the acidic form BH^+ and ϵ the extinction coefficient of the mixture of the two forms.

Procedure.—The first step was to obtain the absorption spectra curves of the compound in a series of buffers in order to ascertain regions in which the acidic and basic forms of the compound differ significantly. The second step was to select suitable wave lengths for a more careful study using a much wider series of buffer solutions. A plot of the extinction coefficients against *p*H served to locate the *p*H regions at which the absorption of the pure acidic and basic forms may be obtained. Such plots also showed that multiple ionization was absent in the *p*H range covered.

Typical spectrophotometric data are given for 2-aminopteridine in Table I in order to illustrate the type of precision attainable. The calculation of pK^* is illustrated in Table II. The variance (s^2) of a single value of pK^* is 0.00114 as estimated from the deviation of the individual values from the average. The expected variance can also be estimated from the data in Table I using the principle of propagation of error. The contribution to the variance of pK^* due to spectrophotometric errors is about 0.0005, and that due to variance of *p*H determinations is about 0.0009, giving a total variance of 0.0014. The two variance estimates are in excellent agreement. Simple averaging of the pK^* values is permissible since it can be shown that all the values have nearly the same weight. The actual number of independent determinations of pK^* is three, since three samples of 2-aminopteridine were used for each *p*H range (a separate sample at each *p*H value of Table I). Thus the variance of the average is 0.00038, corresponding to a standard deviation of the average of 0.020 pK unit.

Pteridine itself offered considerable difficulties. It was found that spectrophotometer readings drifted and it was necessary to obtain a series of readings over a period of about an hour. The zero time reading was obtained by extrapolating a plot of log ϵ against time back to zero time. The instability of the spectral data resulted in rather larger uncertainty in pK^* for this compound. A "weighted" average of 4.17 was calculated, based on variance estimates of individual pK^* values due to spectrophotometric errors. This differs very little from the straight average, and there are an insufficient number of measurements to justify the use of weighting.

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The Selective Demethylation of Homoveratrylamine[1]

BY K. E. HAMLIN AND F. E. FISCHER

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During the course of another investigation,[2] substantial quantities of isovanillin or a compound leading to 3-hydroxy-4-methoxyphenethylamine were required. Synthesis of isovanillin by various literature methods including the application of a variety of demethylating agents to veratraldehyde[3] has not been satisfactory. The experiments of Birch[4a,b] involving the demethylating action of sodium and liquid ammonia on various phenol ethers suggested a possible solution to the problem. Significantly, by this reaction, Birch was able to convert 3,4-dimethoxytoluene to 4-methoxy-*m*-cresol in 70% yield.

Accordingly, the action of sodium and liquid ammonia on a group of veratryl compounds was studied. The application of this method to veratraldehyde, veratric acid and homoveratronitrile was singularly unfruitful. In these cases, guaiacol was the only identifiable product and was found only in trace amounts. However, when homoveratrylamine was treated with sodium and liquid ammonia, a selective demethylation occurred, and 3-hydroxy-4-methoxyphenethylamine was obtained in excellent yields. Inasmuch as homoveratrylamine is readily available, it may now serve as a convenient source of isovanillyl derivatives.

Experimental

3-Hydroxy-4-methoxyphenethylamine.—With stirring, 63.4 g. (0.35 mole) of 3,4-dimethoxyphenethylamine was added in a slow stream to a solution of 26.2 g. (1.14 atoms) of sodium in 700 cc. of liquid ammonia. The resulting mixture was allowed to stand for six hours until it reached room temperature and was then decomposed by cautious addition of ice. This material was extracted with ether to remove unreacted amine, and the aqueous phase was aerated to remove excess ammonia and was finally made acidic while cooling. Following ether extraction, the acid layer was treated with excess sodium bicarbonate solution and the amine thus released was extracted by means of butanol. The butanol extract was dried over anhydrous magnesium sulfate and was then treated with ethereal hydrogen chloride. The crystalline material thus formed was recrystallized from methanol–ether. In this manner, 61 g. (85% yield) of 3-hydroxy-4-methoxyphenethylamine hydrochloride was obtained melting at 204–205.5°; reported[5] m.p. 201–203°.

