N-Hydroxyamide-Containing Heterocycles. Part 2.[1] Synthesis and Iron(III) Complex-Forming Tendency of 1-Hydroxy-2(1*H*)-pyrimidinone and -pyrazinone

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The reaction of *N*-(benzyloxy)urea with 1,1,3,3-tetraethoxypropane, 4,4-dimethoxy-2-butanone, and 2,4-pentanedione under acidic conditions gave the corresponding 1-benzyloxy-2(1*H*)-pyrimidinones (**3** and **3′**) in moderate yields. In contrast, the reaction of *N*-(benzyloxy)urea or *N*-methoxyurea with 1-phenyl-1,3-butanedione exclusively gave 3-alkoxyimino derivatives (**4**). 1-Benzyloxy-2(1*H*)-pyrazinones (**9a** and **9b**) were synthesized via three steps starting from *N*-(*t*-butoxycarbonyl)glycine. The hydrogenation or treatment with 30% HBr in acetic acid of compounds **3c**, **9a**, and **9b** afforded 1-hydroxy-4,6-dimethyl-2(1*H*)-pyrimidinone (**HOPY**), and 1-hydroxy- (**HOPR-H**), and 1-hydroxy-5,6-dimethyl-2(1*H*)-pyrazinone (**HOPR-Me**), respectively. They form 3:1 complexes of iron(III) with the *N*-hydroxyamide groups in the acidic region, but the stability constants of their iron(III) complexes are far below that of natural ferrioxamine B.

Siderophores are low-molecular-weight iron-chelating compounds secreted by microorganisms to solubilize iron(III) and transport it into the cell through the membrane. Two common functional groups found in siderophores are hydroxamic acid and catechol, which act as strong bidentate chelators to iron(III).[2] A naturally-occurring siderophore, desferrioxamine B, which has three hydroxamic acid groups per molecule, is now the only choice for clinical use in patients with β-thalassemia. However, desferrioxamine B is orally inactive and possesses a number of side effects.[3] Consequently, much effort has been devoted to the design and synthesis of siderophore analogues in order to develop orally active and nontoxic chelators instead of the natural desferrioxamine B. Recently, *N*-hydroxyamide-containing monoazines such as 1-hydroxy-2(1*H*)-pyridinone (**HOPO**)[4] and 3-hydroxy-2(1*H*)-pyridinone[5] have received much attention owing to their efficient removal of iron(III) from transferrin, oral activity, and no apparent toxicity.[6] On the other hand, no papers concerning the iron(III) complex-forming tendency of *N*-hydroxyamide-containing diazines such as 2-hydroxy-2(1*H*)-pyrimidinone and -pyrazinone have been reported, to the best of our knowledge. These diazines would be expected to have high solubilities in water and low pK_a values by the introduction of the second nitrogen atom into the monoazine ring system.

In this paper, we describe the syntheses of 1-hydroxy-2(1*H*)-pyrimidinone and -pyrazinone and their iron(III) complex-forming tendencies.

