Kinetics of Iodination of Nickel(II)-Coordinated Pyrazole[1]

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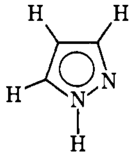
Abstract: Coordination of pyrazole by nickel(II) in aqueous solution produced changes in the rate of iodination and in the order in hydrogen ion. Thus, at pH 6, the rate of iodination was about twice that of pyrazole and the order in hydrogen ion was −1.3, while at pH 7.2, the rate was eight times that of pyrazole and the order in hydrogen ion was nearly −2; the order in hydrogen ion for uncoordinated pyrazole was −1 over the same range of pH values. A hydroxide ion catalytic step was added to the reaction scheme for uncoordinated pyrazole to account for the change in hydrogen ion order attending coordination. The change in rate was interpreted in terms of changes in individual steps in the reaction scheme and the alteration in the acid dissociation constant K_a of the substrate.

Previous studies of electrophilic substitution in aromatic substrates indicate that coordination by transition metal ions causes deactivation of substitution sites.[2–6] The extent of the deactivation may be modest, as in the case of imidazole,[5] or it may be drastic, as in the cases of aniline[2] and 8-hydroxyquinoline-5-sulfonic acid.[4] In all such cases, however, the rate of substitution by an electrophilic reagent was reduced by coordination. In contrast to expectation, pyrazole (I) undergoes iodination more rapidly when coordinated with nickel than when not. The purpose of this research was to investigate this rate enhancement through a detailed kinetic study of the iodination of nickel-coordinated pyrazole. Kinetic data on the iodination of unsubstituted pyrazole has been reported,[7] as have the stability constants of the nickel(II) complexes of pyrazole.[8]



I

Experimental Section

Materials. Pyrazole was recrystallized three times from cyclohexane, mp 68.5°. Pyrazole-*3,4,5-d*$_3$ was prepared by heating pyrazole in excess D_2O (99.5% from Merck Sharp and Dohme of Canada, Ltd.) at 250° for 12 hr. The deuterated product was extracted from the heavy water by ether, recovered by evaporation of the ether, and then recrystallized three times from cyclohexane. Nuclear magnetic resonance spectroscopy indicated that more than 95% of the original pyrazole was deuterated. Reagent grade iodine was further purified by sublimation. Aqueous solutions were prepared from twice distilled water. All other chemicals were reagent grade not further purified.

Kinetic Runs. The kinetic runs were made in aqueous solution at 30 and 40°. The ionic strength was adjusted to 1.00 M with 2.50 M NaCl. Runs with coordinated pyrazole were buffered with either $Na_2B_4O_7$–HCl or $NaC_2H_3O_2$–HCl; runs with uncoordinated pyrazole utilized borate buffer. In all runs, the molar ratio of pyrazole to triiodide was greater than 20 as was the molar ratio of iodide to triiodide. The concentration of Ni(II) ions was held at least tenfold larger than that of the ligand.[9] The rate of reaction was followed by the disappearance of triiodide absorbance at 460 mμ;[10] this wavelength avoided the Ni(II) absorbance slightly shifted to the blue by coordination at 394 mμ. Bausch and Lomb Spectronic 600 and Spectronic 20 spectrophotometers fitted with thermostated cells were used. Reactions followed through three half-lives exhibited pseudo-first-order kinetics. Rate constants were reproducible to within less than ±10%.

pH Control and Measurement. To control the pH of the reaction medium, it was desirable to select buffers that interact minimally with Ni(II) ions. Thus, ammonia and phosphate buffers used in the earlier study on the iodination of uncoordinated pyrazole[7] were not suitable because of strong complexation with nickel by ammonia and precipitation of nickel by phosphate. The borate and acetate buffers were chosen because their nickel salts are soluble in aqueous solution and they coordinate relatively weakly with Ni(II).[11] To minimize the likelihood that the base components of the buffer interact with the ligand substrate through the metal ion, the concentration of buffer was kept as small as possible, consistent with adequate buffer power. In a typical run, with $[HB_4O_7^-] = 1.02 \times 10^{-2}$ M and $[H_2B_4O_7] = 1.48 \times 10^{-2}$ M, the pH decreased from 7.05 ± 0.01 to 7.00 ± 0.01 after three half-lives. This change in pH over three half-lives can produce up to 20% reduction in rate (see Results). Accordingly, first-order rate constants were determined from absorbance data taken over a single half-life but with no correction made for the decrease in pH over that time interval.

pH measurements were made with the Cary 31 vibrating reed electrometer fitted with a Cary pH electrode adapter. pH values were reproducible to ±0.01 unit.

