a white solid: mp 88–89 °C; IR (CCl_4) 3020, 2960, 1466, 1295 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.72 (m, 4 H), 2.08–1.32 (series of m, 10 H), 0.68 (br d, J = 8.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$) 58.6 (s), 41.1 (d), 38.9 (t), 27.1 (t) ppm; mass spectrum, m/e calcd 176.1201, obsd 176.1206.

Anal. Calcd for $C_{12}H_{16}O$: C, 74.97; H, 8.39. Found: C, 74.76; H, 8.36.

Further elution with 45% ethyl acetate in hexane yielded 1.62 g (59%) of diketone **26**.

Methylene Blue-Sensitized Photooxygenation of 4. A solution of **4** (910 mg, 5.69 mmol) and methylene blue (110 mg, 2.7 mmol) in 110 mL of dry acetonitrile (distilled from CaH_2) was irradiated in the above manner for 65 h while oxygen was continuously introduced through a frit in the base of the reaction vessel. The solvent was evaporated, and a portion of the residue was taken up in $CDCl_3$ and its ^1H and ^{13} NMR spectra were recorded. The reaction was found to be 30% complete with diketone **26** present as the only product. TLC analysis also indicated the absence of epoxide. The combined residue was dissolved in dichloromethane (5 mL) and filtered through silica gel (15 g) with pentane to remove unreacted **4** (485 mg). Further elution with 70% ethyl acetate in hexane afforded 204 mg of **26** as a white solid, in all respects identical with authentic material.

Tetraphenylporphin-Sensitized Photooxygenation of 4. A solution of **4** (830 mg, 5.19 mmol) and tetraphenylporphin (115 mg) in 100 mL of 1,2-dichloroethane (distilled from Na_2CO_3) was irradiated in the predescribed manner for 76 h. The solvent was evaporated, and the spectra of the residue were recorded. These data and the subsequent isolation only of **26** served to indicate that only diketone had been formed.

Acknowledgment. We are grateful to the National Cancer Institute (Grant CA-12115) for financial support and to Dr. Richard Eizember (Eli Lilly Co.) for the field desorption mass spectrum of **25**.

Dioxygen Transfer from 4a-Hydroperoxyflavin Anion. 3. Oxygen Transfer to the 3-Position of Substituted Indoles

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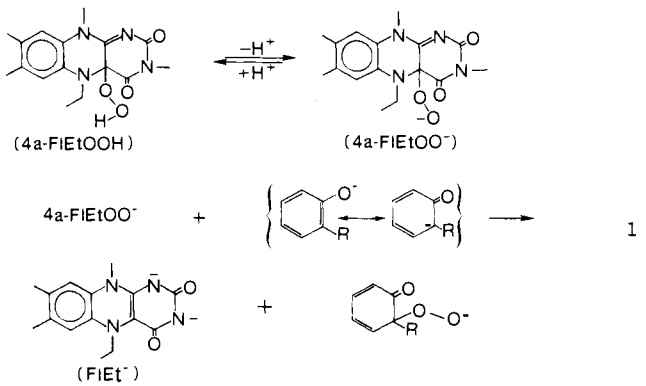
Contribution from the Department of Chemistry, University of California at Santa Barbara, Santa Barbara, California 93106. *Received May 27, 1980*