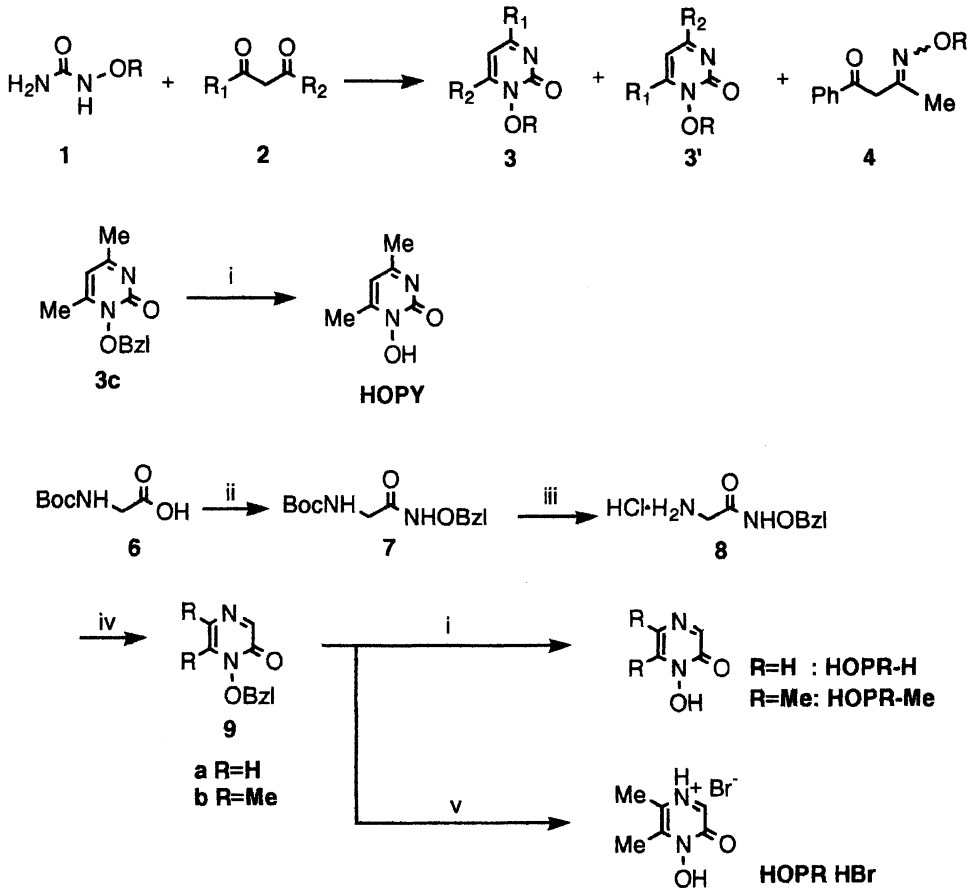
Results and Discussion

Synthesis of 1-Hydroxy-2-(1*H*)-pyrimidinone and -pyrazinone. A benzyl group was used for protection of the hydroxyl group in the *N*-hydroxyamide moiety. Three papers on the synthesis of 1-alkoxy-2-(1*H*)-pyrimidinones have been reported.[7] Interestingly, only 2,4-pentanedione was employed as a β-diketone, which was one of the starting materials. 1-Benzyloxy-2(1*H*)-pyrimidinones (**3a**—**c** and **3′b**) were synthesized by the condensation of *N*-(benzyloxy)urea (**1**, R=Bzl), which was derived form *O*-benzylhydroxylamine and sodium cyanate, with 1,1,3,3-tetraethoxypropane, 4,4-dimethoxy-2-butanone, and 2,4-pentanedione under various acidic conditions (Scheme 1), and the results are summarized in Table 1. The reaction with 4,4-dimethoxy-2-butanone gave a mixture of 1-benzyloxy-4-methyl- (**3b**) and 1-benzyloxy-6-methyl-2(1*H*)-pyrimidinone (**3′b**) which was easily separated by column chromatography on silica gel. The structural assignment of the two isomers **3b** and **3′b** was carried out on the basis of the following data. The 4- and 6-methyl protons of 1-methoxy-4,6-dimethyl-2(1*H*)-pyrimidinone[7b] appeared at $\delta=2.31$ and 2.39, respectively, and $\Delta\delta$ ($\delta_{4-Me}-\delta_{6-Me}$) was only 0.08 ppm, while the $\Delta\delta$ value of 1-benzyloxy-4-methyl- (**3b**) and 1-benzyloxy-6-methyl-2(1*H*)-pyrimidinone (**3′b**) was 0.19 ppm. This difference may be attributable to the anisotropic effect of the benzene ring at the N-1 position as mentioned previously for the ^{1}H NMR spectra of 1-aryl-4,6-dimethyl-2(1*H*)-pyrimidinones.[8a] In contrast, the reaction of *N*-(benzyloxy)urea (**1**, R=Bzl) with 1-phenyl-1,3-butanedione gave 4-methyl pyrimidinone (**3d**) in only a 2% yield, a trace of 6-phenyl-pyrimidinone (**3′d**), and β-(benzyloxyimino)ketone (**4d**) was isolated as a major

Table 1. Reaction of *N*-Alkoxyureas with β-Diketones

Urea **1**	β-Diketone **2**			Yields/%		
R	R_1	R_2	Conditions	**3**	**3′**	**4**
a Bzl	H	H[a)]	10 M HCl/EtOH/r.t.(3 d)	33		0
b Bzl	Me	H[b)]	H_2SO_4/EtOH/reflux (1 h)	44	16	0
c Bzl	Me	Me	H_2SO_4/EtOH/reflux (2 h)	42		0
d Bzl	Ph	Me	H_2SO_4/dry ether/r.t. (2 h)	2	Trace	45
e Me	Ph	Me	6% HCl/EtOH/reflux (28 h)	5	0	28

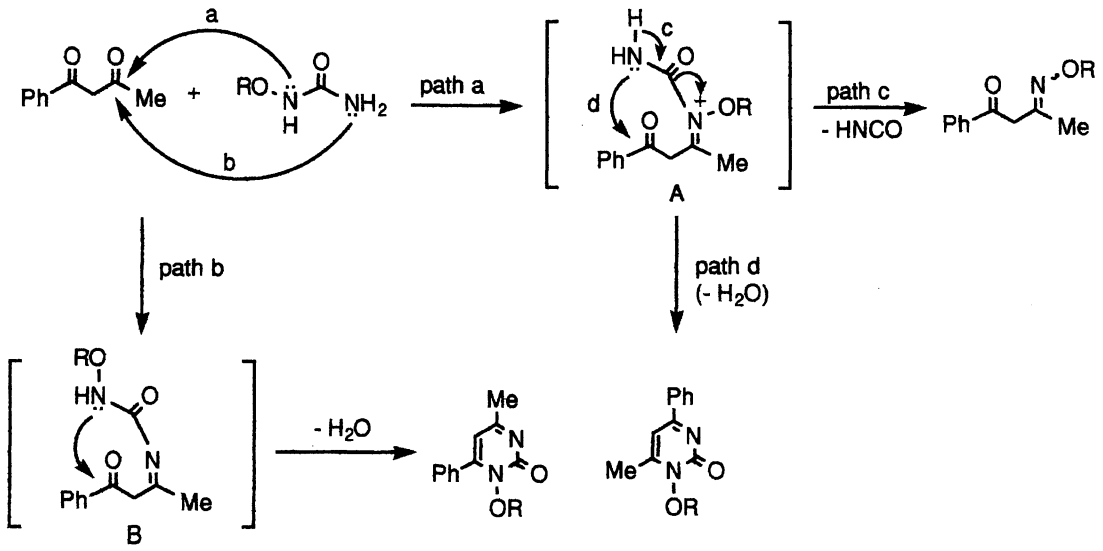
a) 1,1,3,3-Tetraethoxypropane. b) 4,4-Dimethoxy-2-butanone.



