

The thermograms exhibit three exothermic peaks. The nature of the changes was determined by taking X-ray diffraction patterns at temperatures just below and above the peaks on the thermograms. The pattern for ZrS_2 persists up to the temperature of the first exothermic peak ($300-330^\circ$) whereupon it is converted to cubic ZrO_2 . Analysis of the samples at this point showed that they still contained 2-5% sulfur. The sulfur could not be washed out with CS_2 , water or dilute acid. This sulfur stabilizes the zirconia in the cubic form. The broad exothermic region above 360° in the thermograms results from the burning of this sulfur. As soon as enough sulfur is burned out, the cubic zirconia reverts to the monoclinic form, producing the final sharp peaks.

An equimolar mixture of ZrO_2 and ZrS_2 heated in a sealed evacuated Vycor tube yielded $ZrOS$. Complete reaction was achieved in about 30 hours at 1000° .

Powdered zirconium metal was found to reduce the disulfide to lower sulfides. Heating an equimolar ratio of reactants at $900-1000^\circ$ for 4 hours

yielded a mixture of Zr_3S_4 (90%) and Zr_3S_2 (10%).¹³ With increased proportions of zirconium metal the proportion of Zr_3S_2 in the product increased.

Reduction of zirconium disulfide also was accomplished at $900-1000^\circ$ with magnesium metal. In this case, too, a mixture of Zr_3S_4 and Zr_3S_2 was obtained together with MgS as a by-product.

Zirconium carbonitride was treated with hydrogen sulfide at 1100° , and zirconium metal with carbon disulfide at $800-1000^\circ$ in the hope of obtaining reduced zirconium sulfides. In both cases zirconium disulfide resulted.

Acknowledgment.—The author wishes to express his sincere thanks to Mr. M. J. Franey for valuable technical assistance, to Mr. C. W. F. Jacobs for assistance with the differential thermograms and to Mr. W. B. Blumenthal for many helpful suggestions throughout the course of this work.

(13) For a more complete description of these sulfide phases and their X-ray diffraction patterns see H. Hahn, B. Harder, U. Mutschke and P. Ness, *Z. anorg. allgem. Chem.*, **292**, 82 (1957).

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Studies on the Chemistry of Halogens and of Polyhalides. XVII. Halogen Complexes of Pentamethylenetetrazole¹

BY ALEXANDER I. POPOV, CARLA CASTELLANI BISI² AND MARILYN CRAFT

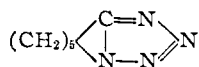
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Electron donor properties of a convulsant agent, pentamethylenetetrazole (PMT), were investigated by studying its complexes with iodine and iodine halides. A stable solid complex $PMT \cdot ICl$ was prepared. The stability of these complexes was investigated spectrophotometrically in carbon tetrachloride solution and the formation constant values were, respectively, 2.0×10^3 for $PMT \cdot ICl$, 1.5×10^2 for $PMT \cdot IBr$ and 7.5 for $PMT \cdot I_2$. The infrared absorption spectra of PMT and of $PMT \cdot ICl$ were determined in the sodium chloride region.

Introduction

Study of the synthesis and pharmacological properties of neurological drugs has been a very active field of research for a number of years. Yet, it is surprising how little information is usually available on the chemical and physico-chemical properties of physiologically active substances, some with a long and a successful clinical history behind them. It seems quite natural to expect, however, that certain of these chemical properties must be in some way related with their action in living organisms. It is with this thought in mind that a detailed physico-chemical study of convulsant and anticonvulsant drugs has been undertaken in this Laboratory.

This study was begun with pentamethylenetetrazole (hereafter abbreviated as PMT). This compound is a well-known convulsant agent which has been quite widely used in shock therapy and as a stimulant in general. Numerous derivatives of



(1) Presented before the Medicinal Chemistry Division at the 133rd Meeting of the American Chemical Society, San Francisco, California, April 16, 1958.