Abstract: The 4a-hydroperoxyflavin anion (4a-$FlEtO_2^-$) spontaneously decays with a rate constant of 4.2×10^{-2} s^{-1} (*tert*-butyl alcohol, 30 °C). In the presence of the anions of 2,3-dimethylindole (**1a**$^-$) and 5-methoxy-3-methyl-2-phenylindole (**2a**$^-$) the pseudo-first-order rate constants (k_{obsd}) for disappearance of 4a-$FlEtO_2^-$ increase. Plots of $1/k_{obsd}$ vs. $1/[\mathbf{1a}^-]$ and $1/[\mathbf{2a}^-]$ are linear, and the limiting rate constants for 4a-$FlEtO_2^-$ disappearance at high values of $[\mathbf{1a}^-]$ and $[\mathbf{2a}^-]$ were calculated, from the intercepts, to be 0.33 and 0.37 s^{-1}, respectively. In a previous study the limiting rate constants were 0.36 and 0.37 s^{-1} when the anions of 2,6-di-*tert*-butyl-4-methylphenol and 3,5-di-*tert*-butylcatechol were employed. This limiting rate constant of 0.36 s^{-1} is assigned as the forward rate for the conversion of 4a-$FlEtO_2^-$ (in an endothermic equilibrium) to a species (X) which, on being trapped by substrate anion, transfers a peroxy moiety to the trapping agent. The yields of the dioxygen-transfer products formed from **1a**$^-$ and **2a**$^-$ are 24% and 41%, respectively. The singlet oxygen-trapping agents, 2,5-dimethylfuran and tetramethylethylene, do not increase the rate of disappearance of 4a-$FlEtO_2^-$ and, therefore, do not trap X. Species X cannot be solvent separated $^1O_2$ and $FlEt^-$. Moreover, the rate constants for reaction of triplet oxygen with **1a**$^-$ and **2a**$^-$ are 10^3–10^4 too small for X to be solvent separated $^3O_2$ and $FlEt^-$. The possibility of X being solvent separated $FlEt\cdot$ and $O_2^-\cdot$ is considered. Possible identities for X include a complex of an oxygen and a flavin species and a 4a,10a-dioxetane of reduced flavin.

In parts 1 and 2 of the present study, it was established that the 4a-hydroperoxyflavin anion (4a-$FlEtOO^-$) transfers a dioxygen species to a number of ambident phenolate anions (eq 1).[1,2] The



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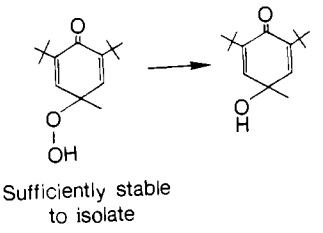
products realized from the peroxidized substrate are very dependent upon their structure (for example, eq 2–4). Regardless of the nature of the phenolate anion employed, dioxygen transfer proceeds only after the conversion of 4a-$FlEtO_2^-$ to an intermediate



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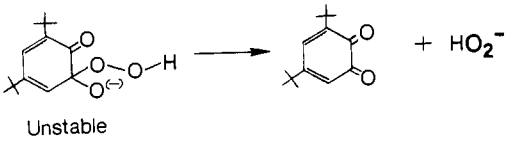

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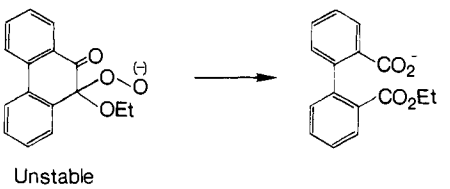


4

(1) Kemal, C.; Bruice, T. C. *J. Am. Chem. Soc.* **1979**, *101*, 1635.
(2) Muto, S.; Bruice, T. C. *J. Am. Chem. Soc.* **1980**, *102*, 1465.

0002-7863/80/1502-7559$01.00/0

(X) whose formation is rate-determining at high substrate (ArO^-) concentration (eq 5).

$$4a\text{-}FlEtO_2^- \underset{k_2}{\overset{k_1}{\rightleftharpoons}} X \xrightarrow{k_3[ArO^-]} FlEt^- + O{=}Ar{-}OO^- \quad (5)$$

It is our goal to elucidate the mechanism of dioxygen transfer from 4a-FlEtOO$^-$ and to determine the extent to which the reaction may be extended. In this study we deal with dioxygen transfer to the substituted indoles **1a** and **2a**.

Experimental Section

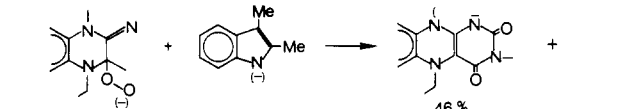
General Data. All melting points are measured on a Thomas Model 40 micro hot-stage apparatus and were uncorrected. Proton NMR spectra were recorded on a Varian T60 spectrometer using Me_4Si as an internal reference. Ultraviolet and visible measurements were performed on a Cary 118 spectrophotometer thermostated at 30.0 ± 0.2 °C. Rapid spectral changes were followed with a Durham stopped-flow spectrometer under an oxygen-free N_2 atmosphere.

