phenyls. This allows all the peaks to be well shaped and still well separated.

Yields of all products were derived by comparison of peak areas with the peak area of the internal standard. Standardizations were made in the form of calculated molar-response factors. These were determined for each individual product by analysis of an accurately known mixture of the product in question and the internal standard, chromatographed under conditions close to those encountered in a typical reaction analysis.

Various products from these reactions were isolated by preparative glpc. The column found most effective was a 4.5 ft × $^{3}/_{8}$ in. aluminum column packed with 17% Carbowax 200 M on Chromosorb P, using a helium flow of about 100 cc/min. The reaction solution was concentrated to about 1 ml, all of which was injected. Collections were made in U tubes cooled in Dry Ice–isopropyl alcohol. The resulting samples were then analyzed for melting point, infrared spectrum, and/or mass spectrum, as described below.

Identification of Products. ***p*-Chloroiodobenzene** was isolated from expt 1 and 3, Table I. The sample from expt 1 had mp 52–53° and both samples had infrared spectra in excellent agreement with that of an authentic sample.

***p*-Chlorobiphenyl** was isolated from expt 1. The sample had mp 72–75° (lit.[21] 77.2°) and an infrared spectrum with strong absorptions at 692, 760, and 833 cm^{-1}. Conley[22] lists absorptions at 690–710 and 730–770 cm^{-1} for a monosubstituted benzene, and at 810–833 cm^{-1} for a 1,4-disubstituted benzene. Thus a 4-substituted biphenyl is suggested. Mass spectrography showed parent peaks at *m/e* 188 and 190, and other prominent peaks at 152–153 and 76.[23] These data are clearly indicative of a chlorobiphenyl.

Biphenyl was isolated from expt 1 and 4. The sample from expt 1 had mp 68–69°, that from expt 4 had mp 66–67°. Both samples gave infrared spectra which agreed excellently with the spectrum of an authentic sample.

Iodobenzene was isolated as a product from expt 4. It was identified by the identity of its infrared spectrum with that of an authentic sample.

***m*-Chlorobiphenyl** was isolated from expt 4 and was identified by the identity of its infrared spectrum with that of an authentic sample.

Two isomeric iodobiphenyls, clearly separated by glpc, were isolated from expt 3. The two samples gave nearly identical mass spectrograms. The parent peak was at *m/e* 280 with prominent peaks at 152–153 and 76–77.

Two isomeric chloroiodobiphenyls, clearly separated by glpc, were isolated from expt 3. Mass spectrometric evidence from both samples showed parent peaks at *m/e* 314 and 316. The fragmentation patterns were not identical, however. One isomer showed significant peaks at 280 ($I–C_6H_4–C_6H_5$), 152 ($C_6H_4–C_6H_4$), and 76 (C_6H_4). The other isomer showed its prominent peaks at 186, 187, 188, and 189 ($C_6H_4–C_6H_4Cl$ and $C_{12}H_7Cl$), 152 ($C_6H_4–C_6H_4$), and 76 (C_6H_4).

Benzoic acid was isolated from expt 4. The sample had mp 107–115° and its infrared spectrum agreed well with that of an authentic sample.

***p*-Chlorobenzoic acid** was isolated as a precipitate from expt 1. The sample had mp 236–238° and gave an infrared spectrum which agreed excellently with that of an authentic sample.

***p*-Chlorobromobenzene** was shown to be nonexistent as a product of reactions 5–7 by retention-time evidence. Addition of authentic *p*-chlorobromobenzene to these reaction solutions caused the appearance of a new peak in the gas–liquid partition chromatograms where nothing was previously observable.

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(23) We are grateful for the assistance of Mr. Albert H. Smith with the mass-spectrometric analyses.

