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Coördination of Polycyclic Aromatic Hydrocarbons with Silver Ion; Correlation of Equilibrium Constants with Relative Carcinogenic Potencies[1]

BY ROBERT E. KOFAHL AND HOWARD J. LUCAS

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The relative nucleophilic character of twenty-four polycyclic aromatic hydrocarbons has been determined by measuring the equilibrium constant for the argentation reaction, *i.e.*, the coördination with a silver ion to form an ionic complex in solution. The compounds investigated include phenanthrene, anthracene and twenty-two compounds containing the benz[a]-anthracene or benzo[c]phenanthrene structure. The equilibrium constants show good correlation with the relative carcinogenic potencies in mice and also significant correlation with electronic properties calculated by the methods of quantum mechanics.

In the two decades since it was demonstrated that certain polycyclic aromatic hydrocarbons are, in varying degrees, carcinogenic, *i.e.*, capable of inducing tumors in animals, much work has been done to determine relative carcinogenic potencies and to relate these potencies to chemical reactivity,[2] structure,[3] and theoretical electronic properties[4] of these molecules. Some significant correlations have been found.

Quantum mechanical calculations both by the valence bond and by the molecular orbital method indicate that in benz(a)anthracene and its homologs the region of the 5,6- or *meso*-bond possesses a higher density and availability of electronic charge than do ordinary aromatic bonds.[4,5] This bond corresponds to the reactive 9,10-bond of phenanthrene which, relative to benzene, has high reactivity toward double-bond reagents.

These facts suggested the need for an experimental method of measuring the relative nucleophilic character of polycyclic aromatic hydrocarbons. The task of developing and applying such a method to a series of hydrocarbons was undertaken as one of the series of investigations in the field of nucleophilic coördination reactions of unsaturated compounds which has been carried on in these laboratories.[6] The method finally developed is based on the one described by Andrews and Keefer, who determined argentation constants of benzene, naphthalene, phenanthrene and numerous benzene derivatives by measuring solubilities in aqueous solutions of silver nitrate and potassium nitrate at unit constant ionic strength.[7] Their method was modified by the use of a medium equimolal in water and methanol, employing sodium nitrate and silver nitrate at an ionic strength of 0.5, in order to increase the solubilities of the high molecular weight hydrocarbons and also make possible the use of moderately high silver concentrations. This mixed solvent was suggested by the work of P. L. Nichols.[8]

Experimental

Materials.—All inorganic chemicals were of reagent grade. J. T. Baker absolute methanol was fractionated in a stream of nitrogen from a small amount of sodium through 55 cm. of glass helices and pure methanol was taken over a 0.2 degree boiling range. Eastman Kodak Spectro Grade 2,2,4-trimethylpentane was distilled before use.

The following hydrocarbons were obtained from Eastman Kodak: benz(a)anthracene, 7,12-dimethylbenz(a)anthracene, 1,2,5,6-dibenzanthracene and 3-methylcholanthrene. Yellow oxidation impurities were removed from several of these compounds by repeatedly extracting their benzene solutions with sulfuric acid carefully adjusted in concentration so as to afford maximum extraction of oxygenated derivatives without appreciable extraction of the hydrocarbons. The yellow impurity, 1,2,6,7-dibenzanthracene, was removed from 1,2,5,6-dibenzanthracene by selective oxidation with lead tetraacetate.[9] Phenanthrene obtained from the Mathieson Company was found to contain about 1% anthracene, which was removed as the dimer by two or three exposures of the benzene solution to sunlight. Anthracene obtained from Eastman Kodak was purified by repeated extraction of the benzene solution with sulfuric acid.[10] The compound 9,10-dihydroanthracene was prepared by reduction of anthracene with sodium in 1-propanol.[11] The compound benzo(a)pyrene was obtained from Hoffmann–La Roche, Inc., and was used first as received and then after purification through the picrate.

Ten of the monomethyl benz(a)anthracenes, the 1- and 4-isomers being excepted, also benzo(c)phenanthrene and its six monomethyl homologs were donated in 2-g. quantities by Dr. Melvin Newman of The Ohio State University. The numbering systems for the hydrocarbons as illustrated in Fig. 1 are those of "Chem. Abstracts."

Solutions.—All stock solutions of silver nitrate and sodium nitrate in equimolal water–methanol medium were prepared by weight, were stored in the dark in glass-stoppered bottles, and were used within one to two weeks of the time of preparation.