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PMT and of similar tetrazoles have been prepared and were shown to have a wide spectrum of convulsant and even of depressant activity.³ Literature search revealed, however, that while reports on PMT's pharmacological and clinical activity are extremely numerous, its chemical properties remain virtually unknown. Several solid metal complexes of PMT with cadmium, copper, mercury and silver have been prepared by pouring together concentrated solutions of PMT and the respective salt, but were not adequately identified or described.⁴

It was of particular interest in this investigation to study the basic or the electron donor properties of PMT. The donor strength of a molecule can be very conveniently determined from the study of its halogen complexes, and actually a basicity scale based on the strength of the iodine complex has been proposed.⁵ This is especially true for rather weak bases in which case the determination of their basicity constants K_b with respect to the hydrogen ion may be rather difficult. Also, since complexation with halogens can be carried out in non-aqueous

(3) (a) E. G. Gross and R. M. Featherstone, *J. Pharmac., Exper. Therap.*, **87**, 291 (1946). (b) F. W. Schueler, S. C. Wang, R. M. Featherstone and E. G. Gross, *ibid.*, **97**, 266 (1949).

(4) (a) J. L. Zwicker, *Pharm. Weekblad.*, **71**, 1170 (1934); (b) A. Dister, *J. Pharm. Belg.*, **3**, 193 (1946).

(5) G. Kortum, *J. chim. phys.*, **49**, C127 (1952).

solvents, this method permits one to evaluate donor strength of substances insoluble in water.

Experimental Part

Reagents.—Pentamethylenetetrazole was obtained from Knoll Pharmaceutical Company (under the registered name Metrazol) and was purified by several recrystallizations from ether. The m.p. of the purified product was 61°, lit. val. 58°. Iodine, iodine monochloride, iodine bromide, chloroform and carbon tetrachloride were obtained and purified as described in earlier publications.⁵

PMT-ICl Complex.—This complex, in the form of yellow powder, was prepared by mixing equimolar amounts of PMT and of iodine monochloride in carbon tetrachloride solutions. The precipitate obtained was filtered, washed with carbon tetrachloride and dried. It could be recrystallized easily from chloroform and the product appeared in the form of large, yellow, transparent, rhombohedral crystals. The m.p. was 116–118°. The crystals are easily soluble in chloroform, alcohol, acetonitrile, acetone and other polar or semi-polar solvents. In water, as is often the case with halogen complexes, it dissolved with decomposition. The complex was analyzed by dissolving it in hot glacial acetic acid and titrating the resulting solution iodometrically.

Anal. Calcd. for PMT·ICl: C, 23.96; H, 3.33; equiv. wt., 150.25. Found: C, 23.98; H, 2.11; equiv. wt., 153.

An attempt was made to recrystallize the complex from chloroform to which a small amount of HCl was added. This was done in order to obtain PMT·HCl₂ complex by analogy with the 2,2'-bipyridine HCl₂ complex obtainable in this manner.⁷ However, the attempt was unsuccessful since the same iodine monochloride complex was obtained each time. These results indicate that PMT has a very weak affinity for the hydrogen ion as compared with 2,2'-bipyridine.

Attempts to prepare corresponding PMT-iodine and PMT-iodine bromide complexes by the same technique were unsuccessful.

Absorption Measurements.—Absorption measurements in the visible and ultraviolet regions were made on a Cary Recording Spectrophotometer Model 11, in silica cells of 1.00 ± 0.01 cm. path lengths. Measurements were done at room temperature of approximately 25°. Infrared spectra were obtained with Perkin-Elmer Model 21 Spectrometer, in KBr pellets containing 2 mg. of investigated substance per 400 mg. of potassium bromide.

Results and Discussion

The PMT·ICl complex, when dissolved in carbon tetrachloride, gave an absorption maximum at 327 mμ. In order to see if the structure of the complex in solution was the same as in the crystalline state, a method of continuous variation⁸ was run on the PMT-ICl system in carbon tetrachloride solution. The results shown in Fig. 1 confirm the 1:1 complex.

