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Synthesis and Proton Dissociation Constants of 2,2′-Iminodimethylene Dipyridine (2,2′-Dipicolylamine)

J. KIRK ROMARY, JIM E. BUNDS, and J. D. BARGER
Department of Chemistry, Washburn University, Topeka, Kan.

Synthesis of 2,2′-iminodimethylene dipyridine has been accomplished in good yield by reaction of 2-chloromethyl pyridine with excess 2-aminomethyl pyridine. Stepwise proton dissociation constants have been determined. At 25° C. and at an ionic strength of 0.10 in KNO_3, $pK_1 = 7.30 \pm 0.02$, $pK_2 = 2.60 \pm 0.02$, and $pK_3 = 1.12 \pm 0.04$.

WHILE the literature describes the synthesis of such substituted pyridines as *N*-picolyl-1,2-diaminoethanes (*2*), 2,2′-dipyridylmethane (*6*), di-(3-pyridylmethyl) amine (*3*), and others (*4*), the synthesis of 2,2′-iminodimethylene dipyridine (2,2′-dipicolylamine) has not been previously reported. This work describes the synthesis of the latter by reaction of 2-chloromethyl pyridine with a fivefold excess of 2-aminomethyl pyridine.

EXPERIMENTAL

The NMR spectra were obtained on the Varian A-60 spectrometer. The samples were run in carbon tetrachloride solution using tetramethylsilane as an internal reference standard. Infrared spectra were obtained with a Perkin-Elmer Model 521 Spectrophotometer using KBr plates. Potentiometric titrations were made with a Metrohm Hereassau 388 research pH meter with a Beckman E-2 glass electrode. Melting points were taken with a Thomas-Hoover melting point apparatus. Elemental analyses and molecular weight determinations were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. The aminomethyl pyridine and the 2-chloromethyl pyridine monohydrochloride were obtained from Aldrich Chemical Co.

Chloromethyl pyridine hydrochloride (25 grams; 0.15 mole) was dissolved in 50 ml. of water and neutralized slowly (with cooling in an ice bath) with 15 ml. of saturated aqueous K_2CO_3. The chloromethyl pyridine free base, which separates as a straw yellow oil, was removed from the aqueous layer and used immediately without further purification in order to minimize decomposition. The free base was added directly to 82.5 grams (0.75 mole) of 2-aminomethyl pyridine, which had been previously cooled to 5° C. by immersion in an ice bath. During the addition, the reactants were vigorously stirred and kept at 5° C. The reaction mixture was then removed from the ice bath and allowed to warm up to room temperature while vigorous stirring was continued. Chemical reaction began at about 15° C. as evidenced by a gradual color change from light yellow to reddish brown. If no additional cooling was employed, the temperature gradually rose to a maximum of 35° C.

When the reaction was complete, the product mixture was acidified with aqueous tartaric acid, extracted several times with ether, and neutralized with 30% aqueous KOH. To separate the aqueous and organic layers, KOH pellets were added with stirring and cooling. The pH of the mixture reached 9-10. The separated organic layer was removed and further dried with anhydrous $MgSO_4$. The liquid at this point was wine-red and clear. The secondary amine product and the unreacted primary amine were then separated by distillation at reduced pressure. This separation was easily accomplished owing to the 80° boiling point difference.

The product, redistilled at 1.05 mm., had a boiling point of 148–149° C. The yield was 73%. The very light yellow liquid product was somewhat viscous, had a slight pyridine-type odor, and was highly soluble in water, alcohol, chloroform, and carbon tetrachloride, but only slightly soluble in ether. Under the reaction conditions used, formation of the corresponding trisubstituted amine was not observed.

Although there was a tendency for the chloromethyl pyridine to remain in the aqueous K_2CO_3 phase after neutralization, this could be largely overcome by using a 10% excess of K_2CO_3, keeping the temperature as low as possible, and by repeated vigorous agitation. Also, the use of alcoholic KOH for the neutralization of the acidified amine mixture led to undesirable side reactions which drastically cut the