Anal. Calcd. for $C_9H_{13}NO_2{\cdot}HCl$: N, 6.88. Found: N, 6.85.

N-Acetyl-3-hydroxy-4-methoxyphenethylamine.—A solution of 20.4 g. (0.1 mole) of 3-hydroxy-4-methoxyphenethylamine hydrochloride in 15.3 g. (0.15 mole) of acetic anhydride was stirred while adding portionwise 27 g. (0.32 mole) of sodium bicarbonate. The mixture was then heated on a steam-bath for one hour. After cooling, the resulting crystalline material was filtered, washed with water and dried. After recrystallization from a mixture of absolute ethanol and heptane, the N-acetyl-3-hydroxy-4-methoxyphenethylamine melted at 124–125°; yield 12.9 g., 53%.

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N 6.70. Found: C, 63.30; H, 7.04; N, 6.74.

Acknowledgment.—We are indebted to E. F. Shelberg, Chief Microanalyst, and his staff for the analytical data.

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[1] Presented before the Medicinal Chemistry Division at the 124th Meeting of The American Chemical Society, Chicago, Illinois, 1953.

[2] M. B. Moore, H. B. Wright, M. Freifelder and R. K. Richards, *J. Am. Pharm. Assoc.*, in press.

[3] M. B. Moore, personal communication.

[4] (a) A. J. Birch, *J. Chem. Soc.*, 102 (1947); (b) George W. Watt, *Chem. Revs.*, **46**, 339 (1950).

[5] F. A. Ramirez and A. Burger, THIS JOURNAL, **72**, 2781 (1950).

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The Reaction of Cyclohexene with Bromine, Iodine Monobromide and Iodine Monochloride

BY ALEXANDER GERO, JOSEPH J. KERSHNER AND RICHARD E. PERRY

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As a preliminary to studies on enol titration, we have investigated the relative rates of addition of various halogens to an olefin. Rate studies on such additions have been performed[1] but we know of no comparative studies on the rates of addition of various halogens to the same olefin, under the same conditions.

Cyclohexene was chosen as the standard olefin because it is easily available in good purity, sufficiently high-boiling for easy handling and non-

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[1] For literature, see A. E. Remick, "Electronic Interpretations of Organic Chemistry," 2d ed., John Wiley and Sons, Inc., New York, N. Y., p. 432 ff.

polar. Its reactions with bromine, iodine bromide and iodine chloride were studied, using carbon tetrachloride and acetic acid as solvents. In this way, polarity effects were brought out clearly.

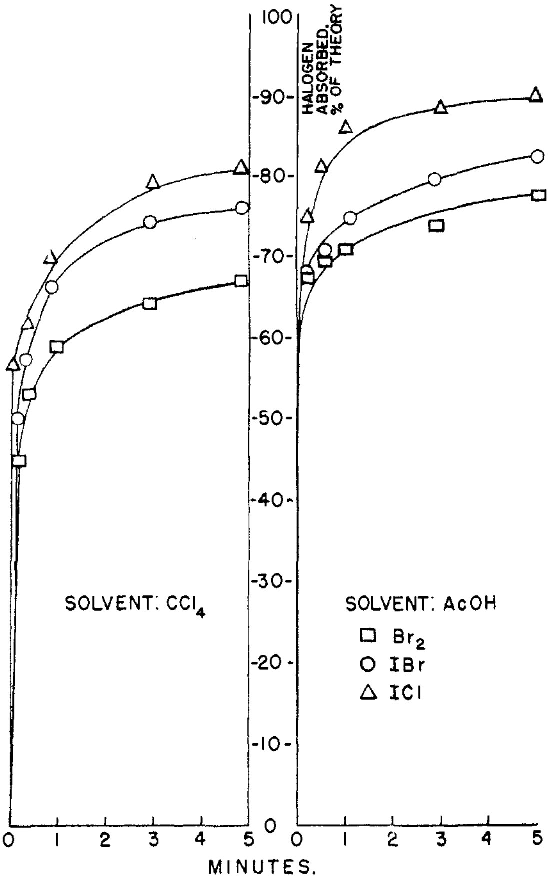

Fig. 1.

