

cedure described for 2,7-dimethoxy-1,8-naphthalic anhydride. No homogeneous product could be isolated from the base-insoluble fraction. After crystallization of the base-soluble material from methanol-water, there was obtained 17 mg (18%) of lactone 7, mp 112.5–114.5°. This material was combined with the products from two other similar runs, and, in solution in 10 ml of ether-hexane (2:3), was applied to a column of 10.6 g of Woelm alumina (activity III). Elution with ether-hexane, then with ether, while observing band movement in uv light, revealed only a single blue band, which was finally eluted with ether. Crystallization of the eluted product (49 mg) from hexane yielded 43 mg of white crystals, mp 115.0–116.5°; two additional crystallizations gave the analytical sample of 7, mp 115.5–116.5°, ν 5.87 μ (carbonyl), uv (Table II), nmr (Table I).

Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.1; H, 5.7. Found: C, 64.0; H, 5.9.

Registry No.—1, 6398-92-1; 2, 518-86-5; 3, 39050-28-7; 4, 26495-88-5; 5, 5657-01-2; 6, 39050-31-2; 7, 39050-32-3; $NaBH_4$, 16940-66-2; $LiAlH_4$, 16853-85-3; 1,8-naphthalic anhydride, 81-84-5; diborane, 19287-45-7; 3-methoxy-1,8-naphthalic anhydride, 5289-78-1; 5-methoxy-2,1,3-*peri*-naphthopyran, 39050-34-5; 1,2-naphthalic anhydride, 5343-99-7; 2,7-dimethoxy-1,8-naphthalic anhydride, 32432-09-0; 2,7-dimethoxy-1,8-naphthalide, 39050-37-8.

Notes

Addition of Amide Ion to Isoquinoline and Quinoline in Liquid Ammonia. Nuclear Magnetic Resonance Spectra of Anionic σ Complexes¹

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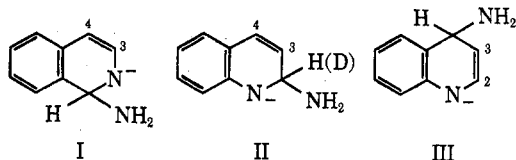
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Anionic σ complexes are formed by the addition of nucleophiles to aromatic and heteroaromatic molecules.² Recent studies of such complexes, commonly called Meisenheimer-type complexes, have provided new insights into the effects of structure on the addition of nucleophiles to unsaturated carbon centers.

We wish to call attention to a class of anionic σ complexes long postulated³ but largely uncharacterized. The complexes are formed by the reaction of amide ion with hetarenes.

We now report the first unambiguous evidence in the form of nmr spectra for the existence of anionic σ complexes I–III formed by the addition of amide ion to



isoquinoline and quinoline. Amide ion adds faster to C-2 than to C-4 of quinoline to give II but the C-4 adduct (III) is more stable; *i.e.*, kinetic and thermodynamic products are formed, respectively.

Complexes I–III have long been postulated to occur in the Chichibabin amination of isoquinoline and

quinoline.^{4,5} Some appear to have been isolated by Bergstrom in the 1930's, but owing to their instability in the solid state they were characterized only superficially.

Results and Discussion

In the presence of excess KNH_2 , reaction with isoquinoline or quinoline is complete and rapid; no heteroarene can be detected by nmr when mixtures are examined shortly after preparation. When substrate is present in excess, spectra of both complexed and free heterocycles are observed, and there is no evidence of signal averaging between these two, either in coupling constants or chemical shifts.

A significant change occurs in the pattern of a single multiplet of a complex as the amide ion concentration is varied. The multiplicity decreases as the concentration of KNH_2 increases. This means that amide ion catalyzes proton transfer between the amino group of an adduct and solvent, leading to spin decoupling.^{7,8} When the amide ion concentration is low, this exchange is slow and spin coupling is observed. This multiplicity change serves as a useful way to recognize the proton signal of the tetrahedral center of the complex and provides direct evidence for a complex containing an amino group. In the absence of amide ion, isoquinoline and quinoline in NH_3 show no evidence of adduct formation.

