[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Solubility of Carcinogenic and Related Hydrocarbons in Water

BY W. W. DAVIS, M. E. KRAHL AND G. H. A. CLOWES

The immediate stimulus for the present investigation arose during a study of the reactions of polycyclic hydrocarbons with sterols in mixed surface films.[1] It was observed that there were, under certain conditions, irreversible losses of hydrocarbon from the films at rates which appeared, from preliminary observations with 10-methyl- and 10-amyl-1,2-benzanthracenes, to vary in a direct relationship to the water solubility of the hydrocarbons. Solubility determinations on a large number of hydrocarbons were therefore desirable in order to define the characteristics of the mixed surface films.

Data on solubilities of the various polycyclic hydrocarbons in aqueous media are also of great potential biochemical interest in connection with the cancer producing activities of certain of these compounds, since the hydrocarbons have to depend, both for reaching the particular cells upon which they act and for elimination, on transport through aqueous media containing bile acids, proteins, protein–lipid complexes, and other potential hydrocarbon solubilizing and dispersing agents. Even the solubilities of the hydrocarbons in pure water are of considerable biochemical value, since such data make it possible to know the concentration of a given carcinogen which can be brought to bear—as in *in vitro* experiments on tissues, bacteria and protozoa—upon individual cells developing in aqueous media under well-defined experimental conditions.

The nephelometric method for solubility determination described in the previous paper[2] has been here employed to determine the solubilities of thirty-one hydrocarbons in water.. Analogous experiments with more complex aqueous solvent media, including solutions of proteins and protein–lipid complexes, are now under way.

Experimental Results

Solubility measurements on each of thirty-one polycyclic hydrocarbons are presented in Table I. The compounds are grouped in the following order: three ring compounds, four ring compounds and their acyclic derivatives, five ring compounds and their acyclic derivatives, and a six ring compound.

Column I gives the order of increasing solubility among the thirty-one compounds here examined.

Column II gives the key number by which the source, melting point, structural formula, and surface film behavior of each of the hydrocarbons can be obtained readily from Figs. 1 and 2 and Table II of a previous paper.[1]

Column III gives the name of the compound according to the terminology in Fieser's book.[3]

Column IV gives individual values obtained in separate solubility determinations. These values were obtained by extrapolation of the straight lines fitted free hand to the experimental points along segments A and B of the nephelometric curves.[2] The figure after the $\pm$ sign indicates the maximum variation which can be introduced by alternate placement of the straight lines fitting the experimental points.

Column V gives, for each compound, an arbitrarily weighted average of the values in Column IV. Only the first two figures in each value are significant. These data were acquired principally for purposes where the relative order of solubility of the various hydrocarbons appeared to be of more importance, at least at the present level of knowledge regarding the mechanism of hydrocarbon carcinogenesis, than the absolute solubility values. Consequently, no effort has been made to collect a sufficiently large number of observations to establish the validity of the results on a statistical basis. Even if time permitted, it is doubtful whether such a procedure would be justified in view of the limitations in the method which were discussed in the previous paper.[2]

Column VI gives a qualitative indication of whether a given compound is carcinogenic (+), non-carcinogenic (−), or of doubtful activity (±). If the compound has been used by subcutaneous injection, results by this method are here given preference because the samples used for the animal

(1) W. W. Davis, M. E. Krahl and G. H. A. Clowes, THIS JOURNAL, **62**, 3080 (1940).

(2) W. W. Davis and T. V. Parke, *ibid.*, **64**, 101 (1942). Whether the hydrocarbon particles in the suspensions used for these solubility determinations are amorphous or crystalline cannot be decided from the available data. Further investigation of this point is in progess.

(3) L. F. Fieser, "The Chemistry of Natural Products Related to Phenanthrene," second edition, Reinhold Publishing Corporation New York, N. Y., 1937, pp. 81–110 and 349–357.