Scheme 1. Reagents and conditions: i) H_2/10% Pd-C in MeOH, r.t., 20 min.; ii) Isobutyl chloroformate/Et_3N/H_2NOBzl, −15°C to r.t., overnight; iii) 4 M HCl in dioxane, 0°C, 1 h; iv) Glyoxal for **9a** or 2,3-butanedione for **9b**/5 M NaOH, −30°C to r.t., overnight; v) 30% HBr in AcOH, r.t., 2 h.

product in a 45% yield. The structures of the two isomers **3d** and **3'd** were assigned by means of ^{1}H NMR. 4-Phenyl derivative **3'd** showed a typical benzoyl pattern, and an olefinic proton signal at the C-5 position of **3'd** appeared at a ca. 0.6 ppm lower field than that of 4, 6-dimethyl derivative **3c** attributable to the anisotropic effect of the phenyl group[8b] which is nearly coplanar with the pyrimidinone ring. The structure of **4d** was confirmed by comparison of the spectral data with an authentic sample prepared by the condensation of 1-phenyl-1,3-butanedione with *O*-benzylhydroxylamine in the presence of *p*-toluenesulfonic acid. A similar result was observed in the reaction with *N*-methoxyurea (**1**, R=Me) instead of *N*-(benzyloxy)urea; 3-methoxyimino-1-butanone derivative **4e** was obtained in a 28% yield in addition to 1-methoxy-6-methyl-4-phenyl-2(1*H*)-pyrimidinone (**3e**) in only a 5% yield. A reasonable reaction mechanism is shown in Scheme 2. Two unshared electron pairs of the urea attack the acetyl carbonyl carbon to give intermediates A and B (paths a and b). In the case of path a, the elimination of isocyanic acid from intermediate A affords the 3-(*N*-alkoxy)imino derivative (path c), while an unshared electron pair of nitrogen attacks the benzoyl carbonyl carbon to afford 1-alkoxy-6-methyl-4-phenyl-2(1*H*)-pyrimidinone (path d). In the case of path b, dehydration from intermediate B affords 1-alkoxy-4-methyl-6-phenyl-2(1*H*)-pyrimidinone. It is worth noting that the reaction pathway is dramatically changed by only the displacement of the methyl group by phenyl one on the β-diketone. This difference is explained as follows. In the case of the relatively reactive formyl and acetyl carbons of β-diketones compared to a benzoyl carbon, the reaction mainly proceeds via path d from the intermediate A to give 2(1*H*)-pyridinones. The hydrogenation of 2(1*H*)-pyrimidinone **3c** in the presence of 10% Pd-C under hydrogen atmosphere gave 1-hydroxy-4,6-dimethyl-2(1*H*)-pyrimidinone (**HOPY**) in an 83 % yield.[7b]

The synthetic procedure for 1-hydroxy-2(1*H*)-pyrazinones (**HOPR-H** and **HOPR-Me**) is also depicted in Scheme 1. *N*-(*t*-Butoxycarbonyl)glycine (**6**) was coupled with *O*-benzylhydroxylamine by means of the mixed anhydride method,[9] and the Boc group of compound **7** was removed with 4 M HCl (1 M=1 mol dm^{-3}) in dioxane to give *N*-(benzyloxy)glycinamide hydrochloride (**8**). The condensation of the salt (**8**) with glyoxal and 2,3-butanedione under basic conditions at −30°C afforded 1-benzyloxy- (**9a**) and 1-benzyloxy-5,6-dimeth-



Scheme 2. A reasonable reaction mechanism.

yl-2(1*H*)-pyrazinone (**9b**) in 28 and 53% yields, respectively. The deprotection of compounds **9a** and **9b** with 10% Pd-C in a hydrogen atmosphere gave 1-hydroxy- (**HOPR-H**) and 1-hydroxy-5,6-dimethyl-2(1*H*)-pyrazinone (**HOPR-Me**). The treatment of compound **9b** with 30% HBr in acetic acid[7b] gave the hydrobromide salt (**HOPR-Me HBr**). The high solubility of **HOPY**, **HOPR-H**, and **HOPR-Me** in water is notable.

Measurement of the pK_a Values. The pK_a values of **HOPR-H** and **HOPR-Me** were measured in aqueous solution, and the results are shown in Table 2 together with previously reported values of **HOPY**[7b] and **HOPO**.[4b] The relative acidity decreases in the order of **HOPR-H**>**HOPR-Me**≫**HOPO**>**HOPY**.

Iron(III) Complex Formation. The UV-vis spectra of a 3:1 molar mixture of **HOPR-Me** and iron(III) in aqueous solution under various pH conditions are shown in Fig. 1. The absorption maximum due to the ligand-to-metal charge transfer was observed at 400—500 nm. With an increase in pH in the acidic region, the absorption maximum was blue shifted with an increase of absorbance, reflecting the transformation of the 1:1 complex into a 1:2 and then into a 1:3 complex. At pH 4.0, the λ_{max} and ε values of the **HOPR-Me**–Fe(III) complex were 425 nm and 4237 $dm^3\ mol^{-1}\ cm^{-1}$, respectively. Similar results were obtained for **HOPR-H** (λ_{max}=445 nm and ε=2980 $dm^3\ mol^{-1}\ cm^{-1}$ at pH 2.2) and **HOPY** (λ_{max}=405 nm and ε=3470 $dm^3\ mol^{-1}\ cm^{-1}$ at pH 6.0). These λ_{max} and ε values of the iron(III) complexes are comparable to those of the **HOPO**–Fe(III)=3:1 complex previously reported by Raymond and co-workers,[4b] which indicates that these diazinones form 3:1 iron(III) com-