The Iodination of Coordinated Imidazole[1]

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Contribution from the Department of Chemistry, Vanderbilt University,
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Abstract: When imidazole is coordinated at the "pyridine" nitrogen (3 position) to nickel(II), its rate of iodination follows a law different from that for the iodination of free imidazole. The reaction is first order in iodine and first order in nickel complex; no term corresponding to a self-catalyzed path is found. For variation of iodide or hydrogen ion concentration, the results for the nickel(II) complex are more complicated than those for free imidazole. The results can be correlated with a mechanism involving reaction of both $[Ni(ImH)]^{2+}$ and $[Ni(Im)]^{+}$ with the iodine molecule. The energy and entropy of activation is the same, within experimental error, for the uncatalyzed reaction of the free ligand as for the reaction of the coordinated ligand. The principal consequences of these results for the mechanism of the iodination of imidazole itself is to rule out the iodonium ion as a probable attacking species.

Imidazole is one of the few heterocyclic molecules for which extensive kinetic data on substitution reactions are available.[2] The iodination of the ligand has been examined by two groups of workers,[3,4] and the deuterium isotope effect has also been studied.[5] In addition, complexes of the ligand with nickel(II) are quite stable.[6] As part of a general program involving comparison of the reactivity of the coordinated and uncoordinated ligand,[7] the iodination of the nickel(II) complex of imidazole was studied.

Experimental Section

Materials. The imidazole, recrystallized three times from benzene, melted at 88.5° (lit.[3,4] 88.0, 89.0°). All other chemicals

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(1) Grateful acknowledgment is made of the support of this work by the Air Force Office of Scientific Research through Grant AF-AFOSR-630-64.

(2) For a summary, see W. Adam and A. Grimison, *Tetrahedron*, **22**, 835 (1966).

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(5) A. Grimison and J. H. Ridd, *J. Chem. Soc.*, 3019 (1959).

(6) (a) B. L. Michel and A. C. Andrews, *J. Am. Chem. Soc.*, **77**, 5291 (1955); (b) N. C. Li, T. L. Chu, C. T. Fujii, and J. M. White, *ibid.*, **77**, 859 (1955).

(7) M. M. Jones in "Mechanisms of Inorganic Reactions," Advances in Chemistry Series, No. 48, American Chemical Society, Washington, D. C., 1965, pp 153–162.

were reagent grade and were used without further purification. The deionized water was freshly boiled immediately before use.

Kinetic Measurements. All solutions were made to an ionic strength of 1.00 M by addition of sodium nitrate. In order to avoid complications caused by adding buffers, a Fisher titrimeter was used to maintain the pH at the desired value. The electrodes were soaked in 1 M hydrochloric acid between each use since long standing in iodine affects their sensitivity.

Appropriate amounts of imidazole, nickel(II) nitrate hexahydrate, and sodium nitrate were weighed into 100-ml volumetric flasks, then freshly boiled water was added with enough perchloric acid to bring the pH to about the required value. The flasks were transferred to the constant temperature bath. After 30 min, iodine–iodide solution at the bath temperature was pipetted into the flask, and the contents were transferred to a double-jacketed vessel through which water from the constant temperature bath was pumped. The pH was brought to the desired value by addition of concentrated acid or base, using a Fisher titrimeter. Since little variation of the pH during the course of the reaction was noted, for slow reactions the solution was put into the closed flasks after adjustment of the pH. Periodically, samples were withdrawn for measurement of the absorbance at 350 mμ, near the maximum of the I_3^- ion.[8] First-order rate constants (k_1) were obtained by multiplying the slope of a plot of log ($D_t - D_\infty$) *vs.* time by 2.303. Iodine evaporation occurred in the open systems at a rate independent of the pH but dependent on the iodide concentration. The measured first-order rate constant for iodine evaporation (reproducible to ±10%) was subtracted from the first-order rate constant measured with imidazole present, to give the corrected first-order constant. Second-order rate constants (k_2) were found by dividing the corrected first-order constant by the concentration of imidazole, since under the conditions used the imidazole is all in the form of the complex. For example, at pH 7.0, 98% of the imidazole is present as $Ni(ImH)^{2+}$ and the remainder is in higher complexes.[6]

Rate constants were reproducible to ±10%, which corresponds to a relative error in the pH of ±0.05 unit, though the absolute error in the pH may be as high as ±0.1 unit.