Product Analysis. The product of the iodination was prepared at 40°. The initial concentrations of reagents were 0.02 M pyrazole, 0.01 M $NiCl_2$, 0.025 M $Na_2B_4O_7$, with no NaCl or HCl added. The iodide-iodine solution (0.025 M KI, 0.005 M I_2) was added in 10-ml increments; each increment was intended to iodinate 4% of the ligand. Another increment was added when triiodide ion was essentially depleted. Since the accumulation of iodide drastically retarded the rate of iodination (see Results), 10 ml of 0.4 M $AgNO_3$ was added periodically to reduce the iodide concentration; the precipitated silver iodide was allowed to collect in the bottom of the reaction flask. After sufficient aqueous iodine was added to monoiodinate the ligand, aqueous hydrochloric acid was added (to pH 1) to disrupt the complex, followed by addition of solid sodium

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[1] Colorado State University Department of Chemistry Contribution No. 18-69.

[2] N. K. Chawla, D. G. Lambert, and M. M. Jones, *J. Amer. Chem. Soc.*, **89**, 557 (1967).

[3] N. K. Chawla and M. M. Jones, *Inorg. Chem.*, **3**, 1549 (1964).

[4] K. E. Maguire and M. M. Jones, *J. Amer. Chem. Soc.*, **85**, 154 (1963).

[5] D. G. Lambert and M. M. Jones, *ibid.*, **88**, 5537 (1966).

[6] M. M. Jones, "Ligand Reactivity and Catalysis," Academic Press, New York, N. Y., 1968, p 75.

[7] J. D. Vaughan, D. G. Lambert, and V. L. Vaughan, *J. Amer. Chem. Soc.*, **86**, 2857 (1964).

[8] T. R. Musgrave and E. R. Humburg, Jr., *J. Inorg. Nucl. Chem.*, **32**, 2229 (1970).

[9] $K_1 = 76$, $K_2 = 25$, $K_3 = 8$, $K_4 = 2.7$, $K_5 = 0.9$, and $K_6 = 0.3$ for the nickel–pyrazole system at ionic strength 0.20 M at 25°; $K_1 = 82$ at ionic strength 1.00 M at 25°.[8] For $[Ni^{2+}] = 0.10$ M and [pyrazole] = 0.010 M, the ligand is estimated to be 88% coordinated in the 1:1 complex and 8% in the 1:2 complex.

[10] The Beer–Lambert law was tested at 460 mμ for stoichiometric iodine concentrations from 2×10^{-4} to 8×10^{-4} M. A linear relationship between absorbance and iodine concentration was found; least-squares ε 908.2 cm^{-1} M^{-1}, correlation coefficient $r = 1.00$.

[11] D. P. Graddon, "An Introduction to Coordination Chemistry," Pergamon Press, London, 1961, p 57.

carbonate to neutralize the solution and to precipitate nickel carbonate.[5] The ligand was extracted from the now alkaline solution with ether, collected by ether evaporation, and then recrystallized three times from cyclohexane. An nmr spectrum of the product indicated it to be 4-iodopyrazole. The melting point was 109° (lit. 108.5[7] and 112[12]).