Saturation and Analysis of Solutions.—Three problems are important in measuring the solubilities: (a) attainment of equilibrium, (b) removal of clear, saturated solution uncontaminated by suspended solid particles of hydrocarbon, and (c) prevention of changes in hydrocarbon concentration resulting from evaporation or from temperature variations during sampling and analysis. The following procedure was finally developed to give reproducible results:

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[1] This investigation was supported by a research grant from the National Cancer Institute, of the National Institutes of Health, Public Health Service.

[2] (a) L. F. Fieser and M. Fieser, "Organic Chemistry," 2nd ed., D. C. Heath and Co., New York, N. Y., p. 838. (b) L. F. Fieser, *Am. J. Cancer*, **34**, 37 (1938). (c) G. M. Badger, *J. Chem. Soc.*, 456 (1949). (d) L. F. Fieser and W. P. Campbell, THIS JOURNAL, **60**, 1142 (1938).

[3] L. F. Fieser and M. Fieser, ref. 2a, p. 834; A. Haddow, *Brit. Med. Bull.*, Vol. IV, 314 (1947).

[4] (a) R. Daudel, *Rev. sci.*, **84**, 37 (1946); M. Buu Hoi, *et al.*, *Compt. rend.*, **225**, 238 (1947); A. Pullman, *ibid.*, **225**, 738 (1947); B. Pullman and J. Baudet, *ibid.*, **237**, 986 (1953); A. Pullman, *J. chim. phys.*, **50**, 548 (1953); (b) C. A. Coulson, "Advances in Cancer Research," Vol. I, Academic Press, Inc., New York, N. Y., 1953, p. 1.

[5] (a) H. H. Greenwood, *Brit. J. Cancer*, **V**, 441 (1951); (b) A. Pullman, B. Pullman and G. Berthier, *Compt. rend.*, **236**, 2067 (1953).

[6] F. R. Hepner, K. N. Trueblood and H. J. Lucas, THIS JOURNAL, **74**, 1333 (1952), and papers there listed in references 2 a-d; K. N. Trueblood and H. J. Lucas, *ibid.*, **74**, 1338 (1952).

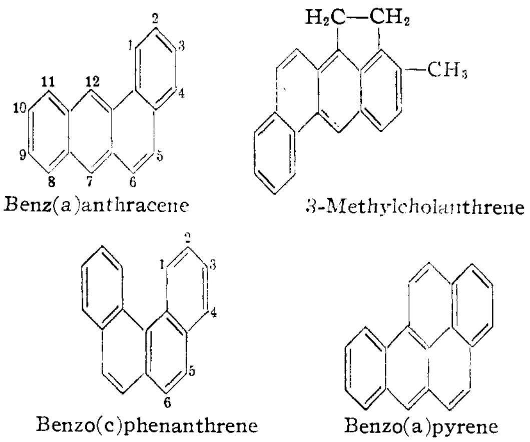
[7] L. J. Andrews and R. M. Keefer, *ibid.*, **71**, 3644 (1949).

[8] P. L. Nichols, *ibid.*, **74**, 1091 (1952), determined the argentation constants of methyl oleate and methyl elaidate by measuring the solubility of these compounds in 60 to 100% aqueous methanol containing silver nitrate in concentrations of 1.0 to 0.05 *M*.

[9] L. F. Fieser and E. B. Hershberg, *ibid.*, **60**, 1893 (1938).

[10] J. Mathieu, *Ann. chim.*, **20**, 215 (1945).

[11] H. Wieland, *Ber.*, **45**, 492 (1912).



Benz(a)anthracene 3-Methylcholanthrene

Benzo(c)phenanthrene Benzo(a)pyrene

Fig. 1.—Polynuclear aromatic hydrocarbons.