Product Analysis. The preparation of product for analysis was carried out under the kinetic conditions except that sodium nitrate was omitted; 0.1 M imidazole, 0.2 M $Ni(NO_3)_2$, 5×10^{-3} M I_2, and 8×10^{-3} M NaI were put into a 2-l. flask and allowed to react at 40° for 3 days. Most of the excess nickel(II) was precipitated by the addition of 1 M K_2CO_3 and, after filtration, hydrochloric acid was added to the filtrate to disrupt the complex. The filtrate was divided into 250-ml portions and each portion was extracted five times with ether; a total volume of 1 l. of ether was used. After the ether had been evaporated, the product was recrystallized from water and dried; the compound melted at 182° (lit.[3] 182°), indicating that the product is 2,4-diiodoimidazole.

Results and Discussion

Iodination of Imidazole. The rate law for the iodination of imidazole at iodide concentrations greater than 0.01 M is[3,4]

$$k_2 = (1/(H^+)(I^-)^2)[k_0 + k_{cat}(Im)] \qquad (1)$$

where k_2 is the observed second-order rate constant, (H^+) is the concentration of hydrogen ions, (I^-) is the concentration of iodide ions, k_0 is the rate constant for the "uncatalyzed" reaction, k_{cat} is the rate constant for the "catalyzed" reaction, and (Im) is the concentration of free imidazole.

Table I shows that this rate law is applicable at 5×10^{-3} M iodide, and other experiments showed no deviation from eq 1 to at least 1×10^{-3} M iodide. The k_0 used to compute the catalytic constants listed in Table I was 10.7×10^{-13}.

Order in Complex. It was established that the rate of reaction is independent of the (Ni^{2+})/(Im) ratio from 2 to 200. In contrast to the behavior of imidazole, iodination of the nickel–imidazole complex is accurately first order in complex, as shown in Table II. This result demands that the catalytic term in eq 1 be negligible in iodination of the complex. Coordination of imidazole occurs at the "pyridine" nitrogen in the 3 position.[9] If the catalytic term in eq 1 is due to base catalysis of the iodination by the imidazole molecule,[10] coordination at this basic site would eliminate the possibility of base catalysis by the imidazole molecule.

Table I. Iodination of Imidazole[a]

(Im) × 10^3, M	$k_2(H^+)(I^-)^2$ × 10^{13}, M^2 sec^{-1}	k_{cat} × 10^{11}, M sec^{-1}
1.0	11.5	8
2.0	12.5	9.0
5.0	15.1	8.8
6.0	15.7	8.4
10.0	19.6	8.9
15.0[b]	22.9	8.12
20.0[b]	27.8	8.65
25.0[b]	31.5	8.42
30.0[b]	36.2	8.50

[a] 40°; 5×10^{-3} M NaI; 5×10^{-5} M I_2; 1.00 M $NaNO_3$. [b] Data from ref 4 at 4×10^{-2} M iodide.

Table II. Variation of the Rate with Complex Concentration[a]

(Im) × 10^3, M	k_1 × 10^4, sec^{-1}	k_2 × 10^2, M^{-1} sec^{-1}
5.00	1.99	3.98
10.0	4.05	4.05
20.0	8.10	4.05
30.0	12.1	4.04
40.0	16.3	4.09
50.0	19.9	3.98

[a] 40°; 2.5×10^{-3} M NaI; 5×10^{-5} M I_2; 0.1 M $Ni(NO_3)_2$; 0.7 M $NaNO_3$; pH 6.5.

Hydrogen Ion Variation. The rate of reaction of the complex with iodine was determined at several pH values at two temperatures; these results are given in Table III, which clearly shows that the reaction is less than inverse first order in hydrogen ion concentration. From Table III the heat of activation at pH 7 is 18.9 ± 3 kcal, and the activation entropy is +4 ± 7 eu; for imidazole the corresponding values for the uncatalyzed reaction are[4] 18.6 ± 2 kcal and 0.3 ± 5.0 eu, showing that under these conditions there is little difference in the activation parameters for the coordinated ligand compared with the uncoordinated ligand.