Results

Order with Respect to Coordinated Pyrazole. To establish the order in pyrazole, the concentration of pyrazole was varied from run to run while other reagent concentrations were held constant. Pseudo-first- and second-order rate constants for the iodination of coordinated and uncoordinated ligands are given in Table I. The pH of the solutions containing nickel ions was lower than that for the solutions without nickel ions, because of the hydrolysis of nickel ions

$$Ni^{2+} + H_2O \rightleftharpoons Ni(OH)^+ + H^+$$

Table I. Dependence of the Rate of Iodination of Coordinated Pyrazole upon the Pyrazole Concentration[a] at 30.0°

[Pyrazole] × 10^3, *M*	$[Ni^{2+}]$/[pyrazole]	$k_1^{obsd} \times 10^4$, sec^{-1}	($k_1^{obsd} \times 10$)/[pyrazole], sec^{-1} l. mol^{-1}
1.0	100	1.10, 1.08	1.10, 1.08
2.0	50	2.28, 2.15	1.14, 1.08
4.0	25	4.88, 4.78	1.22, 1.20
6.0	16.7	7.68, 8.06, 7.38	1.28, 1.34, 1.23
8.0	12.5	9.84, 9.99, 10.00	1.23, 1.25, 1.25
10.0	10.0	13.6, 13.2, 13.2, 13.2	1.36, 1.32, 1.32, 1.32
8.0	0.0	1.93, 1.91[b]	0.24, 0.24

[a] $[Na_2B_4O_7] = 2.5 \times 10^{-2}$ *M*, $[HCl] = 3.98 \times 10^{-2}$ *M*, $[KI] = 8.00 \times 10^{-3}$ *M*, $[NiCl_2] = 1.00 \times 10^{-1}$ *M*, ionic strength = 1.00 *M*, pH 7.03. [b] Corrected from pH 7.71 to pH 7.03.

It was shown in the previous investigation[7] and confirmed in this one (see Table III) that the iodination of uncoordinated pyrazole is rigorously inverse first order in hydrogen ion concentration; accordingly, the rate constants for uncoordinated ligand were adjusted to the lower pH by the equation $k_1^{obsd}(\text{at pH } 7.03) = k_1^{obsd}(\text{at pH } 7.71)10^{7.03}/10^{7.71}$. Coordination by nickel ions thus led to a fivefold enhancement of the rate under the particular experimental conditions in these kinetic runs.

A plot of log $\{k_1^{obsd}/[\text{pyrazole}]\}$ *vs.* [pyrazole] for coordinated pyrazole gave a least-squares slope of 1.09 (correlation coefficient $r = 0.999$). Therefore, the order in coordinated ligand is sensibly first order. However, the slight increase in rate attending a decrease in ratio of nickel to pyrazole would be consistent with a larger rate of iodination of the higher complexes relative to the 1 : 1 complex.[9]

Order with Respect to Iodide. In Table II, it is seen that the rate constant for the iodination of coordinated pyrazole is inverse second order except for very small iodide concentrations. A plot of log k_1^{obsd} *vs.* log $[I^-]$ indicated the slope to be −2 for $[I^-] \geqslant 0.0080$ *M*, decreasing in magnitude to ∼−1.2 for $[I^-] = 0.003$ *M*.

Table II. Dependence of the Rate of Iodination of Coordinated Pyrazole upon the Iodide Concentration[a] at 30.0°

$[I^-] \times 10^3$, *M*	$k_1^{obsd} \times 10^4$, sec^{-1}	$k_1^{obsd}[I^-]^2 \times 10^7$, mol^2 $l.^{-2}$ sec^{-1}
2	108.0	0.43
4	45.1	0.72
8	15.1, 15.3, 15.4	0.97, 0.98, 0.98
10	9.18, 9.25	0.92, 0.92
12	6.51, 6.64	0.94, 0.96
16	3.94, 3.97	1.01, 1.02

[a] $[Na_2B_4O_7] = 2.5 \times 10^{-2}$ *M*, $[HCl] = 3.98 \times 10^{-2}$ *M*, [pyrazole] = 1.00×10^{-2} *M*, $[NiCl_2] = 1.00 \times 10^{-1}$ *M*, ionic strength = 1.00 *M*, pH 7.01.