In each of six special 35-ml. $\overline{T}$19/38 centrifuge tubes was placed 0.3 g. of a hydrocarbon, and the proper volumes of 0.5 *M* silver nitrate and 0.5 *M* sodium nitrate were added by means of pipets to give 25 ml. of solution at an ionic strength of 0.5 and with the desired concentrations of silver. The stoppers were sealed on with paraffin wax, and the tubes were shaken on a reciprocal shaker for 24 hours at room temperature, then rotated in a thermostat for 48 hours at 25.0 ± 0.03°. The saturated solutions were analyzed in groups of three, being maintained at 25° during most of the sampling operation. The glass stoppers were removed and quickly replaced by foil-wrapped cork stoppers and the tubes were centrifuged for five minutes. Then pads of Pyrex wool were centrifuged onto the solid hydrocarbon for three minutes. The clear saturated solutions were sampled by volumetric pipets tipped with small pads of Pyrex wool, and the samples were run into 140-ml. glass-stoppered bottles containing the volume of 2,2,4-trimethylpentane required to give the desired extraction ratio. Then 100 ml. of distilled, nitrogen-saturated water was added and these extraction bottles were shaken for about 50 minutes. The trimethylpentane phases were separated and analyzed for hydrocarbon content by measuring the optical density at selected wave lengths in a Beckman model DU spectrophotometer using 1-cm. glass-stoppered quartz cells.

In the concluding work in pure aqueous solvent, rotation at constant temperature for 24 hours only was sufficient to attain saturation. However, in order to obtain reproducible measurements it was necessary to sample the solution by forcing it through a medium grade sintered glass filter stick.

Results

The solubility data have been treated on the basis of three assumptions: (1) the activity of the hydrocarbon is the same in all solutions, (2) the activity coefficient of the dissolved hydrocarbon is constant for constant ionic strength, and (3) the activity coefficients of the Ag^+ and $ArAg^+$ ions are equal. The assumed coördination reactions, the corresponding equilibrium constants, and the expression for the total concentration of hydrocarbon in the solution, $(Ar)_t$, are shown below. Here

$$Ar + Ag^+ \rightleftharpoons ArAg^+ \quad K_1 = (ArAg^+)/(Ar)(Ag^+)$$

$$ArAg^+ + Ag^+ \rightleftharpoons ArAg_2^{++}$$

$$K_2 = (ArAg_2^{++})/(ArAg^+)(Ag^+)$$

$$(Ar)_t = (Ar)_0[1 + K_1(Ag^+) + K_1K_2(Ag^+)^2]$$

$(Ar)_0$ is the concentration of hydrocarbon in 0.5 *M* sodium nitrate solution saturated with the hydrocarbon. Only in the case of phenanthrene was the silver ion involved in complexes appreciable relative to the total silver concentration, and the required correction produced a change of only 1% in the calculated constants. The total concentration of hydrocarbon is a second degree function of the silver ion concentration, and the best values of $(Ar)_0$, and of K_1 and K_2, which have been called argentation constants, may be found by fitting a second degree curve to the data.

Measurements of solubility in methanol–water are not as precise as might be desired. It seemed that the only satisfactory way to treat the data so as to avoid bias was by the method of least squares. The precision indices attached to the calculated constants are the probable errors, calculated in the process of least squares treatment utilizing the principles given by David Brunt.[12]

The solubility data for anthracene in aqueous methanol obtained in three separate runs are tabulated in Table I and the data are shown graphically in Fig. 2 with the least squares curves indicated.

TABLE I

SOLUBILITIES OF ANTHRACENE AT 25° IN EQUIMOLAL WATER–METHANOL CONTAINING SODIUM NITRATE AND SILVER NITRATE AT IONIC STRENGTH 0.5

Run	1	2	3
$AgNO_3$, *M*	—Solubilities, *M* × 10^4—		
0	3.26	3.26	3.23
0.1	3.68	3.68	3.62
.2	4.16	4.13	4.11
.3	4.80	4.76	4.77
.4	5.35	3.55[a]	5.31
.5	5.91	5.93	5.90

[a] Discard. Extraction was performed with silver precipitated as the chloride which adsorbed a major fraction of the hydrocarbon.

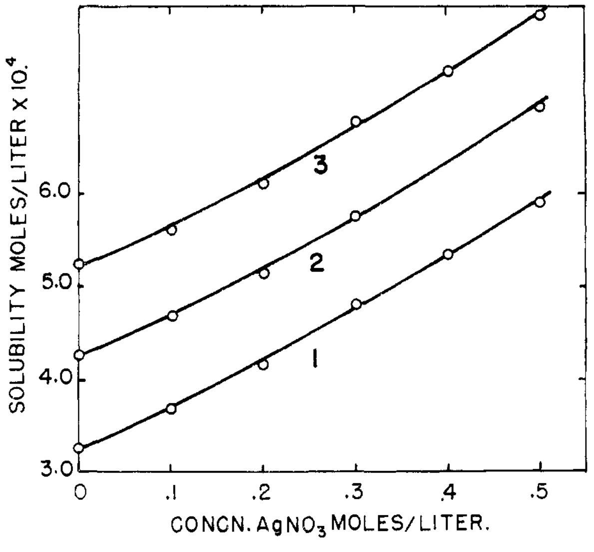


Fig. 2.—Solubility of anthracene in equimolal water–methanol containing sodium nitrate and silver nitrate at ionic strength 0.5. Scales for runs 2 and 3 have been raised one and two units, respectively.