Table III. Rate of Reaction as a Function of pH and Temperature[a]

pH	Rate at 30°	Rate at 40°
6.00	0.198	0.705
6.25	0.322	1.17
6.50	0.701	1.86
6.75	0.905	2.72
7.00	1.35	3.64
7.25	*b*	6.42

[a] $k_2 \times 10^2$, M^{-1} sec^{-1}; 5×10^{-2} M Im; 5×10^{-3} M NaI; 0.1 M $Ni(NO_3)_2$; 0.7 M $NaNO_3$. [b] Precipitation occurred.

Iodide Ion Variation. Table IV contains the data obtained when the iodide ion concentration was varied

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Table IV. Rate of Iodination as a Function of Iodide Ion Concentration at pH 6.0, 6.5, and 7.0[a]

	pH					
	6.0		6.5		7.0	
$I^- \times 10^3$, M	k_2	k^*	k_2	k^*	k_2	k^*
0.100	...	...	101.0	107.0	...	...
0.750	...	...	15.1	21.1	...	...
1.00	...	...	11.2	17.6	26.8	42.2
2.50	...	...	4.06	9.93	10.0	24.4
5.00	0.705	2.74	1.85	7.18	3.66	14.2
10.0	0.0934	0.631	0.430	2.90	1.49	10.1
25.0	0.0194	0.298	0.0516	0.793	0.200	3.07
50.0	0.00544	0.162	0.0145	0.431	0.0631	1.88
100.0	...	...	0.00412	0.241	0.0176	1.04

[a] $k_2 \times 10^2$, M^{-1} sec^{-1}; 40°; 0.1 M Ni(NO$_3$)$_2$; 0.7 M NaNO$_3$.

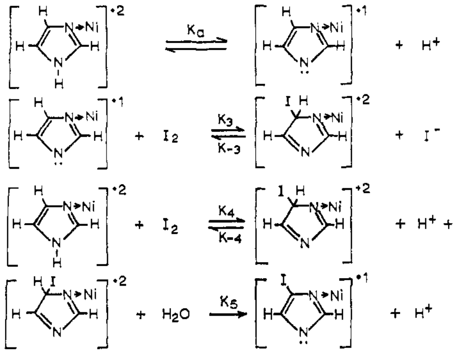

Figure 1. Proposed mechanism for the iodination of the nickel(II) complex of imidazole. Coordinated water molecules have been omitted for clarity.

at three different pH values. The definition of k^* is[11] $k^* = k_2[1 + K_{I_3^-}(I^-)]$, where $K_{I_3^-}$ is the formation constant of the triiodide ion,[12] 575 at 40°.

A plot of log k_2 vs. log (I$^-$) reveals that above 5 × 10^{-3} M iodide the rate of reaction is proportional to (I$^-$)$^{2-}$, whereas at the lower iodide concentrations the rate becomes proportional to (I$^-$)$^{-1}$. Such a change in order is expected if *the iodine molecule* is the attacking species.[10]

Mechanism. Grovenstein and Aprahamian[11] have proposed a mechanism for the iodination of 4-nitrophenol which leads to the reaction scheme shown in Figure 1 in the present case. These authors derive the following equation for the variation of the rate constant with iodide and hydrogen ion concentration.

$$\frac{1}{k^*(\mathrm{H}^+)} = \frac{k_{-3}(\mathrm{I}^-)}{k_3k_5K_a} + \frac{1}{k_4(\mathrm{H}^+) + k_3K_a} \qquad (2)$$