The stability constant of this complex was obtained by a previously outlined method⁹; the results are shown in Table I.

TABLE I
FORMATION CONSTANTS FOR THE REACTION PMT + ICl →
PMT·ICl IN CARBON TETRACHLORIDE AT 25°

Solution 9.59 × 10 ⁻³ M in PMT and in ICl					
λ (mμ)	A _{1:1} ^{compl.}	a _m ^{ICl}	a _m ^{compl.}	α	K × 10 ³
480	0.175	79.8	3.1	0.197	2.16
450	.279	123.0	6.2	.197	2.16
430	.337	134.5	11.5	.192	2.28
400	.450	113.6	30.0	.202	2.04
350	1.095	19.8	135.5	.184	2.51

$$K_{av} = (2.23 \pm 0.16) \times 10^3$$

(6) A. I. Popov, D. H. Geske and N. E. Baenziger, *THIS JOURNAL*, **78**, 1793 (1956); A. I. Popov and W. A. Deskin, *ibid.*, **80**, 2976 (1958).

(7) A. I. Popov and R. T. Pflaum, *ibid.*, **79**, 570 (1957).

(8) P. Job, *Ann. Chim.*, [10] **9**, 113 (1928).

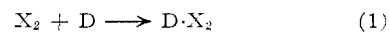
(9) A. I. Popov and R. H. Rygg, *THIS JOURNAL*, **79**, 4622 (1957).

While it seems to be impossible to prepare the corresponding iodine and iodine bromide complexes in the solid state, addition of PMT to carbon tetrachloride solutions of these halogens produced a marked hypsochromic shift.

With increasing amounts of PMT in iodine bromide solution in carbon tetrachloride, a gradual shift of the absorption maximum from 493 mμ (IBr peak) to 363 mμ was observed. This peak is, presumably, characteristic of the PMT·IBr complex. The curves passed through a well-defined isosbestic point at 432 mμ, which is a good indication that only one complex is formed. In the case of iodine, the halogen peak at 517 mμ was shifted to 422 mμ with an isosbestic point at 476 mμ.

Continuous variation method was applied to the study of iodine bromide-PMT solutions. Maxima and minima were obtained (depending on wave length) at 1:1 mole ratio of the two components. In the case of iodine, this method could not be applied since the resulting complex is too weak and is largely dissociated in equimolar solutions.

In both cases, because of the instability of the two complexes, it was quite difficult to obtain the value for the molar absorptivity index of the complex using the same method as in the iodine monochloride case. Even when large excess of PMT was used, the solutions contained some free halogen and the limiting value of absorbance would not be reached. Consequently the formation constants were calculated using Ketelaar's¹⁰ improvement of the Benesi-Hildebrand method, where, in the case of an addition reaction between a halogen X₂ and a donor D



the formation constant is given by

$$K_f = \frac{a_t - a_x}{a_c - a} \times \frac{1}{C_D} \quad (2)$$

where

a_t = apparent molar absorptivity index of X₂ (i.e., absorbance divided by the total concn. of X₂)

a_x = molar absorptivity index of X₂

a_c = molar absorptivity index of the complex

C_D = equilibrium concn. of the donor molecule. If

$$C_D^{\text{total}} \gg C_{X_2}^{\text{total}}, \text{ then } C_D \approx C_D^{\text{total}}$$

This equation can be rearranged to

$$\frac{1}{a_t - a_x} = \frac{1}{a_c - a_x} \times \frac{1}{K_f C_D} + \frac{1}{a_c - a_x} \quad (3)$$

The only unknown factors here are a_c and K_f. A plot of 1/(a_t - a_x) vs. 1/C_D gives a straight line. The intercept then yields the value of a_c and the slope, that of K_f.