Table II presents the calculated constants with their probable errors and the weighted mean values of the argentation constants. The data for anthracene demonstrate roughly the average precision and

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[12] David Brunt, "The Combination of Observations," Cambridge Press, New York, N. Y., 2nd ed., 1931, Chapters 5 and 6.

degree of reproducibility of the determinations reported in this paper. The systematic errors which are apparent in the solubility values for anthracene were not caused by errors in volume calibrations or measuring technique and so probably resulted from slight changes in concentration during the sampling process.

TABLE II

CALCULATED ARGENTATION CONSTANTS FOR ANTHRACENE

Run	K_1	K_2
1	1.400 ± 0.077	0.387 ± 0.108
2	1.299 ± .069	.577 ± .096
3	1.369 ± .089	.489 ± .120
Weighted mean	1.35 ± .04	.48 ± .06

The equilibrium constants for the argentation reaction of naphthalene and phenanthrene in water at unit ionic strength are shown in Table III and those of polycyclic hydrocarbons in aqueous methanol at ionic strength 0.5 in Table IV. The excellent agreement of data taken for naphthalene in the aqueous system with the postulated second degree relation is evidence that both mono- and disilver complexes are formed. The work of Keefer and Andrews provides good evidence for the formation of both mono- and disilver complexes by toluene.[13] The complex of benzene with silver perchlorate has been studied in crystalline form[14] and also the Raman spectrum has been investigated.[15] In the present investigation it was noted that in methanol-water medium at an ionic strength of 0.5 the replacement of sodium ion by silver ion produced a shift of the first absorption peak of 1,2,5,6-dibenzanthracene from 348.0 to 349.5 mμ. Subtraction of curves gave a curve with a maximum at 352.5 mμ which is thought to represent the absorption spectrum of the silver complexes of this hydrocarbon.

TABLE III

ARGENTATION CONSTANTS IN AQUEOUS KNO_3–$AgNO_3$ AT IONIC STRENGTH 1.00 .

Compound[a]	Temp., °C.	Soly. in 1 M KNO_3 M × 10^4	K_1	K_2	K_3
Naphthalene	20	1.78	3.212 ± 0.058	0.966 ± 0.024	
Naphthalene	25	2.19	2.937 ± .040	.909 ± .017	0 ± 0.04
Naphthalene	30	2.66	2.726 ± .054	.866 ± .022	
Phenanthrene	25	0.0537	3.55	.99	0.47
Benzo(c)phenanthrene[b]	25	.0103	3	.3	
9,10-Dihydroanthracene[b]	25	.344	1.24	.65	

First Argentation Reaction of Naphthalene at 25°

$$\Delta F = -638 \pm 8 \text{ cal./mole}$$
$$\Delta H = -2900 \pm 200 \text{ cal./mole}$$
$$\Delta S = -7.5 \pm 1.3 \text{ cal./mole-deg.}$$

Attempted measurements with anthracene in aqueous system failed because of suspended solid hydrocarbon. [b] Solubility and equilibrium data are only approximate because of erratic results.

Measurements of solubilities in aqueous solutions were considerably more precise than those in mixed medium. The solubility data from one run with naphthalene are shown graphically in Fig. 3. The temperature coefficient of K_1 for naphthalene was measured as indicated in Table III, and the change in heat content, the free energy, and the entropy were calculated for the coördination reaction at 25° given the assumptions previously listed regarding activity coefficients. The value of K_1 for naphthalene at 25° is 2.94 which is in fairly good agreement with the value 3.08 found by Keefer and Andrews.[7]