Figure 2 shows a plot of $1/k^*(\mathrm{H}^+)$ vs. (I$^-$) with error limits corresponding to ±0.05 pH unit. In spite of the large experimental error inherent in the method, eq 2 correlates the data well with a single line, as was found previously.[11] From the slope, $k_{-3}/k_3k_5K_a$ is 1.3 × 10^{10}, and from the intercept, $1/[k_4(\mathrm{H}^+) + k_3K_2]$ can be estimated to be approximately 5 × 10^6. Unfortunately, the value of K_a is unknown, so that the individual rate constant ratios cannot be evaluated, but probably k_3 is much larger than k_4 as in the iodination of 4-nitrophenol.[11] From the effect of pH on the rates of iodination of the complex and of free imidazole the following order of reactivity is proposed: imidazole anion > coordinated imidazole anion > coordinated imidazole molecule > imidazole molecule. This order of reactivity is similar to the order observed in the diazo coupling reaction of phenol,[13] but here the effect of coordination is not so marked.

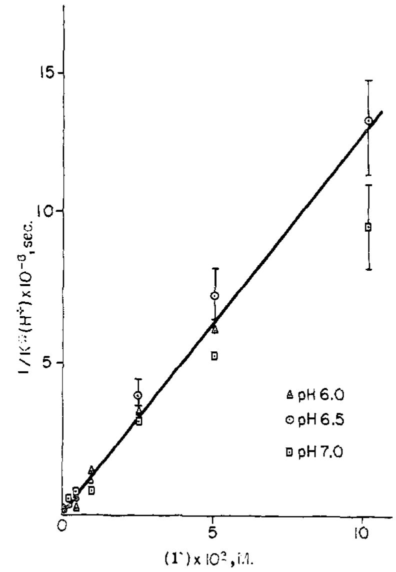

Figure 2. Test of eq 2 for the iodination of the nickel(II) complex of imidazole.

Theoretical calculations[2,14] indicate that the electron density at the 2 and 4 positions in imidazole is nearly the same, though the 4 position was thought to be the initial point of attack in iodination[5] because an isotope effect was observed in the iodination of 4-*d*-imidazole but not 2-*d*-imidazole. Recently 2-*d*-imidazole was found[15] to undergo rapid exchange with water while the 4-*d* compound did not exchange with the solvent under the same conditions. The site of initial reaction in iodination is therefore uncertain both for imidazole and for its nickel complex.

The present results are germane to the mechanism of iodination of imidazole itself. Ridd proposed[3,14] that the catalytic term in eq 1 is due to the interaction of I$^+$ with imidazole to yield the 3-iodoimidazole which attacks the imidazole anion. The coordination of

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[11] E. Grovenstein, Jr., and N. S. Aprahamian, *J. Am. Chem. Soc.*, **84**, 212 (1962).

[12] M. Davies and E. Gwynn, *ibid.*, **74**, 2748 (1952).

[13] K. E. Maguire and M. M. Jones, *ibid.*, **85**, 154 (1963).

[14] For a critique see J. H. Ridd in "Physical Methods in Heterocyclic Chemistry," A. R. Katritsky, Ed., Academic Press Inc., New York, N. Y., 1963, p 109.

[15] T. M. Harris and J. C. Randall, *Chem. Ind.* (London), 1728 (1965).

imidazole to nickel at the 3 position eliminates this term. The uncatalyzed term in eq 1 was ascribed to attack of the anion by I^+, which would demand a strict $(I^-)^{-2}$ dependence of the rate on iodide ion concentration.[10] This explanation is untenable in the iodination of the nickel(II) complex of imidazole because a more complicated dependence of the rate on iodide ion concentration is found. Since the activation parameters for the ligand and complex are so similar, it seems unlikely that coordination of imidazole leads to a change in the iodinating species, so that the iodine molecule probably is the attacking species in the iodination of both imidazole and its nickel(II) complex. The catalytic term in eq 1 is then due to the base catalysis of the reaction by the imidazole molecule,[4] which cannot occur when the basic site is coordinated to nickel(II).