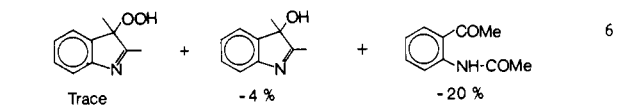
Materials. 2,3-Dimethylindole (1a) and 2-acetamidoacetophenone (1d) were obtained from Aldrich Chemical Co. and were used after recrystallization from methanol. 2,5-Dimethylfuran (**3**) and tetramethylethylene (**4**) were distilled under N_2 and deoxygenated by freeze–pump–thaw technique. *tert*-Butyl alcohol was also deoxygenated (freeze–pump–thaw) after distillation over CaH_2 under N_2 and kept under dry N_2 atmosphere. ***N*⁵-Ethyl-4a-hydroperoxy-3-methyllumiflavin (4a-FlEtOOH)** was synthesized in 90–96% purity (λ_{max} = 370 nm (ϵ = 7000 M^{-1} cm^{-1})).[3] **3-Hydroperoxy-2,3-dimethylindolenine (1b)** was prepared by autoxidation of **1a** initiated by benzoyl peroxide in hexane.[4] Recrystallization from ethyl acetate–hexane gave the hydroperoxide in a yield of 21%, mp 108 °C dec (lit.[4] 113 °C), soluble in both HCl and KOH aqueous solutions. The purity of **1b** (90%) was determined by conventional iodometric titration. UV (λ_{max}, *t*-BuOH): 280 sh (ϵ 3000), 258 nm (3700 M^{-1} cm^{-1}). **3-Hydroxy-2,3-dimethylindolenine (1c)** was synthesized from **1b** by the method of Beer et al.[4] Recrystallization from ethyl acetate–hexane provided colorless crystals, mp 141–142 °C (lit. 143–144 °C), soluble in HCl aqueous solution but not in KOH solution. UV (λ_{max}, *t*-BuOH): 278 sh (ϵ 2800), 256 nm (3600 M^{-1} cm^{-1}). NMR ($CDCl_3$): δ 1.39 (3 H, s, 3-Me), 1.87 (3 H, s, 2-Me), 5.18 (1 H, s, OH), 6.8–7.5 (4 H, m, aromatic protons). **5-Methoxy-3-methyl-2-phenylindole (2a)** was synthesized from *p*-methoxyphenylhydrazine hydrochloride (7.0 g, 0.04 mol) and propiophenone (5.4 g, 0.04 mol) in ethanol. Distillation and recrystallization from methanol three times gave colorless needles (yield 1.9 g (20%), mp 119–120 °C (lit.[4] 120 °C)). UV (λ_{max}, *t*-BuOH): 226 sh (ϵ 29 000), 314 nm (22 000 M^{-1} cm^{-1}). NMR ($CDCl_3$): δ 2.43 (3 H, s, Me), 3.87 (3 H, s, OMe), δ 6.70–7.60 (9 H, m, aromatic protons and >NH). **3-Hydroperoxy-5-methoxy-3-methyl-2-phenylindolenine (2b)** was prepared from **2a** in a manner similar to that employed with **1b**. Recrystallization from benzene–hexane gave yellow prisms in a yield of 80%; mp 149–150 °C dec (lit. 148–150 °C dec). UV (λ_{max}, *t*-BuOH): 242 (ϵ 16 300), 302 (9400), 339 nm (12 600 M^{-1} cm^{-1}). NMR (C_6D_6) δ 1.34 (3 H, s, Me), 3.31 (3 H, s, OMe), 6.60–7.80 (8 H, m, aromatic protons). **3-Hydroxy-5-methoxy-3-methyl-2-phenylindolenine (2c)**: A solution of **2b** (200 mg, 0.74 mmol) in benzene was treated with excess triphenylphosphine at room temperature. After being stirred for 2 h, the solution was chromatographed on silica gel by using chloroform–ethyl acetate (3:1) as an eluant. Unreacted triphenylphosphine was eluted before the product. Evaporation of the solvent gave a yellow solid which was recrystallized from benzene–hexane: yield 120 mg (64%); mp 181–182 °C; UV (λ_{max}, *t*-BuOH) 244 (ϵ 14 300), 303 (8100), 339 nm (ϵ 12 100 M^{-1} cm^{-1}); NMR (CD_3COCD_3) δ 1.61 (3 H, s, Me), 3.83 (3 H, s, OMe), 5.10 (1 H, br s, OH), 6.80–7.65 (8 H, m, aromatic protons). **2-Benzamido-5-methoxyacetophenone (2d)** was synthesized from **2b** according to the method of Beer.[4] Recrystallization from aqueous MeOH gave yellow needles in a yield of 78%; mp 116–117 °C (lit.[4] 116 °C). UV (λ_{max}, *t*-BuOH): 227 (ϵ 23 500), 283 (11 100), 362 nm (6000 M^{-1} cm^{-1}). NMR ($CDCl_3$): δ 2.67 (3 H, s, Me), 3.83 (3 H, s, OMe), 6.90–8.90 (9 H, m, arromatic protons and >NH).