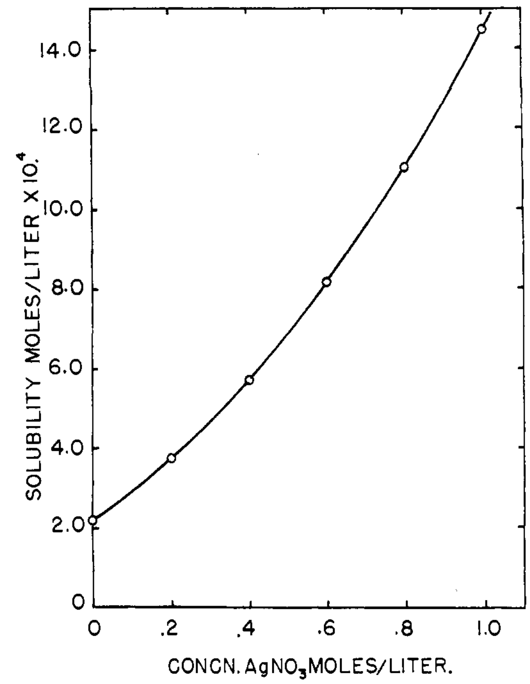

Fig. 3.—Solubility of naphthalene in aqueous potassium–silver nitrate at unit ionic strength and 25°. The line is a second degree curve fitted by method of least squares.

The information for phenanthrene in aqueous medium was found by least squares treatment to fit a third degree equation with r.m.s. deviation of 0.035 as compared to r.m.s. deviation of 0.23 when fitted to a second degree equation. The constants obtained from the third degree equation are K_1 = 3.55, K_2 = 0.99, and K_3 = 0.47, which agree satisfactorily with the over-all picture when compared to those for naphthalene, K_1 = 2.94 and K_2 = 0.91. On the other hand, the second degree fit for phenanthrene yields the values K_1 = 2.56 and K_2 = 2.22, which seem unlikely when compared to the constants of naphthalene. Thus we have fairly good evidence that phenanthrene forms appreciable amounts of a trisilver complex in aqueous silver nitrate. The data of Keefer and Andrews on the solubility of phenanthrene give the values 3.7 and 1.8 for the first two constants.[7] However, these values may be in error because it is believed that their phenanthrene was contaminated with about 1% of anthracene, since no special pains were taken to remove anthracene. Further indication of this is afforded by the fact that their reported value of the extinction coefficient is high by an amount corresponding to a content of 1 or 2% of anthracene.

The steric configuration of these coördination complexes for which the equilibrium constants are

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(13) R. M. Keefer and L. J. Andrews, THIS JOURNAL, **74**, 640 (1952).

(14) R. E. Rundle and J. H. Goering, *ibid.*, **72**, 5337 (1950).

(15) H. J. Taufen, M. J. Murray and F. F. Cleveland, *ibid.*, **63**, 3500 (1941).

TABLE IV

ARGENTATION CONSTANTS OF POLYCYCLIC AROMATIC HYDROCARBONS IN EQUIMOLAL WATER–METHANOL AT μ = 0.5 AND 25°

Compound[a,b]	Wave length, mμ	Molal extinct. coef. (isoöctane)	Solubility in 0.5 M NaNO$_3$ × 10^4	K_1	K_2	Number of detmns.
3-Methylcholanthrene	359.5	8440	0.266	3.31 ± 0.12	0	2
7,12-Dimethylbenz(a)anthracene	363	8860	2.09	1.87 ± .01	0.55	3
Benzo(a)pyrene	403.5	4080	1.15	1.69 ± .05	.36	3
1,2,5,6-Dibenzanthracene	348.5	16400	0.0792	1.65 ± .01	.31	1
Anthracene	370	3890	3.23	1.35 ± .04	.48	3
Phenanthrene	346	219	72.2	1.09 ± .06	.58	2
Benz(a)anthracene	358.5	5260	3.31	1.33 ± .05	.58	1
2-Methylbenz(a)anthracene	359	5760	1.65	1.23 ± .03	.62	2
3-Methylbenz(a)anthracene	360.5	5170	2.04	1.34 ± .02	.55	2
5-Methylbenz(a)anthracene	357	5400	1.30	1.25 ± .02	.58	2
6-Methylbenz(a)anthracene	385.5	1354	2.78	1.35 ± .04	.38	2
7-Methylbenz(a)anthracene	370	6520	2.11	1.66 ± .05	.86	2
8-Methylbenz(a)anthracene	361	5970	1.96	1.41 ± .02	.47	2
9-Methylbenz(a)anthracene	360	4570	1.33	1.32 ± .05	.48	2
10-Methylbenz(a)anthracene	349	5170	5.99	1.25 ± .10	.67	2
11-Methylbenz(a)anthracene	365	3940	3.07	1.34 ± .08	.56	2
12-Methylbenz(a)anthracene	350	7290	1.20	1.64 ± .06	.57	2
Benzo(c)phenanthrene	371	164	28.0	1.30 ± .04	.44	2
1-Methylbenzo(c)phenanthrene	321	9390	3.34	1.34 ± .05	.55	2
2-Methylbenzo(c)phenanthrene	375	380	12.3	1.19 ± .07	.42	2
3-Methylbenzo(c)phenanthrene	355.5	313	16.4	1.37 ± .07	.34	2
4-Methylbenzo(c)phenanthrene	357	295	13.4	1.39 ± .13	.49	2
5-Methylbenzo(c)phenanthrene	356	364	10.6	1.30 ± .03	.46	2
6-Methylbenzo(c)phenanthrene	358.5	341	9.9	1.29 ± .11	.73	2