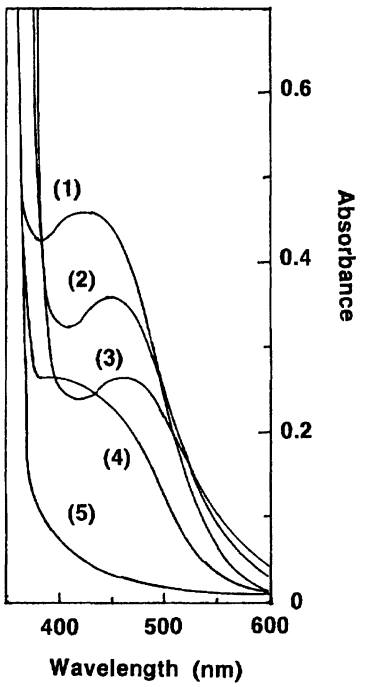


Fig. 1. UV-vis spectra of a [**HOPR**] : [Fe(III)]=3 : 1 mixture in H_2O under various pH conditions: [Fe(III)]=1.0×10^{-4} M. (1) pH 4.0 (ε 4237), (2) pH 2.1, (3) pH 0.8, (4) pH 7.2, (5) pH 9.0.

Table 2. pK_a Values and Stability Constants of Iron(III) Complexes [a]

Ligand	pK_a	log β_3
HOPY	6.1 [b]	22.1
HOPR-H	4.4	18.2
HOPR-Me	4.7	20.2
HOPO	5.8	26.9 [c]
NTA	10.7, 3.07, 3.03 [d]	15.9 [e]

a) Initial concentrations of Fe(ligand)$_3$ and **NTA**, 1.5×10^{-4} M; in acetate buffer (pH 4.0) at 24°C. b) Ref. 7b. c) Ref. 4b. d) Ref. 10. e) log *K*, Ref. 11.

plexes in the acidic region. However, the absorption bands completely disappeared in the basic region (>pH 9.0), suggesting that these complexes are not sufficiently stable to the attack of OH^- ion. For confirmation of the 3:1 complex formation, the absorbance at λ_{max} as a function of the mole ratio of iron(III) to **HOPY**, **HOPR-H**, or **HOPR-Me** was plotted, and the results are shown in Fig. 2 and Table 3. In each case, an intersection was provided nearly at 0.3, indicating the formation of 3:1 complexes of iron(III) with **HOPY**, **HOPR-H**, and **HOPR-Me**, respectively, as shown in Fig. 3.

Stability Constants of the Iron(III) Complexes. The formation of an iron(III) complex with a bidentate ligand is composed of three stepwise reactions as shown in Eq. 1. The log β_3 is obtained by summation of the logarithms of each of the equilibrium constants, K_1, K_2, and K_3 in Eq. 2. In order to estimate the stability constants of the iron(III) complexes of **HOPY**, **HOPR-H**, and **HOPR-Me**, the competitive reaction between nitrilotriacetic acid (**NTA**) and these ligands were carried out using an [Fe(Ligand)$_3$] : [**NTA**]=1.0 : 1.0 mixture.

$$Fe^{3+} + L^- \overset{K_1}{\rightleftharpoons} FeL^{2+} \quad (1)$$

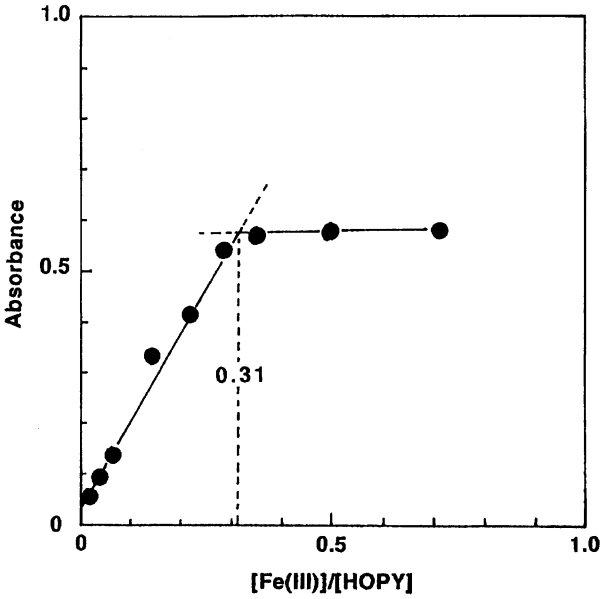


Fig. 2. Plot of absorbance at 405 nm vs. ratio of Fe(III) to **HOPY** in H_2O at pH 6; [**HOPY**]=4.6×10^{-4} M.

Table 3. Data at the Intersection in Mole Ratio Plots for Iron(III) Complex Formation

Ligand	pH	Mole ratio	λ_{max}/nm
HOPY [a]	6	0.31	405
HOPR-H [b]	3	0.31	445
HOPR-Me [c]	4	0.29	425

a) 4.6×10^{-4} M, b) 5.2×10^{-4} M, c) 4.8×10^{-4} M.