Order with Respect to Buffer and Hydrogen Ion. In the borate buffered system, no buffer catalytic effect was discerned, either for coordinated or uncoordinated pyrazole (Table III). This result is not unprecedented: in the earlier investigation of the iodination of pyrazole,[7] it was observed that HPO_4^{2-} was an effective base catalyst but that $H_2PO_4^-$ was not.[13] In acetate buffer, base catalysis by acetate ion was observed (Table IV). A plot of these data yielded the expected straight lines, with intercepts corresponding to the uncatalyzed reaction and slopes to the buffer catalyzed reaction. Because the rate of iodination is slowed drastically by increased hydrogen ion concentration, it was desirable to adjust the pH to a value less than that obtained with borate buffer but larger than the acetate pK_a value (4.74).[14] Accordingly, very large base to acid buffer ratios were required (Table IV), under which

Table III. Dependence of the Rate of Iodination of Coordinated and Uncoordinated Pyrazole upon Borate Buffer Concentration at 30.0°

Buffer concn × 10^2, *M*		$[Ni^{2+}]$/[pyrazole]	pH	$k_1^{obsd} \times 10^3$, sec^{-1}
$[HB_4O_7^-]$	$[H_2B_4O_7]$			
1.02	1.48	10	7.01	1.32, 1.32, 1.36
0.51	0.74	10	7.01	1.36, 1.38
1.02	1.48	0	7.71	0.96, 0.94
0.51	0.74	0	7.71	1.03

Table IV. Dependence of the Rate of Iodination of Coordinated Pyrazole upon Acetate Ion Concentration[a] at 30.0°

$[CH_3OO^-]$, *M*	$[CH_3COO^-]/[CH_3COOH]$	pH	$k_1^{obsd} \times 10^3$, sec^{-1}
0.30	350	6.38	0.443, 0.443
0.20		6.33	0.329, 0.334
0.10		6.30	0.242, 0.228
0.05		6.22	0.156, 0.156
Intercept		6.21[b]	0.11[c]
0.30	175	6.12	0.172, 0.186
0.20		6.05	0.127, 0.128
0.10		5.94	0.084, 0.085
0.05		6.15	0.061, 0.064
Intercept		5.86[d]	0.036[e]

[a] $[Ni^{2+}]/[\text{pyrazole}] = 10$. [b] Correlation coefficient $r = 0.948$. [c] $r = 0.996$. [d] $r = 0.992$, neglecting pH 6.15. [e] $r = 0.993$, neglecting pH 6.15 value for k_1^{obsd}.

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[12] R. Hüttel, O. Schafer, and P. Jochum, *Justus Liebigs Ann. Chem.*, **593**, 200 (1955).

[13] J. D. Vaughan, G. L. Jewett, and V. L. Vaughan, *J. Amer. Chem. Soc.*, **89**, 6218 (1967).

[14] H. D. Crockford and S. B. Knight, "Fundamentals of Physical Chemistry," Wiley, New York, N. Y., 1959, pp 215–216.

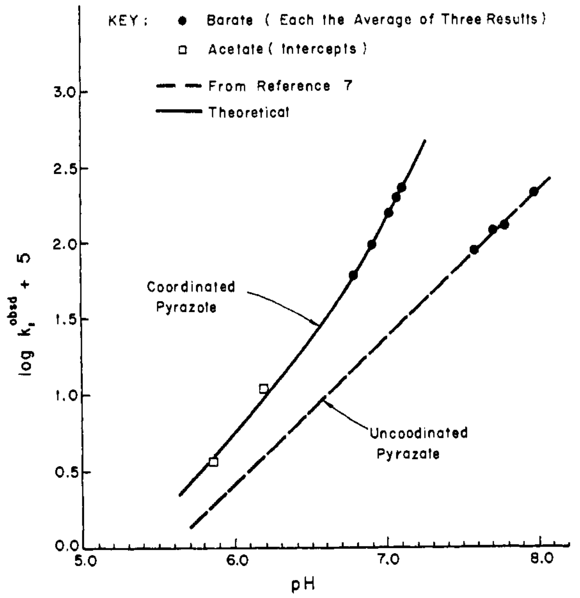


Figure 1. pH profiles for the iodinations of coordinated and uncoordinated pyrazole.

conditions buffer efficiency was very low.[14] The pH values in Table IV are initial values and the corresponding k_1^{obsd} values were calculated from initial rates. To obtain the buffer independent rates of iodination at given pH values in acetate buffer, we calculated linear least-squares intercepts for both k_1^{obsd} and pH as functions of [CH_3COO^-]; these intercepts are given in Table IV. The acetate catalytic rate constants estimated from the slopes[15] of k_1^{obsd} *vs.* [CH_3COO^-] were 1.12 × 10^{-3} sec^{-1} for the higher pH and 0.47 × 10^{-3} sec^{-1} for the lower pH.