[a] Nomenclature of "Chemical Abstracts." [b] Data could not be obtained for 9,10-dihydroanthracene because of destruction of hydrocarbon by autoxidation reaction.

shown in Table IV is closely related to their electronic structure. It is felt that the approximate correlation of the experimental argentation constants with the *meso*-bond electronic indices as calculated by quantum mechanics (see Table V) makes it reasonable to assume that the first silver ion coordinates at the *meso*-bond. The actual position of the silver is probably above the plane of the mole-

TABLE V

COMPARISON OF ARGENTATION CONSTANT, K_1, WITH CHEMICAL, BIOLOGICAL AND THEORETICAL DATA

Compound	K_1	Rate[2c] OsO$_4$ × 10^8	TNF[18] dissocn. × 10^2	Carc. pot.[20] Skin	Carc. pot.[20] Subcutaneous	P.E.[5b] M.O.	Q[21] V.B.
3-Methylcholanthrene	3.31	1.1		++++	++++		1.330
7,12-Dimethylbenz(a)anthracene	1.87	2.7		+++	++++		1.319
Benzo(a)pyrene	1.69	0.94		++++	++++		
7-Methylbenz(a)anthracene	1.66	.91	2.28	+++	++++	3.3006	1.306
1,2,5,6-Dibenzanthracene	1.65	.64		++	++		
12-Methylbenz(a)anthracene	1.64		1.89	++	+++	3.3146	1.296
8-Methylbenz(a)anthracene	1.41		4.50	++	++	3.3213	1.296
6-Methylbenz(a)anthracene	1.35		1.23	+	++		1.298
11-Methylbenz(a)anthracene	1.35		2.31	+	0	3.3248	1.292
3-Methylbenz(a)anthracene	1.34		2.86	0		3.3265	
Benz(a)anthracene	1.33	.48	3.34	0	0	3.3282	1.283
9-Methylbenz(a)anthracene	1.32	.64	1.89	+		3.3248	1.294
5-Methylbenz(a)anthracene	1.27		2.60	+	++		1.298
10-Methylbenz(a)anthracene	1.25		1.92	+	+	3.3213	1.294
2-Methylbenz(a)anthracene	1.23		4.38	0	......	3.3146	
Anthracene	1.35			0	0		
Phenanthrene	1.09	(≪.48)		0	0		
4-Methylbenzo(c)phenanthrene	1.39		4.29	+	0		1.305
3-Methylbenzo(c)phenanthrene	1.37		8.63	+	0		1.304
1-Methylbenzo(c)phenanthrene	1.34		17.1				
5-Methylbenzo(c)phenanthrene	1.30		5.8	+++	+		1.312
Benzo(c)phenanthrene	1.30		9.83	+	0		1.293
6-Methylbenzo(c)phenanthrene	1.29		5.24	++	0		1.310
2-Methylbenzo(c)phenanthrene	**1.19**		**4.96**	+	+		**1.312**

cule approximately between the *meso*-carbon atoms where the π-electron density is greatest. On the basis of electronic symmetry properties Mulliken postulated a similar configuration for the benzene–silver complex.[16] Experimental evidence supporting this configuration has been provided by the X-ray crystal structure determination of the benzene complex[14] and the Raman spectrum of this complex has been interpreted as supporting an axial position for the silver ion.[15] There is no evidence concerning the positions of the second or higher coördinated silver ions.