This equation has the advantage over that of Benesi-Hildebrand since the latter is only valid when a_c >> a_x and a_t >> a_x, that is, when essentially all of the absorption is due to the complex. The Ketelaar modification becomes very useful for the study of weak halogen complexes and was used in this case for the determination of formation constants of PMT·IBr and PMT·I₂ complexes.

Figure 2 illustrates the application of this method to the PMT·IBr complex. Satisfactory straight lines were obtained and the molar absorptivity of

(10) J. A. A. Ketelaar, C. v. d. Stolpe, A. Goudsmit and W. Dzenbas, *Rec. trav. chim.*, **71**, 1104 (1952).

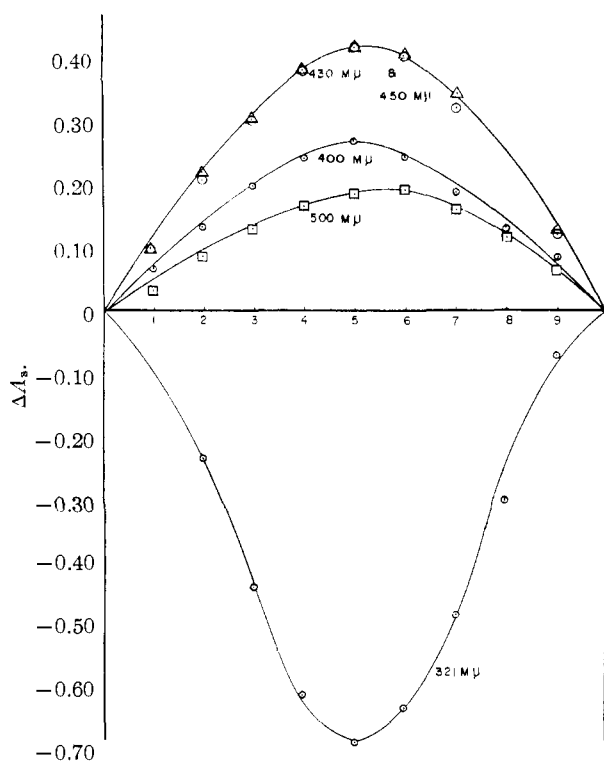


Fig. 1.—Method of continuous variation for the ICl-PMT system in CCl_4 ; total concn. $8.13 \times 10^{-3} M$; $A_s = A_s^{\text{obsd}} - A_s^{\text{calcd}}$ vs. mole fraction P.M.T.

the complex as well as the formation constants were calculated. The results, in the case of iodine bromide and of iodine, were less satisfying than those obtained for iodine monochloride complexes. There was a fairly large variation in the value of formation constant with the wave length at which the calculations were made. The range was 130 to 170 (340–390 $m\mu$ region) for PMT·IBr and 3.5–9.5 (390–430 $m\mu$ region) for PMT·I₂. These results were reproducible experimentally and were shown to be independent of halogen concentration or of the method of calculation. The most likely explanation seems to be that a second complex might be formed, which, although too weak to show up on the continuous variation plots, does affect absorbance values sufficiently to distort the value of the formation constant for the 1:1 complex. Another possibility is that the halogens themselves are associated. Keefer and Allen¹¹ have shown that while the visible spectrum of iodine in carbon tetrachloride solutions obeys Beer's law, there is a considerable deviation from it in the ultraviolet region. This deviation was attributed to I₄ species, which, although present in relatively small amounts, have a high absorbance with a maximum at 288 $m\mu$.

In any case it seems reasonable to assume that the formation constants for PMT·IBr and PMT·I₂ complexes are approximately 150 and 7.5, respectively.