The pH profiles of the uncatalyzed iodination of coordinated and uncoordinated pyrazole are shown in Figure 1. Borate buffer ratios ([$HB_4O_7^-$]/[$H_2B_4O_7$]) were varied between 0.92 and 0.25; higher ratios were not feasible because of the occurrence of nickel hydroxide precipitation at the higher pH values.[4] The slope for uncoordinated ligand is the expected −1,[7] but that for the coordinated ligand varies from nearly −2 at pH 7 to about −1.3 at pH 6. The varying and nonintegral order in hydrogen ion is characteristic of parallel reactions having different hydrogen ion dependences.

Experimental Rate Law. The differential rate equation for the iodination of either coordinated or uncoordinated pyrazole is given by

$$\frac{-d[I_3^-]}{dt} = \frac{k_2[\text{substrate}][I_3^-]}{k_1^{obsd}} \qquad (1)$$

For nickel-coordinated pyrazole, with no effective base catalyst present, we propose that

$$k_2 = \left\{k_{01} + \frac{k_{02}}{[H^+]}\right\}\frac{1}{[H^+][I^-]^2} \qquad (2)$$

whereas, for uncoordinated pyrazole, it has been shown[7] that

$$k_2 = k_0/[H^+][I^-]^2 \qquad (3)$$

for the uncatalyzed reaction. A reasonable fit of the data for the coordinated ligand is obtained with k_{01} = 3.04 × 10^{-13} sec^{-1} M^2 and k_{02} = 5.59 × 10^{-20} sec^{-1} M^3 (solid line in Figure 1); k_0 in eq 3 is 1.5 × 10^{-13} sec^{-1} M^2 (dotted line in Figure 1).[7]

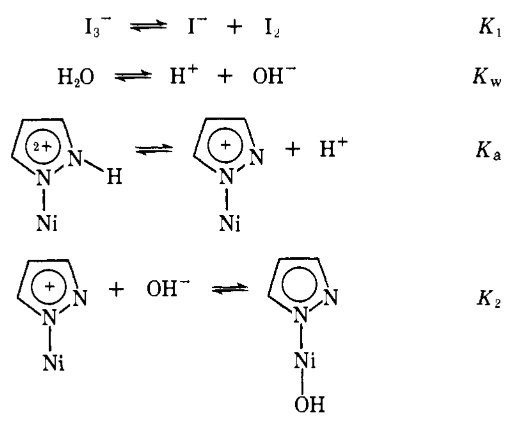
Kinetic Isotope Effect. Rate constants for the iodination of coordinated pyrazole-*3,4,5-d*$_3$ were determined for iodide concentrations of 4.0 × 10^{-3}, 8.0 × 10^{-3}, and 16.0 × 10^{-3} *M* at 30.0°. The ratio of rate constants (k^H/k^D) for the coordinated ligands pyrazole and pyrazole-*3,4,5-d*$_3$ was 4.4 ± 0.1 for each of the iodide concentrations. Similarly, for uncoordinated pyrazole, k^H/k^D = 4.4 was found for [I^-] = 8.0 × 10^{-3} *M*. Iodinations were carried out in borate buffer.

Activation Parameters. Rate constants (uncatalyzed by buffer) determined at pH 7.03 at temperatures of 30.0 and 40.0° yielded an experimental activation energy E_a = 18 ± 2 kcal and log *A* = 12.8 ± 1.5 for the iodination of coordinated pyrazole. Corresponding values for uncoordinated pyrazole[7] are E_a = 18 ± 2 kcal and log *A* = 0.5 ± 2.