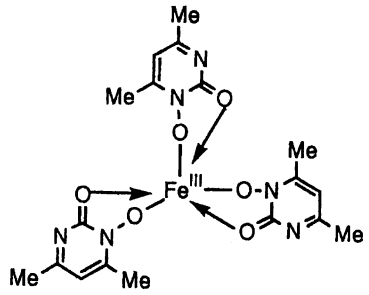


Fig. 3. Possible structure of the **HOPY** : Fe(III)=3 : 1 complex.

$$FeL^{2+} + L^- \overset{K_2}{\rightleftharpoons} FeL_2^+$$
$$FeL_2^+ + L^- \overset{K_3}{\rightleftharpoons} FeL_3$$

$$\log\beta_3 = \log K_1 + \log K_2 + \log K_3 \quad (2)$$

$$Fe^{3+} + 3L^- \overset{K}{\rightleftharpoons} FeL_3 \quad (3)$$

Equation 1 is also expressed by Eq. 3, where the equilibrium constant K means the overall stability constant β_3. The spectral data were analyzed according to Eq. 4,[5]

$$K = [Z/(1-Z)][(E_t - (1-Z)M_t)/(L_t - 3\times ZM_t)^3](\alpha_L^3/\alpha_Y)K_E, \quad (4)$$

where $Z=(A-A_E)/(A_L-A_E)$, A=absorbance of the competing systems at equilibrium, A_E=absorbance of Fe**NTA** in the absence of the sample ligand, and A_L= absorbance of FeL_3 in the absence of **NTA**. α_L and α_Y have the form $1+\Sigma_{i=1}^{3}(H^+)^i/K_{aj}$, and K_{aj} is the three acid dissociation constants of the *N*-hydroxyamide groups of **HOPY**, **HOPR-H**, and **HOPR-Me** or those of **NTA**. E_t, L_t, and M_t are the total analytical concentrations of **NTA**, ligand, and metal ion, respectively, and K_E is the stability constant of Fe**NTA**.[11] The results are summarized in Table 2. The stability constant of Fe(**opy**)$_3$ was greater than that of Fe(**opr-H**)$_3$ or Fe(**opr-Me**)$_3$. These stability constants are close to that of the 4-hydroxy-2(1*H*)-pyridinone–Fe(III)=3 : 1 complex (log β_3=21),[12] but they are far below those of Fe(**opo**)$_3$[4b] and of the natural siderophore, ferrioxamine B (log K=30.5).[13]

Experimental

Melting points were recorded on a Mel-Temp apparatus in open capillaries and are uncorrected. IR spectra were recorded on a JASCO A-100 Infrared Spectrophotometer and UV-vis spectra were recorded on a JASCO Ubest-50 Spectrophotometer. ^{1}H NMR spectra were recorded on JEOL JNM-PMX60 and JEOL GX-270 NMR Spectrometers in $CDCl_3$ and DMSO-d_6 and are reported in ppm (δ) downfield from internal Me_4Si. In the case of D_2O, 3-trimethylsilyl-1-propanesulfonic acid sodium salt was used as an internal standard. Thin-layer chromatography (TLC) analyses were performed on silica gel 60F-254 with a 0.2 mm layer thickness. Column chromatography was carried out with Merck Kieselgel 60 (230—400 mesh). High-performance liquid chromatography (HPLC) was carried out with

a JASCO 880-PU and an 875-UV equipped with a JASCO 807-IT integrator by using a column packed with Finepak SIL $C_{12}S$. pK_a values were determined from data measured on a Horiba F-12 pH meter. Combustion analyses were performed on a Yanaco MT-3 CHN CORDER. *N*-(Benzyloxy)urea (**1**, R=Bzl)[15] and *N*-methoxyurea (**1**, R=Me)[16] were prepared according to the literature methods.

1-Benzyloxy-2(1*H*)-pyrimidinone (3a). A mixture of *N*-(benzyloxy)urea (500 mg, 3 mmol), 1,1,3,3-tetraethoxypropane (525 mg, 2.4 mmol), EtOH (3 ml), and 10 M hydrochloric acid (0.6 ml) was stirred for 3 d at room temperature. After evaporation of the solvent, the residue was dissolved in water. The aqueous solution was adjusted to pH 11 with an aqueous NaOH solution, extracted with $CHCl_3$ (50 ml×3), and dried over anhydrous $MgSO_4$. The crude product was purified by column chromatography on silica gel with a $CHCl_3$–acetone–EtOH (100:20:4) mixture to give the pure product (**3a**), mp 86—90°C, 150 mg (33%). IR (KBr) 1670, 740, and 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ=5.32 (2H, s, CH_2), 6.04 (1H, dd, J=4 and 6 Hz, 5-H), 7.36 (5H, s, Ph), 7.40 (1H, dd, J=2 and 6 Hz, 6-H), and 8.45 (1H, dd, J=2 and 4 Hz, 4-H). Found: C, 62.64; H, 5.27; N, 13.05%. Calcd for $C_{11}H_{10}N_2O_2 \cdot 0.5H_2O$: C, 62.56; H, 5.21; N, 13.27%.