Procedure for the Determination of Reaction Products. All reactions were carried out at 30 °C under anaerobic conditions. Freshly recrystallized indoles (**1a** or **2a**) and *t*-BuO^-K^+ were dissolved in *t*-BuOH. A portion (10 mL) of the solution was added to a solid of 4a-FlEtOOH (typical concentrations: [indole] = 9 × 10^{-3} M, [*t*-BuO^-K^+] = 2 × 10^{-2} M, and [4a-FlEtOOH] = 2.5 × 10^{-4} M). After the mixture was stirred for 10 min, 0.02 mL of deoxygenated glacial acetic acid was added. The yield of $FlEt^-$ was determined as follows. A portion (2 mL) of the acidified solution was transferred to a Thunberg cuvette and mixed with a solution of 4-hydroxy-2,2,6,6-tetramethylpiperidinyl-1-oxy which is known to convert FlEtH to FlEt·.[5] The concentration of FlEt· (=FlEtH) was determined by its absorbence at 640 nm (ϵ 5000 M^{-1} cm^{-1}). The yield of products from indoles was determined by high-pressure LC. The LC analysis was carried out with a DuPont Instrument reverse phase column (Lichrosorb 5 *RP* 8, 25 cm, 4.6 mm), using acetonitrile–water, 30:60 (v/v) at a flow rate 0.7 mL/min and 40:60 (v/v) at a flow rate 1.3 mL/min, as solvent for **1a** and **2a** products, respectively. The products from **1a** and **2a** were monitored at 257 nm (λ_{max} of **1b,c**) and 242 nm (λ_{max} of **2b–d**), respectively. Retention times of authentic **1a**, **1b**, **1c** and **1d** were 80.5, 9.8, 8.6, and 16.6 min, respectively, and those of authentic **2a**, **2b**, **2c**, and **2d** were 52.3, 11.9, 10.1, and 25.2 min, respectively.

Results

All kinetic and product studies were carried out in dry and oxygen-free *tert*-butyl alcohol under an inert (N_2) and dry atmosphere.[1,2] Temperatures were maintained at 30 °C. Product analysis was carried out on reaction mixtures containing the *N*⁵-ethyl-3-methyl-4a-hydroperoxylumiflavin (4a-$FlEtO_2H$) at 3 × 10^{-4} M and indoles **1a** and **2a** (both at 9 × 10^{-3} M) in the presence of sufficient potassium *tert*-butoxide to convert the indoles into their anionic forms (9 × 10^{-3} M). The reaction mixtures were quenched by acidification after 10 min and products determined (Experimental Section). From the rate constant for spontaneous decomposition of 4a-$FlEtO_2^-$ (4.2 × 10^{-2} s^{-1}), and the values of the pseudo-first-order rate constants for the disappearance of 4a-$FlEtO_2^-$ in the presence of the given concentrations of **1a** (1.8 × 10^{-1} s^{-1}) and **2a** (1.5 × 10^{-1} s^{-1}), it follows that the partitioning of 4a-$FlEtO_2^-$ between spontaneous decomposition and reaction





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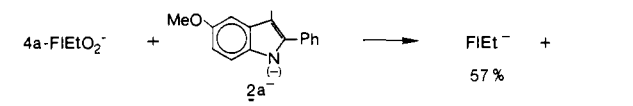

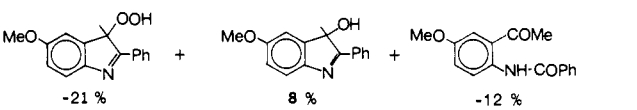

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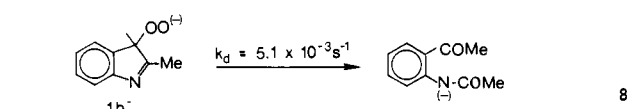
with indoles is 23:77 for **1a** and 28:72 for **2a**. The adjusted yields of products are provided in eq 6 and 7. Since **1c** and **1d** might logically be considered to arise from **1b** and **2c** and **2d** to be formed