Correlations with Carcinogenic Potency

In Table V are presented the experimental values of the argentation constants of a number of polycyclic hydrocarbons (K_1, column 2). Also tabulated are other experimental and theoretical data, namely, the rate of oxidation with osmium tetroxide[2c,17] (column 3), the dissociation constants of the 2,4,7-trinitrofluorenone complexes[18] (TNF, column 4), the carcinogenic potencies as determined in mice[19,20] (skin, column 5, subcutaneous, column 6), the polarization energy of the *meso*-bond carbon atoms resulting from hyperconjugation of methyl groups[5b] (P. E., M. O., column 7), and the total electronic charge at this bond as calculated by the valence bond method[4b,21] (Q, V. B., column 8). The relative carcinogenic potencies are those compiled by Badger,[20] who has critically examined the available biological data.

The correlation of argentation constants with potencies in the benz(a)anthracene series is quite gratifying, even though it is not without exceptions. Large entropy factors in the free energy of the argentation reaction may account for the fact that dibenzanthracene and 5-methylbenz(a)anthracene do not fit very well into the general correlation. The lack of correlation in the benzo(c)phenanthrene series should not at this stage be construed as definitely established because in a number of cases the reproducibility of results was poor, owing to oxidation of hydrocarbons during the extractive process. Moreover, there is a narrow spread in the argentation constants, and this tends to accentuate the effect of errors. Because of this narrow spread it is evident that some factor other than nucleophilic character is involved in carcinogenic potency of the methylbenzo(c)phenanthrenes.

Correlation of carcinogenic potency with other experimental data is reasonably good in the case of the osmium tetroxide reaction, but not so good in the case of the 2,4,7-trinitrofluorenone reaction. Correlation of carcinogenic potency with theoretical electron indices is roughly equal in the case of the valence bond and molecular orbital values. Correlation of argentation constants with theoretical calculations is fairly good for both the valence bond method and the molecular orbital method.

The argentation reaction is presumed to take place at the 5,6-bond of benzanthracene because the double bond at this position, like the 9,10-bond of phenanthrene, possesses more double bond character than do the other bonds of the molecule. Perhaps the reason for the poorer correlation of carcinogenic potency with the 2,4,7-trinitrofluorenone reaction is the likelihood that formation of the complexes of this type involves interaction between many points on the molecules, with their planes oriented parallel, and in close contact.[22]

Acknowledgments.—The authors acknowledge their indebtedness to the National Institutes of Health, Public Health Service, for a grant which supported this work, and to Professor Melvin Newman, for his loan of ten methylbenz(a)anthracenes and benzo(c)phenanthrene and its six methyl derivatives.

PASADENA 4, CALIFORNIA

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(16) R. S. Mulliken, THIS JOURNAL, **74**, 811 (1952).

(17) G. M. Badger, *J. Chem. Soc.*, 1809 (1950). In this reaction, carried out in chloroform solution, irreversible additon takes place at the 5,6-bond of benz(a)anthracene and its homologs to form a cyclic ester which can be hydrolyzed to the corresponding dihydrodiol.

(18) K. H. Takemura, M. D. Cameron and M. S. Newman, THIS JOURNAL, **75**, 3280 (1953). These workers have measured the dissociation constants in chloroform of the 2,4,7-trinitrofluorenone complexes of all the methylbenz(a)anthracenes and the methylbenzo(c)phenanthrenes. The lower the constant, the higher would be carcinogenic potency, if there were correlation.

(19) J. L. Hartwell, "Survey of Compounds which Have Been Tested for Carcinogenic Activity," 2nd Ed., Federal Security Agency, Public Health Service Publication No. 149, U. S. Government Printing Office, Washington, D. C., 1951; J. P. Greenstein, "Biochemistry of Cancer," Academic Press, Inc., New York, N. Y., 1947, chap. 3; 1. Berenblum, *Cancer Res.*, **5**, 561 (1945); J. Iball, *Am. J. Cancer*, **35**, 188 (1939).

(20) G. M. Badger, *Brit. J. Cancer*, **2**, 309 (1948).

(21) A. Pullman, *Ann. chim.*, **2**, 5 (1947). Of particular interest are the π-electron charge density and availability at the 5,6-bond of the benz(a)anthracene structure. Coulson[4b] points out that there is some degree of correlation between results obtained by different methods of calculation and between different theoretical indices.

(22) M. Orchin, *J. Org. Chem.*, **16**, 1165 (1951).