Isoquinolines.—The spectrum of the complex between isoquinoline and amide ion at -10° shows a broad multiplet at τ 2.7–3.65, a triplet ($J_{HCNH} = 7.0$ Hz) at τ 4.66 which collapses to a singlet when amide ion is present in excess and a doublet ($J_{3,4} = 5.5$ Hz) at τ 5.13. The triplet-singlet change and the lack of further splitting indicates that the adduct is formed by

(4) F. W. Bergstrom, *J. Amer. Chem. Soc.*, **56**, 1748 (1934); *Justus Liebigs Ann. Chem.*, **515**, 34 (1934); *J. Org. Chem.*, **2**, 411 (1937); *ibid.*, **3**, 233, 424 (1938).

(5) Simple ions are written here, but early conductance studies indicate that ion pairing is important in ammonia.⁶

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(1) Presented in part at the Gordon Conference on Heterocyclic Chemistry, New Hampton, N. H., June 26–30, 1972.

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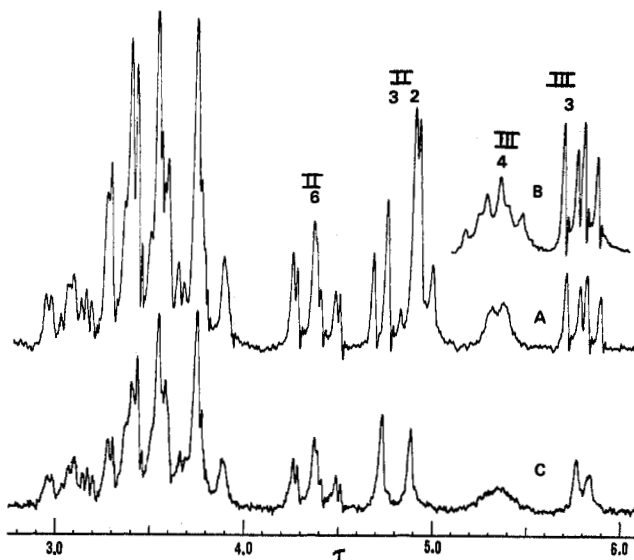
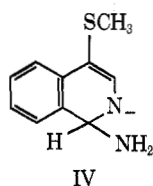


Figure 1.—Nmr spectra of complexes between quinoline and amide ion in ammonia at -45° . Insert B shows H-3 and coupling of the amino group to H-4 of III. Spectra A and C show mixtures of II and III, the former complex being present in larger amount. Quinoline-2-*d* was used to obtain C.

addition of amide ion to C-1. If amide ion had added to any other ring carbon, a more complex multiplet would have resulted.

The doublet at τ 5.13 could be associated with either C-3 or C-4 of the complex. In order to distinguish between these two possibilities a complex between KNH_2 and 4-methylthioquinoline was prepared. (A methylthio group has only a small influence on the shift of a proton at an ortho position.⁹) When similar quantities of the aromatic compound and the complex were present at room temperature, a broad multiplet of the adduct at τ 2.83–3.65 and a triplet ($J_{\text{HCNH}} = 7.2$ Hz) at τ 4.93 (CH-1) and an SCH_3 singlet at τ 8.11 were observed. No other signal at $\tau \sim 5$ was apparent. The anionic σ complex formed in this instance must have structure IV.



The nmr shifts observed for IV allow an unambiguous assignment of the signals of I. The high-field doublet must be associated with C-4. For I and also IV the C-3 signal must lie in the broad multiplet associated with the protons of the carbocyclic ring.

When isoquinoline forms complex I, the signals of C-1 and C-4 shift upfield by 4.1 and ~ 3 ppm, respectively. Similarly, for 4-methylthioquinoline the C-1 and SCH_3 shifts are 4.0 and 0.65 ppm, respectively. Other signals due to ring protons shift by smaller amounts. These shifts² provide further strong evidence for the existence of σ complexes I and IV.