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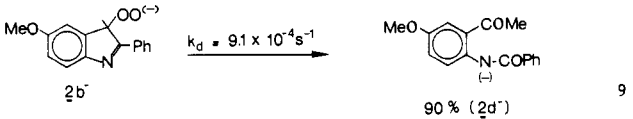

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(3) Kemal, C.; Bruice, T. C. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 996. Kemal, C.; Chan, T. W.; Bruice, T. C. *Ibid.* **1977**, *74*, 405.
(4) Beer, R. J. S.; Donavanik, T.; Robertson, A. *J. Chem. Soc.* **1954**, 4139.
(5) Chan, T. W.; Bruice, T. C. *J. Am. Chem. Soc.* **1977**, *99*, 7287.

from **2b**, both the rate constants for decomposition of $\mathbf{1b}^-$ and $\mathbf{2b}^-$ and percentage yields of **1d** and **2d** were determined. Reactions were initiated by mixing solutions of **1b** and **2b** (final concentrations 1.34×10^{-4} M) with a potassium *tert*-butoxide solution (final concentration 5.47×10^{-3} M). The results are shown in eq 8 and 9. The presence of reduced flavin and traces of water had little influence upon either the rate constants or product yields accompanying the decomposition of $\mathbf{1b}^-$ and $\mathbf{2b}^-$ (eq 10).

$$\mathbf{2b}^- \xrightarrow[\text{presence of FlEtH } (1.10 \times 10^{-4}\text{ M})]{k_d = 1.0 \times 10^{-3}\text{ s}^{-1}} \mathbf{2d}^- \text{ (95\%)}$$

$$\xrightarrow[\text{presence of 0.5\% (v/v) } H_2O]{k_d = 7.9 \times 10^{-4}\text{ s}^{-1}} \mathbf{2d}^- \text{ (93\%)}$$

$$\xrightarrow[\text{presence of 1.0\% (v/v) } H_2O]{k_d = 6.5 \times 10^{-4}\text{ s}^{-1}} \mathbf{2d}^- \text{ (98\%)} \qquad (10)$$

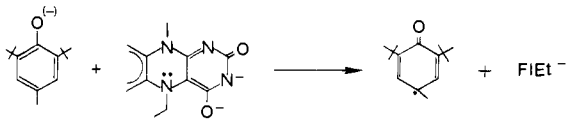
The rate constant for decomposition of $\mathbf{1b}^-$ was also determined by following the exponential decay of chemiluminescent emission. The rate constants determined by spectral and photon counting methods were found to be identical. The quantum yield of light emitted was determined to be 3.7×10^{-7} on the basis of the initial value of [**2b**].

The kinetics for oxygen transfer from 4a-$FlEtO_2^-$ to $\mathbf{1a}^-$ and $\mathbf{2a}^-$ was followed by stopped-flow spectrophotometry. Spectrophotometric titration of **1a** and **2a** (1.88×10^{-4} M) with potassium *tert*-butoxide in absolute *tert*-butyl alcohol (280 nm) established that complete ionization of the indole NH function of **1a** and **2a** occurred when the base concentration equaled ~2× the indole concentration. In the kinetic investigation, potassium *tert*-butoxide was maintained at 4.6×10^{-2} M and the concentration of **1a** and **2a** was varied from 0.21×10^{-2} to 1.2×10^{-2} M; thus, all indole present was ionized. In practice, the disappearance of 4a-$FlEtO_2^-$ was monitored at 370 nm for $\mathbf{1a}^-$ and 390 nm for $\mathbf{2a}^-$. Reactions were monitored by the rapid mixing of a *tert*-butyl alcohol solution of 4a-$FlEtO_2H$ (1.2×10^{-4} M) with *tert*-butyl alcohol solutions containing potassium *tert*-butoxide and varying concentrations of indoles. All reactions were found to obey the first-order rate law to at least $3t_{1/2}$. Plots of the reciprocal of the pseudo-first-order rate constants ($1/k_{obsd}$) vs. 1/[indole] were found to be linear (Figure 1) as would be dictated by the kinetic expression previously established (eq 5) for dioxygen transfer from 4a-$FlEtO_2^{(-)}$ to ambident phenolate anions. From eq 5 (replacing [ArO^-] by [$\mathbf{1a}^-$] and [$\mathbf{2a}^-$]), there follows eq 11. From the slope and intercept

$$1/k_{obsd} = 1/k_1 + k_2/k_1k_3[\text{indole}^-] \qquad (11)$$

value of Figure 1, the constants of Table I can be calculated. Since k_2 is a constant irrespective of substrate, we may compare the relative values of the second-order rate constants for reaction of various substrates with the intermediate X of eq 5 (Table II).