Relative Rates of Base-Catalyzed Enolization of 2-Butanone[1,2]

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Contribution from the Department of Chemistry, McMaster University, Hamilton, Ontario, Canada. *Received June 13, 1966*

Abstract: Base-catalyzed enolization at the α carbons of 2-butanone in D_2O and in D_2O–dioxane mixtures was followed by nmr. In D_2O the reactivity of the methylene protons exceeds slightly that of the α-methyl protons for the catalyst OD^-. With p-$O_2NC_6H_4O^-$ and AcO^- the effect increases in that order. The accelerating effect of the β-CH_3 substituent can be accounted for in terms of a transition state that resembles enol and not enolate.

A large amount of work has been reported concerning substituent effects on rates of enolization of ketones. If the substituent at α-carbon is alkyl, it appears that the rate of base-catalyzed enolization is reduced while that of acid-catalyzed enolization is accelerated, relative to the corresponding rate for unsubstituted ketone. This generalization is based on over-all rates of enolization of aryl alkyl ketones,[3] of dialkyl ketones,[4–6] and of ring-substituted acetophenones,[7–10] as well as on a limited number of experiments in which relative rates at two sites in the same molecule were observed.[11–13] While it is clear that the alkyl-group effect changes sign between strongly basic and strongly acidic media, the borderline region does not appear to be well defined. In order to determine the dependence of substituent effects in enolization on base strength and on medium, we began a study of relative rates of H–D exchange into two α sites of simple dialkyl ketones.

Experimental Section

Materials. Methyl ethyl ketone (Fisher, reagent grade) was distilled through a helices-packed column. The fraction distilling at 78–79° showed no extraneous signals in the nmr and gave only one peak in the gas chromatograph. Deuterium oxide was used as supplied by Merck Sharp and Dohme. Dioxane (Fisher, purified grade) was also used as supplied.

Anhydrous NaOAc (BDH, reagent grade) was finely ground and then heated at 160° for 2 days. The material was cooled in a desiccator. Sodium p-nitrophenoxide was prepared from p-nitrophenol (mp 113–114°, benzene) by shaking 13.9 g of the phenol, in 50 ml of ether, with 50 ml of approximately 2 N NaOH. The orange-yellow curd formed in the aqueous layer was filtered, washed three times with ether and once with water, and recrystallized three times from 95% ethanol, in which the salt but not the phenol is sparingly soluble. The yellow crystals of the tetrahydrate were heated at 160° for 2–3 hr to form anhydrous, red sodium p-nitrophenoxide.[14]

Solutions of sodium deuteroxide were prepared by dissolving sodium hydroxide (BDH, reagent grade) in D_2O. Aliquots were titrated with standard acid to the bromocresol green end point. Solutions of p-nitrophenoxide were titrated using the bright yellow p-nitrophenoxide itself as indicator. Solutions of sodium acetate were prepared in volumetric flasks from the anhydrous salt. All solutions were stored in bottles sealed with rubber serum stoppers.

Procedures. Exchange was followed to one half-life or more by integrating the nmr signals due to the 1 and 3 positions,[15] relative to that of the β-methyl group as internal standard, with a Varian A-60 instrument. Exchanges were carried out in the probe and also in constant temperature baths. The 0° runs were sampled at intervals, and the samples were rapidly quenched by addition to, and shaking with, a phosphate buffer. There was no detectable exchange in such buffered solutions over a period of 16 hr which was much longer than the analysis time. Reactions carried out at 59.2° were quenched by chilling to 0°. Integrations were then performed between 0 and 35°, with negligible exchange during the analysis time.

Results

Pseudo-first-order rate constants and their standard deviations were obtained by fitting experimental values of N_H^t and t to the equation $N_H^t = N_H^0 e^{-kt}$ by means of a nonlinear, least-squares program for the IBM 7040 computer. In the equation N_H^t and N_H^0 represent, respectively, the number of α-hydrogens at a given site at time t and at time zero, relative to the internal standard $N_{\beta\text{-}CH_3} = 3$. Good fits were obtained, even for exchanges followed to two half-lives, suggesting that the secondary isotope effect is small. Representative data

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[1] Financial support of this work by the National Research Council of Canada is gratefully acknowledged.

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