Discussion

Mechanism. The mechanism proposed by Grovenstein and Aprahamian for the iodination of 4-nitrophenol[16] is consistent with the rate law for the iodination of uncoordinated pyrazole.[7] To formulate a mechanism for the iodination of nickel-coordinated pyrazole, it is important to consider similarities as well as any difference in the kinetic behavior of coordinated and uncoordinated ligands. Similarities are (1) identical kinetic isotope effects, (2) comparable activation energies, (3) the same orders in iodide[17] and substrate, and (4) the same substrate substitution site (4 position). However, the order in hydrogen ion is inverse first order for pyrazole but between −1 and −2 for the nickel complex. We can adapt the Grovenstein and Aprahamian mechanism to conform to the iodination of coordinated pyrazole by including hydroxide ion dependence, as in Scheme I. To include buffer catal-

Scheme I



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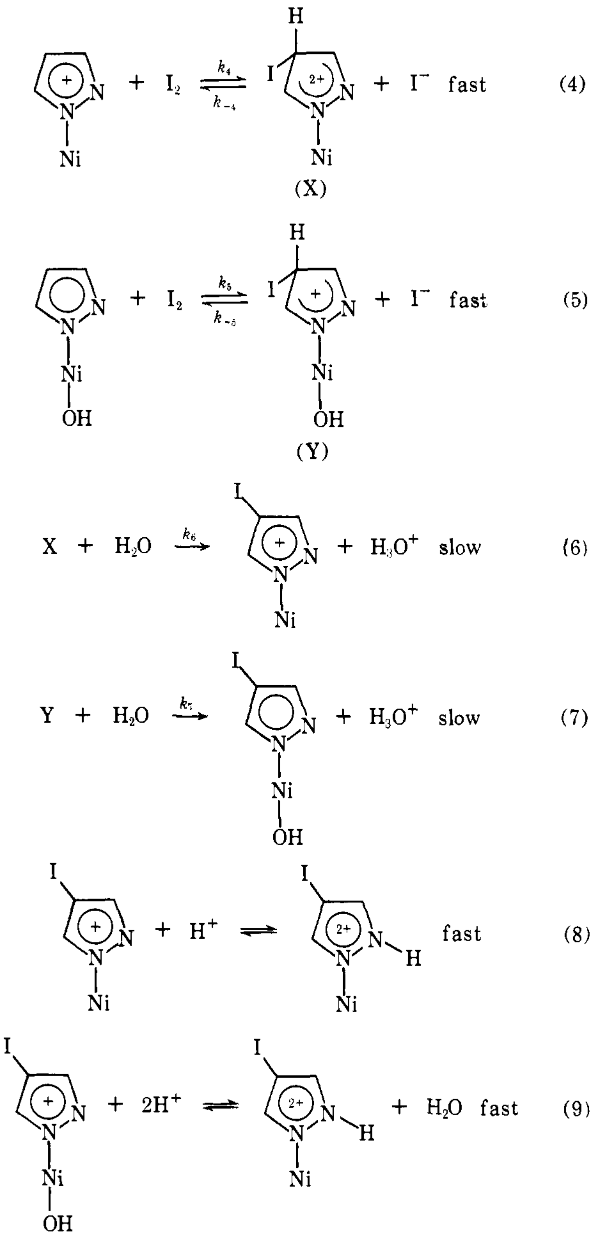
[15] Not corrected for the change in pH attending the variation in buffer concentration at a given buffer ratio.