1-Benzyloxy-4-methyl- (3b) and 1-Benzyloxy-6-methyl-2(1*H*)-pyrimidinone (3′b). To a solution of *N*-(benzyloxy)urea (700 mg, 4.2 mmol) in abs EtOH (7 ml) was added 4,4-dimethoxy-2-butanone (560 mg, 4.2 mmol) and concd H_2SO_4 (0.5 ml) at room temperature. The reaction mixture was refluxed for 1 h. After evaporation of the solvent, H_2O was added to the residue. The aqueous solution was adjusted to pH 11 with a saturated $NaHCO_3$ solution, extracted with CH_2Cl_2 (50 ml×3), washed with brine (50 ml), and dried over anhydrous $MgSO_4$. The crude product was chromatographed on silica gel with a $CHCl_3$–acetone–EtOH (100:20:4) mixture. The first fraction (R_f=0.39) was 1-benzyloxy-4-methyl-2(1*H*)-pyrimidinone (**3b**), mp 135—138°C, 400 mg (44%). IR (KBr) 1650, 745, and 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.35 (3H, s, Me), 5.30 (2H, s, CH_2), 5.95 (1H, d, J=7 Hz, 5-H), 7.28 (1H, d, J=7 Hz, 6-H), and 7.34 (5H, s, Ph). The second fraction (R_f=0.31) was 1-benzyloxy-6-methyl-2(1*H*)-pyrimidinone (**3′b**), mp 136—139°C, 145 mg (16%). IR (KBr) 1650, 740, and 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.16 (3H, s, Me), 5.31 (2H, s, CH_2), 6.03 (1H, d, J=5 Hz, 5-H), 7.40 (5H, s, Ph), and 8.31 (1H, d, J=5 Hz, 4-H). Found (a mixture of **3b** and **3′b**): C, 66.37; H, 5.72; N, 12.58%. Calcd for $C_{12}H_{12}N_2O_2 \cdot 0.1H_2O$: C, 66.10; H, 5.64; N, 12.85%.

1- Benzyloxy- 4, 6- dimethyl- 2(1*H*)- pyrimidinone (3c). The reaction of *N*-(benzyloxy)urea with 2,4-pentanedione gave the product (**3c**) in a 42% yield, mp 130—131°C (lit,[14] mp 131—132°C). ^1H NMR ($CDCl_3$) δ=2.18 (3H, s, Me), 2.31 (3H, s, Me), 5.32 (2H, s, CH_2), 5.92 (1H, s, 5-H), and 7.45 (5H, m, Ph).

1-Benzyloxy-4-methyl-6-phenyl- (3d) and 1-Benzyloxy-6-methyl-4-phenyl-2(1*H*)-pyrimidinone (3′d), and 3-Benzyloxyimino-1-phenyl-1-butanone (4d). To a solution of 1-phenyl-1,3-butanedione (1.45 g, 9 mmol) in dry ether (15 ml) was added *N*-(benzyloxy)urea (1.49 g, 9 mmol) and concd H_2SO_4 (1 ml). After stirring for 19 h at room temperature, the solvent was evaporated, and H_2O (30 ml) was added to the residue. The aqueous solution was adjusted to pH 11 with an aqueous NaOH solution, extracted with CH_2Cl_2 (30 ml×4), and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel with a $CHCl_3$–acetone–EtOH (100:20:1) mixture. The first fraction (R_f=0.7) was 3-benzyloxyimino-1-phenyl-1-butanone (**4d**), 1.07 g (45%). IR (neat) 1690, 755, and 700 cm^{-1}; ^1H NMR ($CDCl_3$, a mixture of *E* and *Z*) δ=1.92 and 1.94 (3H, s, Me), 3.85 and 4.03 (2H, s, CH_2), 5.12 and 5.15 (2H, s, OCH_2), 7.25—7.65 (8H, m, Ph), and 7.8—8.1 (2H, m, Ph). Found: C, 75.09; H, 6.07; N, 4.93%. Calcd for $C_{17}H_{17}NO_2 \cdot 0.2H_2O$: C, 75.39; H, 6.43; N, 5.17%. Compound **4d** was identical with the product which was obtained from the reaction of 1-phenyl-1,3-butanedione with *O*-benzylhydroxylamine in the presence of *p*-toluenesulfonic acid in benzene under reflux. A trace of the second fraction (R_f=0.51) was 1-benzyloxy-6-methyl-4-phenyl-2(1*H*)-pyrimidinone (**3′d**); ^1H NMR ($CDCl_3$) δ=2.21 (3H, s, Me), 5.38 (2H, s, CH_2), 6.50 (s, 1H, CH), and 7.30—7.55 (10H, m, 2Ph). The third fraction (R_f=0.26) was 1-benzyloxy-4-methyl-6-phenyl-2(1*H*)-pyrimidinone (**3d**), 0.05 g (2%), mp 129—130°C. IR (KBr) 1660, 750, and 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.40 (3H, s, Me), 4.96 (2H, s, CH_2), 6.03 (1H, s, 5-H), and 6.6—7.65 (10H, m, 2Ph). Found: C, 72.57; H, 5.89; N, 9.30%. Calcd for $C_{18}H_{16}N_2O_2 \cdot 0.3H_2O$: C, 72.61; H, 5.62; N, 9.41%.