The ambident phenoxide ions which have been shown to undergo dioxygenation by 4a-$FlEtO_2^-$ have also been shown to reduce the flavin radical FlEt· (as in eq 12) with a second-order rate



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constant that would permit this feature to be a portion of the dioxygen transfer mechanism.[1,2] Solutions of FlEt· were prepared by mixing equimolar (2×10^{-4} M) solutions of $Fl_{ox}{}^+Et$ and FlEtH. The comproportionation reaction of eq 13 has been shown previously[6] to lie far to the right. The disappearance of FlEt· (640 nm) was followed when the solution of FlEt· was mixed on the stopped-flow bench with an equal volume of a solution containing indole anion (indole plus twice the molarity of potassium *tert*-butoxide). The disappearance of FlEt· followed good first-order kinetics. The second-order rate constants for the reaction of indole anion with FlEt· were obtained from the slope of plots (Figure 2) of the pseudo-first-order rate constants (k_{obsd}) vs. the concentration of indole anion. The indole anion species $\mathbf{1a}^-$ and $\mathbf{2a}^-$ were employed at concentrations around 9×10^{-3} M in the kinetic studies of dioxygen transfer to these anions from 4a-$FlEtO_2^-$. The pseudo-first-order rate constants for the reactions of eq 14 and 15 are calculated to be 1.8 and 2.4×10 s^{-1}, respectively, when

$$\text{FlEt}\cdot + \mathbf{1a}^- \xrightarrow{2.0 \times 10^2\ M^{-1}\ s^{-1}} \text{FlEt}^- + \mathbf{1a}\cdot \qquad (14)$$

$$\text{FlEt}\cdot + \mathbf{2a}^- \xrightarrow{2.6 \times 10^3\ M^{-1}\ s^{-1}} \text{FlEt}^- + \mathbf{2a}\cdot \qquad (15)$$

(6) Kemal, C.; Bruice, T. C. *J. Am. Chem. Soc.* **1976**, *98*, 3955.

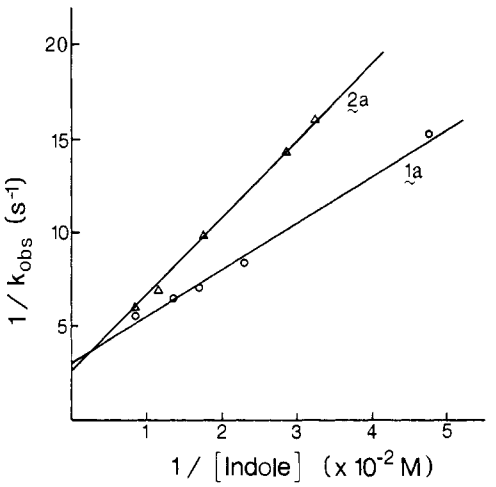
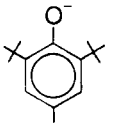
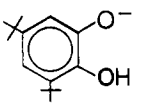
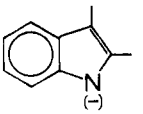
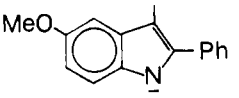


Figure 1. Plots of the reciprocal of the pseudo-first-order rate constants (k_{obsd}) for the disappearance of 4a-$FlEtO_2^-$ vs. the recriprocal of the concentration of the anions of the indoles **2a** and **1a**.