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

[17] Inverse second order, but approaching inverse first order for very dilute iodide; this change is that expected for electrophilic attack by I_2.[5,18] However, the reduction in isotope effect at very low iodide concentrations expected for I_2 attack was not observed.[18]

[18] E. Berliner, *J. Chem. Educ.*, **43**, 124 (1960).



ysis by a buffer component such as acetate, additional slow steps analogous to eq 6 and 7 can be included.[7,13,16] Utilizing the usual steady-state approximation, the derived second-order rate constant is given by

$$k_2 = \left\{\frac{k_4k_6}{k_{-4}} + \frac{k_5k_7K_2K_w}{k_{-5}\,[H^+]}\right\}\frac{K_1K_a[H_2O]}{[H^+][I^-]^2} \qquad (10)$$

which is the same as the experimental rate equation (eq 2) where $k_{01} = k_4k_6K_1K_a[H_2O]/k_{-4}$ and $k_{02} = k_5k_7K_1K_2K_aK_w[H_2O]/k_{-5}$. An alternative to Scheme I would replace eq 5 and 7 by slow proton removal from σ intermediate X by hydroxide ion (Scheme II).[19]

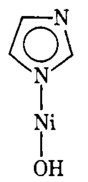
In reactions as complicated as these iodinations, the observed second-order rate constants will depend upon rates of a number of elementary steps as well as solution equilibria. Considering reaction Scheme I for the pyrazole ligand together with curve fitting data (for Figure 1), we find that

$$\frac{k_4k_6}{k_{-4}}K_a \gtrsim \frac{k_4'k_6'}{k_{-4}'}K_a' \qquad (11)$$

$$\frac{k_5k_7}{k_{-5}}K_aK_2 > 0 = \frac{k_5'k_6'}{k_{-5}'}K_a'K_2' \qquad (12)$$

where the primed constants refer to uncoordinated pyrazole. Hence, the catalytic effect of coordination of pyrazole can in part be attributed to the absence of steps 5 and 7 for the uncoordinated ligand. Since coordination is expected to deactivate electrophilic substitution sites,[2-6] one expects $k_4 < k_4'$. In view of eq 11, it would appear that k_6K_a/k_{-4} must be sufficiently larger than $k_6'k_a'/k_{-4}'$ to offset the expected deactivation. It is difficult to assess the relative magnitudes of k_6/k_{-4} and k_6'/k_{-4}'; however, it is likely that $K_a > K_a'$. The coordinating nickel ion would produce weakening of the nearby N–H bond of the ligand through field and inductive effects, thus enhancing the acidity of the coordinated ligand.

Since imidazole is the 1,3 isomer of pyrazole (1,2-diazole), it is of interest to compare the relative effects of coordination upon their rates of iodination. The uncatalyzed iodinations of uncoordinated pyrazole and imidazole occur with about the same rate (at 30°) and according to the same rate law.[7] In either case, attack of the conjugate base (anion) by iodine followed by slow proton removal from the σ intermediate by water is consistent with the rate law. Coordinated imidazole undergoes iodination slower than the uncoordinated ligand;[5] at pH 6.5, the uncatalyzed rate of iodination of imidazole is about 19 times that of the 1:1 nickel complex of imidazole.[20] However, Figure 1 indicates that the rate of iodination of coordinated pyrazole is faster than that for uncoordinated pyrazole by a factor of 2 at pH 6.0 and by a factor of 8 at pH 7.2. The rate law for iodination of coordinated imidazole is consistent with attack of both the coordinated anion and the coordinated molecule[5] by iodine, with slow proton removal by water. In the case of imidazole, processes that are slowed by coordination evidently offset factors that otherwise enhance the rate. Nickel complexes of imidazole[21] are much stronger than those of pyrazole.[8] Deactivation of the substitution site in imidazole would therefore be expected to be greater than that in pyrazole. Also, the rate law for iodination of coordinated imidazole is not consistent with the operation of steps 5 and 7 in Scheme I. The absence of this alternative path for coordinated imidazole could be attributed to the failure of imidazole to form an appreciable amount of complex with bound hydroxide



because of the relatively greater strength of nickel–imidazole coordination.[19]

That the kinetic isotope effect is the same for both uncoordinated and coordinated pyrazole suggests that the C–H (or C–D) bond is weakened to the same extent in their transition states *irrespective* of whether the ligand is or is not coordinated with nickel.

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[19] We are indebted to a referee for suggesting steps 5 and 7 in Scheme I.

[20] Calculated from data given in ref 5.

[21] N. C. Li, T. L. Chu, C. T. Fujii, and J. M. White, *J. Amer. Chem. Soc.*, 77, 859 (1955).