1- Methoxy- 6- methyl- 4- phenyl- 2(1*H*)- pyrimidinone (3e) and 3-Methoxyimino-1-phenyl-1-butanone (4e). A mixture of *N*-Methoxyurea (2.4 g, 0.03 mol) and 1-phenyl-1,3-butanedione in a 6% ethanolic HCl solution (20 ml) was refluxed for 28 h. The reaction mixture was adjusted to pH 11 with an aqueous NaOH solution and extracted with CH_2Cl_2 (50 ml×3). The organic layer was washed with brine (50 ml) and dried over anhydrous $MgSO_4$. The products were chromatographed on silica gel with a hexane–AcOEt (9:1) mixture. The first fraction (R_f=0.18) was 3-methoxyimino-1-phenyl-1-butanone (**4e**), 570 mg (28%), IR (neat) 1680, 750, and 685 cm^{-1}; ^1H NMR ($CDCl_3$, a mixture of *E* and *Z*) δ=1.94 and 1.96 (3H, s, Me), 3.85 (3H, s, OMe), 3.80 and 4.03 (2H, s, CH_2), 7.25—7.65 (3H, m, Ph), and 7.83—8.06 (2H, m, Ph). Compound **4e** was identical with the product which was obtained from the reaction of 1-phenyl-1,3-butanedione and *O*-methylhydroxylamine in the presence of *p*-toluenesulfonic acid in benzene under reflux. Further chromatography by changing the eluent to a $CHCl_3$–acetone–EtOH (100:10:2) mixture afforded 1-methoxy-6-methyl-4-phenyl-2(1*H*)-pyrimidinone (**3e**), 95 mg (5%). ^1H NMR ($CDCl_3$) δ=2.5 (3H, s, Me), 4.12 (3H, s, OMe), 6.6 (1H, s, 5-H), 7.3—7.7 (3H, m, Ph), and 7.8—8.2 (2H, m, Ph). Found: C, 55.60; H, 6.56; N, 11.46%. Calcd for $C_{12}H_{12}N_2O_2$: C, 55.55; H, 6.53; N, 10.79%.

1-Hydroxy-4,6-dimethyl-2(1*H*)-pyrimidinone (HOPY). Compound **3c** (460 mg, 2 mmol) was hydrogenated in abs MeOH (20 ml) with 10% Pd-C (80 mg) for 20 min. After removal of the catalyst, the product (**HOPY**) was obtained by recrystallization from EtOH, mp 179—181°C, 230 mg (83%). IR (KBr) 3350 (broad) and 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.30 (3H, s, 4-Me), 2.45 (3H, s, 6-Me), 6.15 (1H, s, 5-H), and 8.30 (1H, br s, OH). Found: C, 51.29; H, 5.72; N, 19.94%. Calcd for $C_6H_{12}N_2O_2 \cdot 0.5H_2O$: C, 51.10; H, 5.75; N, 19.87%.

***N*-Benzyloxy-N^{α}-(*t*-butoxycarbonyl)glycinamide (7).** To a mixture of *N*-(*t*-butoxycarbonyl)glycine (**6**, 3.97

g, 23 mmol) and Et_3N (2.38 g, 24 mmol) in THF (40 ml) was added dropwise a solution of isobutyl chloroformate (3.28 g, 24 mmol) in THF (20 ml) at −17°C. The reaction temperature was kept for 15 min at −15°C, and then *O*-benzylhydroxylamine (2.5 g, 23 mmol) in THF (10 ml) was added to the mixture. The reaction mixture was kept at −15°C for 3 h and at room temperature overnight, and the resulting Et_3N HCl was then filtered. After evaporation of the solvent, the residue was dissolved in AcOEt (200 ml). The organic phase was washed successively with a 5% aqueous $NaHCO_3$ (100 ml) solution, 5% HCl (100 ml), and H_2O (100 ml), and then dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel with a hexane–AcOEt (1:1) mixture to give the pure product (**7**) as a colorless oil, 4.36 g (77%). IR (neat) 3400, 1690, 740, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.45 (9H, s, Me_3C), 3.60 (2H, m, CH_2), 4.80 (2H, s, OCH_2), 5.75 (1H, br s, $NHCO_2$), and 7.40 (6H, s, NH–O and Ph). Found: C, 58.08; H, 7.29; N, 9.34%. Calcd for $C_{14}H_{20}N_2O_4 \cdot 0.7H_2O$: C, 57.96; H, 7.43; N, 9.66%.

***N*-(Benzyloxy)glycinamide Hydrochloride (8).** 5.8 M HCl in dioxane (26 ml) was added to a solution of compound **7** (8.41 g, 30 mmol) in dry dioxane (12 ml) with stirring in an ice bath. The reaction mixture was stirred for 1 h, and the solvent was then removed under reduced pressure. A small amount of abs EtOH was added to the residue and then evaporated to remove the HCl–dioxane completely. The resulting HCl salt (**8**) was washed with dry ether and used in the next reaction without further purification, 5.4 g (83%).

1-Benzyloxy-2(1*H*)-pyrazinone (9a). To a solution of the HCl salt (**8**, 10.6 g, 0.05 mol) in MeOH–H_2O (1:1, 80 ml) was added glyoxal (7.5 g, 0.05 mol) in a Dry Ice–acetone bath (−30°C). The reaction mixture was adjusted to pH 8 with a 2 M aqueous NaOH solution and then stirred overnight at room temperature. After evaporation of the solvent, the residue was dissolved in $CHCl_3$ (100 ml). The organic phase was washed with H_2O (20 ml), dried over anhydrous $MgSO_4$, and then evaporated. The crude product was purified by column chromatography on silica gel with an AcOEt–hexane (1:1) mixture to give the pure product (**9a**), mp 88—90°C, 2.9 g (28%). IR (KBr) 1670 cm^{-1}; ^1H HMR ($CDCl_3$) δ=5.32 (2H, s, CH_2), 6.98 (1H, d, J=2 Hz, 5-H), 7.10 (1H, d J=2 Hz, 6-H), 7.39 (5H, m, Ph), and 8.29 (1H, s, 3-H). Found: C, 65.58; H, 5.36; N, 13.92%. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86%.