TABLE I

SOLUBILITY OF POLYCYCLIC HYDROCARBONS IN PURE WATER

I Order of increasing soly.	II Key no.	III Hydrocarbon	IV Soly., micrograms/l. individual detns.	V Best value	VI Cancer producing activity
27	37	Anthracene	75 ± 8 72 ± 5 75 ± 5	75	−[c]
31	1	Phenanthrene	1550 ± 50 1620 ± 50 1650 ± 50	1600	−[a]
5	2	Naphthacene	1.0 ± 0.2 1.0 ± 0.5	1.0	−[c]
8	4	Chrysene	1.5 ± 0.5 1.5 ± 0.2	1.5	−[f]
24	28	5-Methylchrysene[g]	65 ± 5 65 ± 5 58 ± 5 55 ± 5 61 ± 3 62 ± 3	62	
25	16	6-Methylchrysene	75 ± 7 75 ± 7 60 ± 6 70 ± 10 65 ± 5	65	+[k]
17	29	5,6-Dimethylchrysene	25 ± 5 25 ± 5 24 ± 5 24 ± 2	25	+[e]
15	3	1,2-Benzanthracene	11 ± 1 11 ± 1 12 ± 1	11	±[e]
22	17	1′-Methyl-1,2-benzanthracene	55 ± 2 54 ± 4 55 ± 2	55	−[h]
26	18	9-Methyl-1,2-benzanthracene	66 ± 3 66 ± 3	66	+[h]
23	19	10-Methyl-1,2-benzanthracene[i]	55 ± 5 55 ± 5 55 ± 5 55 ± 5	55	+[i]
21	32	Tetrahydro-10-methyl-1,2-benzanthracene	45 ± 5 42 ± 5 45 ± 5	44	−[i]
14	33	6-Chloro-10-methyl-1,2-benzanthracene	11 ± 2 9 ± 1	10	+[i]
18	21	10-Ethyl-1,2-benzanthracene	45 ± 5 45 ± 5 35 ± 5 45 ± 3 45 ± 5 40 ± 5 40 ± 8	45	+[i]
13	22	10-Butyl-1,2-benzanthracene	7 ± 0.7 7 ± 0.7 7 ± 0.7 8 ± 1 8 ± 1	8.0	−[i]
4	23	10-Amyl-1,2-benzanthracene	0.9 ± 0.1 0.8 ± 0.3 0.8 ± 0.2	0.8	−[i]
20	20	9,10-Dimethyl-1,2-benzanthracene	43 ± 2 45 ± 4 45 ± 1 43 ± 3 39 ± 4	43	+[i]
19	6	Triphenylene	38 ± 8 36 ± 4 40 ± 4	38	−[c]
28	5	Pyrene	160 ± 10 165 ± 5	165	−[c]
29	12	Fluoranthene	240 ± 20 225 ± 20 240 ± 20	240	−[h]
30	11	4,5-Methylenephenanthrene	1100 ± 100 1250 ± 250 1100 ± 100	1100	
1	7	Perylene		<0.5	−[b]
2	9	1,2,5,6-Dibenzanthracene	0.5 ± 0.1 0.5 ± 0.1	0.5	+[b]
9	26	Picene	2.5 ± 0.5	2.5	−[b]
10	14	3,4′-Ace-1,2-benzanthracene	3.5 ± 0.5 2.5 ± 0.5 2.5 ± 0.5 2.5 ± 0.5	2.7	−[i]
11	13	Cholanthrene	3.5 ± 0.5 3.5 ± 0.5	3.5	+[h]
7	24	20-Methylcholanthrene	1.3 ± 0.3 1.8 ± 0.3 1.8 ± 0.3	1.5	+[e]
12	10	3,4-Benzpyrene	3.0 ± 0.5 4.5 ± 0.5 4.0 ± 0.1 4.0 ± 0.5 3.5 ± 0.5	4.0	+[j]
3	25	5-Methyl-3,4-benzpyrene	0.8 ± 0.2 1.0 ± 0.4 0.8 ± 0.2	0.8	+[j]
16	8	1,2,7,8-Dibenzanthracene	11 ± 1 10 ± 2 13 ± 2	12	±[c]
6	15	15,16-Benzdehydrocholanthrene	1.0 ± 0.2 1.0 ± 0.2 1.0 ± 0.2	1.0	+[d]

[a] E. L. Kennaway, *Biochem. J.*, **24**, 497 (1930). [b] J. W. Cook, I. Hieger, E. L. Kennaway and W. V. Mayneord, *Proc. Roy. Soc.* (London), **B111**, 455 (1932). [c] G. Barry, J. W. Cook, G. A. D. Haslewood, C. L. Hewett, I. Hieger and E. L. Kennaway, *ibid.*, **B117**, 318 (1935). [d] J. W. Cook, G. A. D. Haslewood, C. L. Hewett, I. Hieger, E. L. Kennaway and W. V. Mayneord *Am. J. Cancer*, **29**, 219 (1937). [e] L. F. Fieser, M. Fieser, E. B. Hershberg, M. S. Newman, A. M. Seligman and M. J. Shear, *ibid.*, **39**, 260 (1937). [f] W. E. Bachmann, J. W. Cook, A. Dansi, C. G. M. de Worms, G. A. D. Haslewood, C. L. Hewett and Mrs. A. M. Robinson, *Proc. Roy. Soc.* (London), **B123**, 343 (1937). [g] J. W. Cook and E. L. Kennaway, *Am. J. Cancer*, **33**, 50 (1938), and **39**, 381 and 521 (1940). [h] M. J. Shear, *ibid.*, **33**, 499 (1938). [i] G. M. Badger, J. W. Cook, C. L. Hewett, E. L. Kennaway, Mrs. N. M. Kennaway, R. H. Martin, and Mrs. A. M. Robinson, *Proc. Roy. Soc.* (London), **B129**, 439 (1940). [j] M. J. Shear and J. Leiter, *J. Nat. Cancer Inst.*, **1**, 303 (1940). [k] M. S. Newman, THIS JOURNAL, **62**, 870 (1940).