Quinoline.—A mixture of quinoline and excess KNH_2 or NaNH_2 when examined at -45° shortly after preparation provides a time-dependent spectrum. After the mixture stands for a few minutes or after it is

warmed above -45° , the signals at τ 5–6 increase as those at τ 4–5 decrease. Cooling the sample does not reverse the change. This indicates that two complexes are being formed and that one is being converted into another. Figure 1A shows the spectrum of an adduct mixture at -45° ; about 75% of II and 25% of III are present. When the amide ion concentration is decreased, coupling of ~ 7 Hz to an NH_2 in III becomes apparent. This is shown in Figure 1B. Owing to signal overlap, amino coupling in II is less clear and consequently is not shown. The partial spectrum shown in B was obtained when approximately equal concentrations of quinoline, and its complexes were present. The tetrahedral center (H-2) of II shows a signal at τ 4.9 while that (H-4) for III is at τ 5.3.

Unequivocal identification of II and III results from a consideration of a spectrum of complexes formed from quinoline-2-*d*. Figure 1C shows such a spectrum; again II is present in larger amount than III.

On deuteration the upfield multiplet of II centered at τ 4.8 ($J_{2,3} = 4.3$ Hz) collapses to a doublet due to H-3 ($J_{2,4} = -1$ Hz and $J_{3,4} = 9.0$ Hz). The splitting of H-3 of III at τ 5.8 by H-2 ($J_{2,3} = 6.5$ Hz) also vanishes, leaving a doublet ($J_{3,4} = 4.3$ Hz). No four-bond coupling is observable in adduct III. In addition there is a reduction in area by one proton of the multiplet at τ 3–4 and a change in appearance around τ 3.4, owing to the absence of H-2 of III. Note that the signal of the tetrahedral center in the more stable adduct is not lost on deuteration at position 2, clearly showing that this complex is not II but III.

The multiplet at τ 4.4 of II is tentatively assigned to H-6 rather than to H-7 because it is para to the electron-donating nitrogen center. The shielding of this proton and of H-3 of III relative to H-3 of II suggests that more charge is delocalized into the benzene ring in II than in III.

The signal for H-2 shifts to higher field by 3.8 ppm when II is formed; H-4 shifts by about the same amount on forming III. These large shifts provide strong evidence for the formation of anionic σ complexes.²

Since quinoline is completely converted into III in the presence of a slight excess of amide ion, it is likely that this complex is formed in an exothermic reaction having a transition state which does not closely resemble the product ion.¹⁰ Hence the structural and solvation factors which influence the energies of the transition and product states need not be similar. It therefore is understandable that, even though III is more stable than II, it need not form faster. The allylic type resonance stabilization possible in III but not in II may account for the greater stability of III over II.

In other experiments some consequences of complex formation on the chemical reactivity of quinoline in NH_3 were demonstrated by examining base-catalyzed deuterium-hydrogen exchange. A competition experiment involving quinoline-2-*d* and naphthalene-*d*₈ in $\text{KNH}_2\text{-NH}_3$ was carried out at room temperature. In the absence of adduct formation quinoline is expected to undergo the hydrogen exchange reaction faster than naphthalene does, just as pyridine is more reactive than benzene.¹¹ However, the results of the competition

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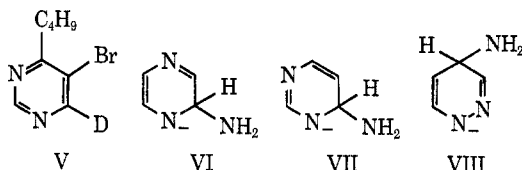
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experiment showed that naphthalene undergoes more extensive D-H exchange than quinoline. This result is understandable in terms of deactivation due to adduct formation. We suggest that such a competition experiment may serve as a simple chemical method of detecting σ complexes in other heterocyclic systems.

Such deactivation due to σ complex formation probably accounts for the observation that 4-*tert*-butyl-5-bromopyrimidine-6-*d* (V) does not undergo significant exchange in $\text{KNH}_2\text{-NH}_3$.¹² In the absence of the addition of amide ion the pyrimidine is expected to be more reactive than deuterated pyridine in an H-D exchange reaction;¹¹ yet it is less reactive.