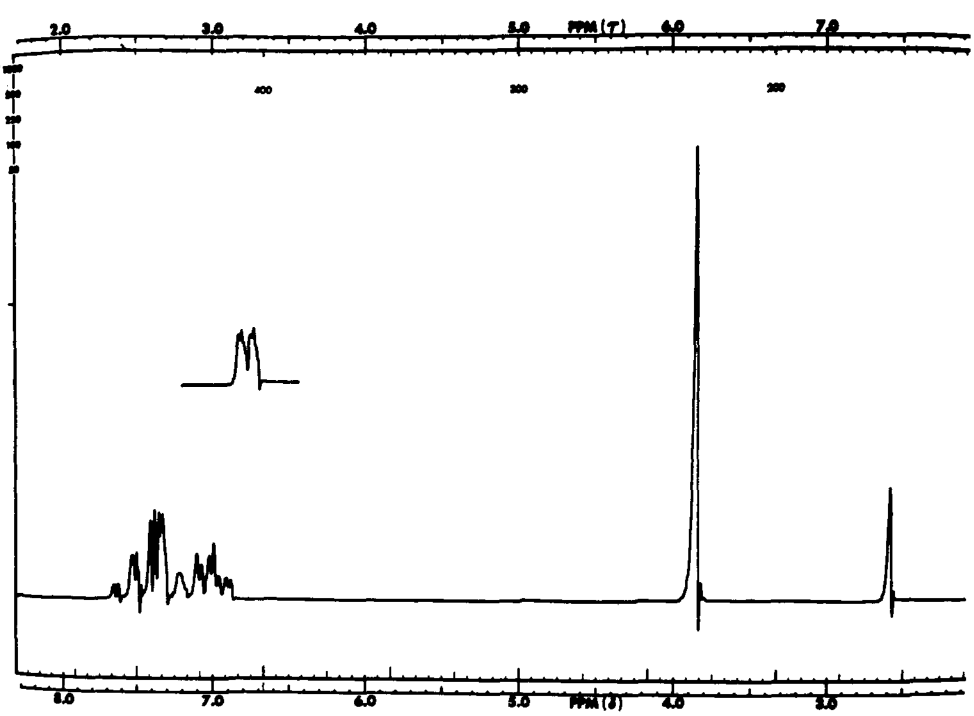

Figure 1. NMR spectrum of 2,2′-iminodimethylene dipyridine in carbon tetrachloride with tetramethysilane as an internal reference standard

Inset corresponds to 100 c.p.s. offset

yield of product and produced a large amount of tarry residue after distillation. In the interest of safety, the use of chloromethyl pyridine free base should be done with gloves and in a hood since it is both a vesicant and lachrymator.

The infrared spectrum shows sharp absorption at 3300, 3050, 2850, 1575, 1450, and 800 cm^{-1}. The NMR spectrum, shown in Figure 1, consists of a band from 1.6 to 3.2 due to aromatic hydrogen, a peak at 6.15 due to methylene hydrogen, and a peak at 7.42 due to amine hydrogen. The area ratios for the three resonance regions are 8:4:1, respectively, in agreement with theory. Also n_D^{25} = 1.5750. Anal. Calcd. for $C_{12}H_{13}N_3$: C, 72.33; H, 6.57; N, 21.10; M.W., 199.2. Found: C, 72.35; H, 6.67; N, 21.24; M.W., 202.

The trihydrochloride was prepared by dissolving the amine free base in absolute ethanol followed by saturation with dry HCl gas. The crystals were twice recrystallized from absolute ethanol, which was saturated with HCl gas. The purified product was white, very light, and had a melting point of 199–200° C. Anal. Calcd. for $C_{12}H_{13}N_3 \cdot 3HCl$: C, 46.70; H, 5.23; N, 13.61; Cl, 34.46. Found: C, 46.71; H, 5.26; N, 13.60; Cl, 34.46.

The proton dissociation constants of the tri-basic compound were determined by potentiometric titration of the protonated ligand with KOH at an ionic strength of 0.10 in KNO_3 and at 25° C. The potentiometric data were rigorously treated by the method of Bjerrum (*1*).

For the proton dissociation reaction of a ligand, Li

$$\mathrm{LiH}_n^{+(n)} \rightleftarrows \mathrm{LiH}_{n-1}^{+(n-1)} + \mathrm{H}^+$$

the dissociation constant is here defined as

$$\mathrm{K}_n = [\mathrm{LiH}_{n-1}^{+(n-1)}][\mathrm{H}^+]/[\mathrm{LiH}_n^{+(n)}]$$

Also

$$\mathrm{pK}_n = \mathrm{pH} - \log\{[\mathrm{LiH}_{n-1}^{+(n-1)}]/[\mathrm{LiH}_n^{+(n)}]\}$$

If the consecutive proton dissociation reactions are independent, it has been shown (*1*) that

$$[\mathrm{LiH}_{n-1}^{+(n-1)}]/[\mathrm{LiH}_n^{+(n)}] = (n - \bar{n})/(\bar{n} - n + 1)$$

where $\bar{n}$ is the average number of protons bound per ligand molecule. At values of $\bar{n} = n - \frac{1}{2}$ the corresponding values of pK$_n$ are equal to the pH. Thus, a graph of $\bar{n}$ *vs.* pH for the proton dissociation reaction, the so called "dissociation" curve, permits determination of the stepwise pK$_n$'s at half-integral values of $\bar{n}$. If, however, the assumption of independent, or stepwise, dissociation is not strictly valid then the "dissociation" curve is considered to yield only temporary pK$_n$ values.