work and for the solubility work were often from the same batch prepared in Dr. Fieser's laboratory. If results by subcutaneous injection are not available, then results by the skin painting technique are quoted. It is not desired to attempt to draw parallels between carcinogenicity and solubility except to point out that, within a

given series of like structure, such as the alkyl-1,2-benzanthracene derivatives, compounds of lowest water solubility are least carcinogenic. Such a parallel cannot be drawn when considering compounds of more widely differing structures. The solubility is regarded, by the present authors, as merely one of a large number of factors which may have to be taken into account in considering the mechanism of hydrocarbon carcinogenicity. It may be that certain hydrocarbons will prove to be too soluble to be retained long enough to exhibit carcinogenesis except following repeated applications, while other hydrocarbons cannot exhibit carcinogenesis because they are so insoluble that they cannot reach a potential site of action rapidly enough to exceed their rate of destruction there.

From a purely chemical point of view certain of the results are interesting because they show that introducing a methyl group may either raise or lower the solubility of a given compound. For example, the 1'-, 9- and 10-methyl-1,2-benzanthracenes have solubilities of 55, 66 and 55 micrograms per liter, respectively, as compared with 11 for 1,2-benzanthracene. Likewise, the values for the 5- and 6-methylchrysenes are 62 and 65, respectively, as compared with 1.5 for chrysene. On the other hand, 5-methylbenzpyrene, with 0.8, is lower than 3,4-benzpyrene with 4. Since the extent of the solubility is determined by the excess of energy liberated by attraction of hydrocarbon for water molecules over that necessary to remove it from the particles of the hydrocarbon, the increased solubilities of the methyl-1,2-benzanthracenes and methylchrysenes as compared to those of the respective parent hydrocarbons may be provisionally accounted for by a decrease in the energy required to remove the molecules of the methyl derivatives from the solid, rather than by increase in attraction of the methyl derivatives for water. This suggestion is supported qualitatively by the fact that the methyl derivatives have lower melting points than the parent hydrocarbon. In the case of 5-methyl-3,4-benzpyrene and its parent hydrocarbon, the introduction of the methyl group apparently has little effect on the energy of binding of the hydrocarbon in the solid; consequently the solubility of the methyl derivative is decreased because of decreased water affinity. In a similar way, the solubilities of the 10-methyl-, 10-ethyl-, 10-butyl- and 10-amyl-1,2-benzanthracenes decrease as the water affinity of the whole molecule decreases with increasing length of side chain, even though the energies required to remove the hydrocarbon molecules from their respective solids, as indicated qualitatively by the melting points, decrease in the same order.

The authors are indebted to Mr. T. V. Parke for his coöperation in certain phases of the experimental work here described.

Summary

By means of the nephelometric method described in the preceding paper,[2] the approximate solubilities of thirty-one polycyclic hydrocarbons in pure water have been measured at 27°. These were found to vary from about 0.5 microgram per liter for 1,2,5,6-dibenzanthracene up to about 1600 micrograms per liter for phenanthrene.

INDIANAPOLIS, INDIANA RECEIVED JULY 14, 1941

[CONTRIBUTION FROM THE BUTTERFIELD CHEMICAL LABORATORY, UNION COLLEGE]

Studies on the Hydrogel of Zirconia. I. The Time of Set

BY CHARLES B. HURD, WALTER A. FALLON[1] AND ROBERT W. HOBDAY[2]

Introduction

Although the literature contains a number of observations of the formation of a hydrogel of zirconia, apparently only Prakash[3] has determined the time of set. His data do not show the relation of temperature to time of set.

A series of determinations of the time of set of zirconia hydrogels under carefully controlled conditions should prove interesting, because of the relations between zirconium, titanium, and silicon, and because of the large amount of data available on time of set of hydrogels of silica, often called silicic acid gels.

It has been found much more difficult to control the setting of these hydrogels of zirconia than the corresponding silicic acid gels. Nevertheless,

(1) Present address: Eastman Kodak Company, Rochester, N. Y.

(2) Present address: General Chemical Company, New York City.

(3) Prakash, *J. Phys. Chem.*, **36**, 2483 (1932).