The present results along with those given in our earlier report dealing with the formation of complexes VI-VIII from diazines¹³ show that σ complex forma-



tion between amide ion and heteroarenes is extensive. Clearly an area awaits further profitable investigation. It promises to provide a wealth of new information, especially about complexes of simple heteroaromatic compounds which do not react in the more widely employed solvent-base systems.²

Experimental Section

Quinoline-2-*d* was prepared by heating equal volumes of quinoline and D_2O at 225° for 2 days in a bomb.¹⁴ Nmr analysis indicated >95% deuteration. Naphthalene-*d*₈ (>95% D) was obtained from Merck Sharpe and Dohme of Canada.

The general procedure for obtaining nmr spectra of ammonia-amide ion reaction mixtures has been presented.¹⁵ Trimethylamine (τ 7.87) or benzene (τ 2.60) served as a shift standard. A Varian A-60A spectrometer having a V-6040 variable temperature controller was employed.

Competitive Hydrogen-Deuterium Exchange of Quinoline-2-*d* and Naphthalene-*d*₈ in Ammonia.—Potassium amide (0.3 *M*) was generated by the method indicated above. To a precooled Parr metal bomb, flushed with nitrogen, was added 60 ml of amide solution. This was followed by the addition of 0.0074 *m* of naphthalene-*d*₈ and 0.0051 *m* of quinoline-2-*d*. The sealed bomb was heated in running tap water for 45 min, cooled in acetone-Dry Ice, and opened; the reaction was quenched by the addition of 3.2 g of NH_4Cl . After evaporation of the solvent, the residue was treated with 50 ml of 18% KOH to remove salts and then dissolved in ether. The aqueous solution was extracted with 2 × 30 ml of ether. The combined ether phases were exposed to 2 × 30 ml of 1 *M* HCl. Evaporation of the ether gave naphthalene which was sublimed. The nmr spectra of a mixture of purified naphthalene and *tert*-butyl alcohol (area standard) indicated that 74% dedeuteration had resulted.

Quinoline was recovered from the HCl following neutralization with Na_2CO_3 and extraction with ether (2 × 25 ml). Nmr analysis of the ether solution showed that 20% dedeuteration had taken place.

Registry No.—II, 38896-70-7; III, 38896-68-3; IV, 38896-69-4; isoquinoline, 119-65-3; quinoline, 91-22-5; 4-methylthioisoquinoline, 38896-71-8; amide ion, 17655-31-1.

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Covalent Amination of Heteroaromatic Compounds¹

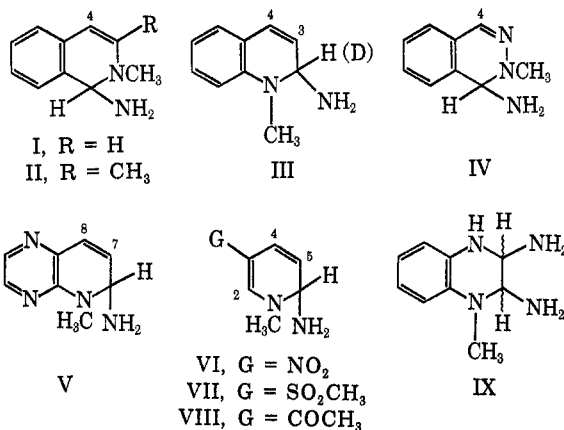
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The discovery that heteroaromatic molecules may be transformed into their covalent hydrates in aqueous solution is of great importance. In the hydration process a water molecule or hydroxide ion serving as a nucleophile adds to a ring carbon atom to give a hydroxy derivative. This brings about major changes in the physical and chemical properties of the original substance.^{2,3}

We wish to call attention by this report to analogous structural transformations involving heteroaromatic molecules in ammonia solvent. Covalent amination results.⁴ Examples reported here include quaternized isoquinoline, quinoline, phthalazine, triazanaphthalene, 3-substituted pyridines and quinoxaline. These cations are converted in liquid ammonia, free of added amide ion, into aminodihydro structures I-IX. The amina-



tion reactions are remarkable in that they are complete in minutes below 0°. No starting material could be detected by nmr at equilibrium.

The present study complements our other investigations which show that uncharged heteroaromatic molecules such as the diazines, isoquinoline, and quinoline react rapidly and completely with amide ion in am-

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