In the latter case the temporary pK$_n$ values must be refined in order to obtain the final stepwise values. This may be accomplished by use of Bjerrum's successive approximations procedure (*1*, *5*). This method is based upon the equation

$$\bar{n}\prod_{n=1}^{N}\mathrm{K}_n + \sum_{n=1}^{N}\left[(\bar{n} - n)\,[\mathrm{H}^+]^n \prod_{n+1}^{N}\mathrm{K}_n\right] = 0$$

for the dissociation of multiprotonated ligands. Here N is the maximum value of n for a given ligand. As an alternate to the use of the approximations method the experimental values of $\bar{n}$ and $[\mathrm{H}^+]$ can be used with the above equation to set up a series of simultaneous equations which may then be solved for the constants.

In any event, the reliability of the final stepwise constants must be confirmed by generation of a theoretical proton "dissociation" curve. The theoretical curve is obtained by means of the above dissociation equation and the set of final stepwise dissociation constants. Theoretical values of $\bar{n}$ are calculated for several preselected pH values. All calculations leading to the results reported here have been performed by use of a set of previously described (*7*) digital computer programs. (Copies of these programs, including more detailed description of the calculations, are available for distribution.)

The experimental dissociation curve (Figure 2) for 2,2′-dipicolylamine provides for the direct determination of pK$_1$ at $\bar{n}$ = 0.5. However, since the pyridine nitrogen sites are so weakly basic and are nonstepwise in their dissociation reactions, it is possible to obtain only temporary values for pK$_2$ and pK$_3$ from the curve (at $\bar{n}$ of 1.5 and 2.5,

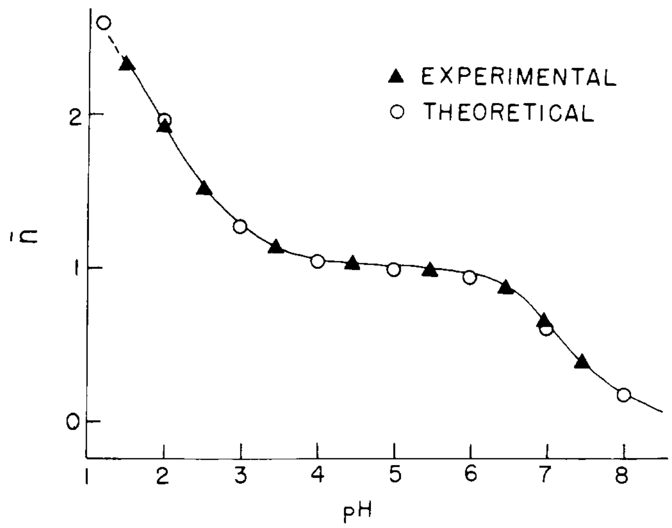

Figure 2. Experimental and theoretical proton dissociation curves for 2,2′-iminodimethylene dipyridine

respectively). The temporary values were then refined to obtain the stepwise constants with one part per thousand agreement. The reliability of the final stepwise pK_n's was confirmed by generation of a theoretical dissociation curve as shown in Figure 2. The final stepwise values were $pK_1 = 7.30 \pm 0.02$, $pK_2 = 2.60 \pm 0.02$, and $pK_3 = 1.12 \pm 0.04$.

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Graphical Determination of Virial Coefficients by the Burnett Method

Isopentane and Neopentane

I. H. SILBERBERG
Texas Petroleum Research Committee, Austin, Tex.
DAVID C.K. LIN and J. J. McKETTA
Department of Chemical Engineering, University of Texas, Austin, Tex.

A new graphical analysis has been developed for data obtained from the Burnett method of compressibility measurement. This method of analysis, based upon the Leiden virial equation of state, permits accurate determination of the second and third virial coefficients as well as the gas density at the initial pressure in the series of expansions. If the experimental data are sufficiently precise, fourth virial coefficients may also be obtained. In this paper, the method is applied to data on isopentane and neopentane from 30° to 200° C.

SINCE its introduction 30 years ago, the Burnett method (*2*) of gas compressibility measurement has slowly but steadily increased in importance as a rapid means of obtaining vapor phase *PVT* data with high precision. The method has been used from temperatures as low as −140° C. (*4, 5*) to as high as 1200° C. (*12*) and at pressures ranging from sub-atmospheric (*6*) to greater than 525 atm. (*4, 5*). The method has been employed with gases of extremely high purity, with binary gas mixtures, and with multicomponent (natural) gas mixtures. At the present time, a number of Burnett apparatus research projects are known to be active in the United States.

Investigators in the past have generally analyzed Burnett experimental data either graphically to give compressibility factors or analytically, assuming some form of an equation of state, to give virial or virial-type coefficients. Both graphical and analytical methods were discussed in detail in an earlier paper (*10*). The purpose of the present paper is to introduce a new method of graphical analysis capable of generating second, third, and (with sufficiently precise