Representative results are shown in Figs. 1 and 2. They are in agreement with the accepted polar mechanism of olefin addition reactions,[1] since the most polar halogen (iodine monochloride) adds fastest, the least polar (bromine) slowest, and the more polar solvent (acetic acid) accelerates the addition. It is remarkable that bromine is consumed far beyond the theoretical limit of addition; in carbon tetrachloride in two days 137%, and in three days 152% of the theoretical amount of bromine had disappeared. In acetic acid the bromine absorption was 106% after three days and 118% after five days. No evidence of substitution was found with either of the mixed halogens in any solvent. This seems to indicate that the polarity of an inter-halogen molecule inhibits its break-up into atoms as required for substitution.[2] The inference is that bromine is also somewhat polarized in acetic acid solution.

Solutions of iodine monobromide, which are no more difficult to prepare than those of bromine, might well replace the latter, now generally used, for quantitative unsaturation tests. With iodine monobromide decoloration occurs much more rapidly and substitution is absent.

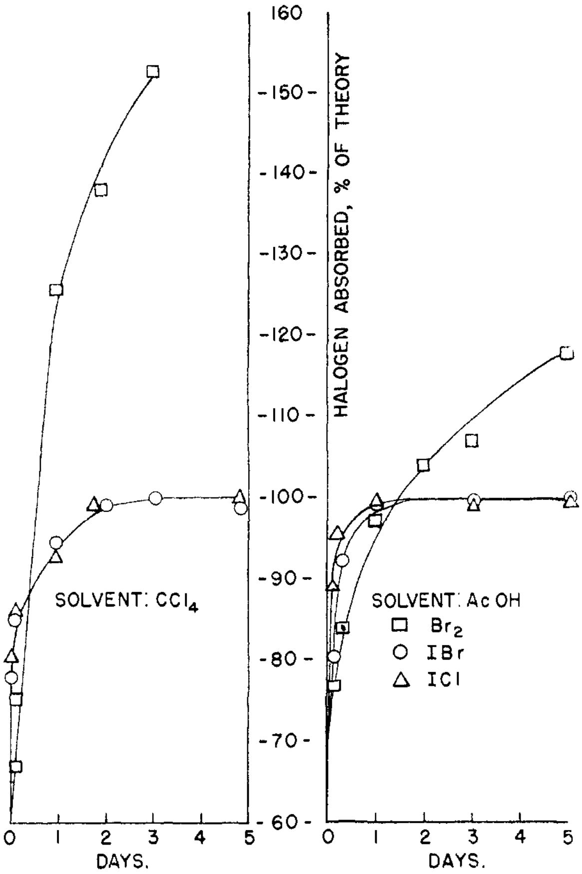

Fig. 2.

Experimental

Ten mg. of cyclohexene was mixed with 5 ml. of $0.05N$ halogen solution and kept in the dark at 25° for periods ranging from 15 seconds to five days. Then the mixture was stirred mechanically into excess aqueous iodide solution and the liberated iodine titrated. With acetic acid as the solvent, the iodide solution was also buffered with disodium phosphate, for the dihalocyclohexanes are easily dehalogenated by iodide ion at low *p*H. From the results of the titration the halogen absorbed by the cyclohexene was calculated.

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[2] H. C. Brown, M. S. Kharasch and T. H. Chao, THIS JOURNAL, **62**, 3435 (1940).

The Application of the Glass Electrode in Liquid Ammonia Systems[1,2]

BY ARNO H. A. HEYN AND MARTHA J. BERGIN

RECEIVED MARCH 24, 1953

Glass electrodes have been used for measurement of the hydrogen ion activity in some cases in nonaqueous solutions.[3,4] However, a glass electrode which had been thoroughly hydrated by immersion in water was used. It is likely, therefore, that the system measured was "non-aqueous" only with respect to the solution before the electrode had been immersed and that equilibria with the hydrated glass surface established the potentials. Work by

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[1] From a Ph.D. Thesis of Martha J. Bergin, May, 1952.

[2] Supported in part by a Grant-in-aid of the Research Corporation, New York, N. Y.

[3] L. Lykken, *et al.*, *Ind. Eng. Chem.*, *Anal. Ed.*, **16**, 219 (1944).

[4] L. Lykken, ASTM Symposium on *p*H Measurement, Technical Publication No. 73, p. 71 (1946).