1-Benzyloxy-5,6-dimethyl-2(1*H*)-pyrazinone (9b). Similar reaction of the HCl salt (**8**) (3.1 g, 14.3 mmol) with 2,3-butanedione (1.5 g, 17 mmol) afforded the product (**9b**), mp 118—121°C, 1.8 g (53%). IR (KBr) 1650, 740, and 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.18 (3H, s, 5-Me), 2.27 (3H, s, 6-Me), 5.29 (2H, s, CH_2), 7.45 (5H, s, Ph), and 8.14 (1H, s, 3-H). Found: C, 67.75; H, 6.17; N, 11.84%. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17%.

1-Hydroxy-2(1*H*)-pyrazinone (HOPR-H). Compound **9a** (500 mg, 2.5 mmol) was hydrogenated in abs MeOH (15 ml) with 10% Pd-C (60 mg) for 20 min by the same procedure used for **HOPY**. The product (**HOPR-H**) was obtained by column chromatography on silica gel with a $CHCl_3$–MeOH (6:1) mixture, mp 168—170°C (lit,[17] mp 166—168°C), 194 mg (70%). IR (KBr) 3420—3310 and 1630 cm^{-1}; ^1H NMR (D_2O) δ=7.58 (1H, d, J=5.8 Hz, 5-H), 8.06 (1H, d, J=5.8 Hz, 6-H), and 8.10 ppm (1H, s, 3-H).

1-Hydroxy-5,6-dimethyl-2(1*H*)-pyrazinone (HOPR-Me). Compound **9b** (345 mg, 1.5 mmol) was hydrogenated in abs MeOH (20 ml) with 10% Pd-C (60 mg) for 20 min. The product (**HOPR-Me**) was obtained by recrystallization from an EtOH–hexane mixture, mp 147—149°C (lit,[7c] mp 145—149°C), 160 mg (76%).

1-Hydroxy-5,6-dimethyl-2(1*H*)-pyrazinone Hydrobromide (HOPR-Me HBr). A solution of compound **9b** (143 mg, 0.62 mmol) in 30 % HBr in acetic acid (3 ml) was stirred under reflux for 10 min. To the mixture was added Et_2O (15 ml). The resulting precipitate was collected by filtration, washed with Et_2O, and then dried in vacuo to give a pale red solid, 111 mg (81%). ^1H NMR (D_2O) δ=2.47 (3H, s, Me), 2.48 (3H, s, Me), and 7.71 (1H, s, 3-H). Found: C, 30.12; H, 4.85; N, 11.65%. Calcd for $C_6H_9BrN_2O_2 \cdot H_2O$: C, 30.14; H, 4.65; N, 11.72%.

Measurement of the pK_a value: A Typical Example. HOPR-Me (47 mg) was dissolved in deionized water (30 ml). The pH of the solution was measured after every 0.1 ml-addition during titration with a 0.08 M NaOH solution at room temperature under an argon atmosphere. The pK_a was calculated from the pH at the midpoint of neutralization.

Measurement of the UV-vis spectra of Iron(III) Complexes: A Typical Example. The pH of an aqueous solution of [**HOPR-Me**] : [Fe(III)]=3 : 1 mixture ([Fe(III)]=1.04×10^{-4} M which was prepared from iron(III) nitrate solution) was adjusted to an appropriate value with 0.01 or 0.1 M NaOH and 0.01 or 0.1 M HNO_3 solutions. The UV-vis spectra were measured at room temperature.

Iron(III)-Binding Ratio: A Typical Example. To an aqueous solution of **HOPY** (9.28×10^{-3} M, 0.5 ml) was added an appropriate amount of a standarized aqueous iron(III) nitrate solution (3.28×10^{-4} M). The pH of the solution was adjusted to 6.0 with 0.01 or 0.1 M NaOH and then diluted to 10.0 ml. After 1 h, the visible spectrum of each solution was measured. The absorbance at 405 nm was plotted as a function of the mole ratio of iron(III) to **HOPY**.

Iron(III)-Exchange reaction: A Typical Example. A solution of **HOPR-Me** (9×10^{-3} M, 1.0 ml), Fe(III) (3×10^{-3} M, 1.0 ml), and KNO_3 (0.4 M, 1.0 ml) was adjusted to pH 4.0 with aqueous NaOH before dilution to 1.0 ml with an acetate buffer solution, [Fe(**opr-Me**)$_3$]=3×10^{-4} M. An **NTA** solution was prepared by dilution of 1.0 ml of an aqueous **NTA** stock solution (3.0×10^{-3} M) and 1.0 ml of an aqueous KNO_3 solution (0.4 M) to 10.0 ml with an acetate buffer solution. The reaction was initiated by putting 1.0 ml of the **NTA** solution into 1.0 ml of the Fe(**opr-Me**)$_3$ solution. The spectral change was followed by observing the decrease in absorbance at 425 nm in a 10 mm quartz cell. The sample solution was maintained at 24°C for a week to attain equilibrium. The stability constant K for Fe(**opr-Me**)$_3$ was calculated according to Eq. 4.

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