[18]Beckman Expandometer SS-2, Beckman Instr., Inc., Fullertown, CA

[19]Hitachi 200, Perkin-Elmer Corp., Norwalk, CT

[20]Swinny No XX3001200, Millipore Corp., Bedford, MA

[21]Thelco Model 15, Precision Sci. Co., Chicago, IL

[22]Fisher-Johns 12-144, Fisher Sci. Co., Pittsburgh, PA

[23]IBM 370/155, IBM, White Plains, NY

[24]Hewlett Packard Model 9810A, Hewlett Packard Calculator

[25]Ten-gallon, Sears-Roebuck and Co.

[26]Benchmark No. 737, Markson Science, Inc., DelMar, CA

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