Comparison of the infrared spectra of PMT and PMT·ICl complex revealed that the two compounds show considerable differences in the position and the intensity of the absorption bands. The re-

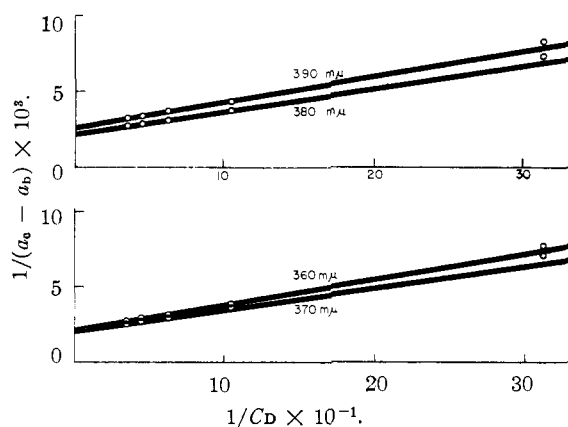


Fig. 2.—Ketelaar's plots for PMT-IBr system in CCl_4 at various wave lengths; see eq. 3.

sults are listed in Table II. While no definite band assignments can be made at the present time, this work is being continued. Previous work¹² done on the I-Cl stretching frequency in the presence of complexing agents showed that PMT shifted this band from 375 to 310 cm^{-1} and since the magnitude of the shift is proportional to the formation constant of the complex, this shift correlated rather well with the formation constant of 2×10^3 .

TABLE II
INFRARED SPECTRA OF PMT AND PMT·ICl IN SODIUM CHLORIDE REGION

2 mg./400 mg. KBr			
PMT (μ)	A_s	PMT·ICl	A_s
3.425	0.618	3.400	0.760
3.500	.458	3.490	.448
6.550	.840	6.475	.700
6.800	1.150	6.725	1.300
6.930	1.050	6.910	1.080
7.000	1.240	6.975	1.310
7.300	0.440	7.350	0.660
7.375	.280
7.440	.240
7.500	.420	7.450	0.415
...	...	7.650	.505
7.875	0.665	7.750	.535
8.025	2.040	7.950	.540
...	...	8.050	.122
8.425	0.238	8.350	.440
8.550	0.235	8.500	.208
8.975	1.050	8.975	.970
9.125	0.470	9.075	.412
9.200	.400	9.175	.675
9.300	.392	9.250	.900
9.750	.102	9.725	.293
10.075	.485	9.825	.645
10.340	.470	10.295	.560
11.200	.670	11.200	.600
11.575	.350	11.575	.690
12.025	.070	12.000	.145
12.550	.365	12.480	.540
13.450	.240	13.600	.365
14.050	.045	14.075	.065
14.800	.640	14.825	1.030

(12) W. B. Person, R. H. Humphrey, W. A. Deskin and A. I. Popov, THIS JOURNAL, **80**, 2049 (1958).

(11) R. M. Keefer and T. L. Allen, *J. Chem. Phys.*, **25**, 1059 (1956).

On the other hand, the iodine chloride fundamental vibration is also shifted to 310 cm.^{-1} by 2,2'-bipyridine in solution.¹³ This shows that the donor strengths of PMT and of 2,2'-bipyridine *vis-a-vis* ICl are approximately the same. Yet PMT does not show any appreciable coordinating tendency toward hydrogen ion,⁴ while 2,2'-bipyridine is a moderately strong base with a pK_b of 9.56.¹⁴ One, therefore, should not necessarily relate the donor strength of a compound with its proton affinity, especially if the latter were determined in aqueous solutions.

Conclusions

In general, it is seen that PMT is a moderately strong donor molecule. Its basic strength *vis-a-vis* iodine halides places it in an intermediate position between weak donors such as aromatic substances and acetonitrile on one hand and the strong donors such as pyridine and trialkylamines on the other. It is interesting to note that most of the convulsant agents, such as strychnine, metathamide, hydra-

(13) Ray E. Humphrey, Ph.D. Thesis, State University of Iowa, June 1958.

(14) P. Krumholz, *THIS JOURNAL*, **73**, 3487 (1951).

zides, etc., likewise have donor properties which seem to be of approximately the same magnitude. In a recent publication Jenney and Pfeiffer report a study on convulsant activity of hydrazides¹⁵ and conclude that there is only a very gross correlation between the pK_a values of compounds and the convulsant activity. It is possible that electron donor properties and complexing ability of these compounds may show a better correlation with their physiological properties.

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(15) E. H. Jenney and C. C. Pfeiffer, *J. Pharmac. Exper. Therap.*, **122**, 110 (1958).

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Some Octet and Bond Refractivities Involving Boron

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The Lorentz-Lorenz molar refractivity R has been calculated from literature data for n and d for a fairly large number of organoboron compounds. A preliminary attempt has been made to evaluate some octet and bond refractivities involving boron. The resulting values show deviations up to 1 cc./mole, and merely approximate average refractivities can be given (in cc./mole for the D-line and 20°) for the octets $B:\ddot{O}:C$ (3.1) and $B:\ddot{Cl}:$ (6.8) as well as for the bond $B:C_{aliph}$ (1.75). If one assumes in aromatic compounds the Kekulé structure for the C_6 ring, an average apparent value of 3.0 cc./mole results for the bond $B:C_{arom}$. A satisfactory additivity of molar refractivity obtains for homologous series of organoboron compounds. For six such series, equations of the type $R_{obs} = an + b$ have been derived, in which n is the number of carbon atoms in an alkyl chain.

A search of the literature has disclosed no information regarding the refractivity of any bonds or octet groups in which both elements boron and carbon are involved. An early investigation based on only a few compounds was made¹ in order to evaluate an atomic refraction for boron. However, according to certain investigators,² the ordinary atomic refractivities³ have no simple physical significance, and account must be taken of the electronic structure of the molecules, since optical properties depend on the state of the valence electrons. Values for bond and octet refractivities have been tabulated^{4,5} for the generally known Lorentz-Lorenz molar refraction. This molar refraction R is a measure of the looseness or tightness with which the valence electrons are held by the atomic cores, and is expressed in cc./mole.

(1) A. Ghira, *Atti R. Accad. Lincei*, **2**, i, 312 (1893); *Z. physik. Chem.*, **12**, 764, 768 (1893).

(2) K. Fajans and C. A. Knorr, *Ber.*, **59**, 249 (1926).

(3) F. Eisenlohr, *Z. physik. Chem.*, **75**, 585 (1910); **79**, 129 (1912).

(4) J. R. Partington, "An Advanced Treatise on Physical Chemistry," Vol. 4, Longmans, Green and Co., 1953, pp. 69-71.

(5) K. Fajans in A. Weissberger, "Physical Methods of Organic Chemistry," 2nd ed., Vol. I, Interscience Publishers, Inc., New York, N. Y., 1949, p. 1164.

The present investigation is concerned with the evaluation of some octet and bond refractivities involving boron. Values for the refractive index n (for the D-line) and the density d for a large number of organoboron compounds were selected from a recent comprehensive report on the organic compounds of boron.⁶ This information was used to calculate the observed molar refraction, R_{obs} . Assuming, as a first approximation, exact additivity, the sum of the shares of known⁵ bond and octet refractions, R_{kn} , was subtracted from R_{obs} , in order to calculate the unknown value, R_x , involving boron. The difference between R_{obs} and R_{kn} has been divided by the number of such bonds or octets present in the compound. For the compounds selected, these octet and bond refractivities were evaluated: $B:\ddot{O}:C$, $B:\ddot{Cl}:$, $B:C_{aliph}$ and $B:C_{arom}$.

The resulting values for the $B:\ddot{O}:C$ octet range in Table I from 2.92 (compound 17)⁷ to 3.51 (compound 9). This variation is hardly due to experi-

(6) M. F. Lappert, *Chem. Revs.*, **56**, [5] 959 (1956).

(7) A still lower value, 2.74, is obtained from compound 19, which contains a phenyl group. See the discussion of Table IV.