Table I. Derived Rate Constants for the Dioxygen Transfer from 4a-$FlEtO_2^-$ to Indole Anions $\mathbf{1a}^-$ and $\mathbf{2a}^-$

substrate	k_1, s^{-1}	$10^2k_2/k_1k_3$, s M	k_2/k_3, M
1a	0.33	2.5	8.3×10^{-3}
2a	0.37	3.6	1.3×10^{-2}

Table II. Relative Second-Order Rate Constants for the Reaction of Ambident Anions with X

Substrate	$k_3(M^{-1}s^{-1} \times k_2)$
	5×10^3 (Ref. 1)
	3×10^3 (Ref. 2)
	1×10^2
	8×10^1

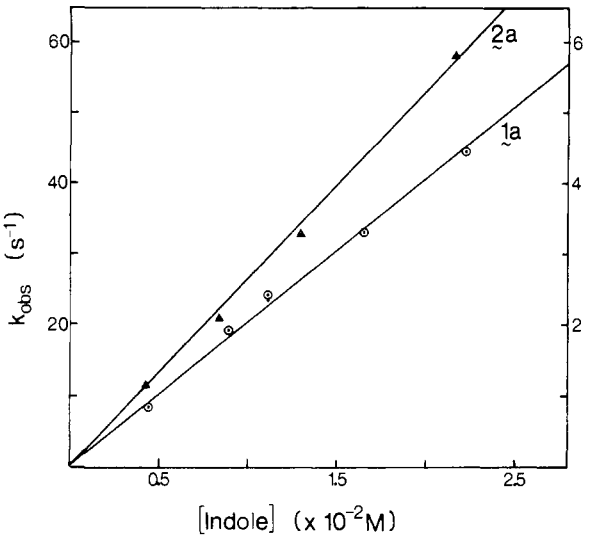


Figure 2. Plots of the pseudo-first-order rate constants (k_{obsd}) for the disapperance of the flavin radical (FlEt·) vs. the concentration of the anions of the indoles **1a** and **2a**. (The right-hand ordinate pertains to **1a** and the left-hand ordinate to **2a**.)

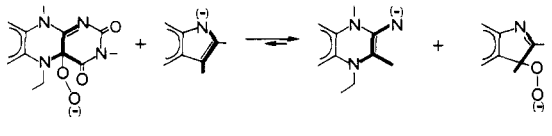
1a$^-$ and **2a**$^-$ are at 9×10^{-3} M. The spontaneous decomposition rate constant for 4a-FlEtO$_2^-$ in *tert*-butyl alcohol has been shown to be independent of the concentration of *tert*-butoxide ion in excess of that required to bring about the ionization: 4a-FlEtO$_2$H + *t*-BuO$^-$ → 4a-FlEtO$_2^-$ + *t*-BuOH.[1,2] The value of the rate constant for spontaneous decomposition of 4a-FlEtO$_2^-$ in *tert*-butyl alcohol is 4.6 ± 0.2 s^{-1}. A comparison of the rate constant for spontaneous decay of 4a-FlEtO$_2^-$ with the calculated pseudo-first-order rate constants for reaction of **1a**$^-$ and **2a**$^-$ with FlEt· reveals that the latter are significantly larger.

The decomposition of 4a-FlEtO$_2^-$ in the presence of 2,5-dimethylfuran (**3**) and tetramethylethylene (**4**) was investigated in order to assess the possibility that the intermediate X of eq 5 represents FlEt$^-$ + $^1O_2$. *tert*-Butyl alcohol solutions of 4a-FlEtO$_2$H (1×10^{-4} M) were mixed on the stopped-flow bench with solutions of **3** and **4** ((0.35–1.9) × 10^{-1} M) which contained potassium *tert*-butoxide at a constant concentration of 4×10^{-3} M. The rate constant for disappearance of 4a-FlEtO$_2^-$ remained invariant with change in [**3**] and [**4**] and was equal to that in the absence of **3** and **4**.

The disappearance of **1a**$^-$ (2.5×10^{-4} M) and **2a**$^-$ (7.4×10^{-5} M) on reaction with molecular oxygen (3.15×10^{-3} M) in *tert*-butyl alcohol containing potassium *tert*-butoxide was monitored at 284 and 314 nm, respectively. The reactions followed good first-order kinetics and the pseudo-first-order rate constants were determined to be 3.37×10^{-6} s^{-1} for **1a**$^-$ disappearance and 2.55×10^{-6} s^{-1} for **2a**$^-$ disappearance. Assuming first-order dependence upon oxygen provides the apparent second-order rate constants of 1.1×10^{-3} and 8.1×10^{-4} M^{-1} s^{-1} for **1a**$^-$ and **2a**$^-$, respectively.

Discussion

The transfer of an O_2 moiety from N^5-ethyl-4a-hydroperoxy-3-methyllumiflavin anion (4a-FlEtO$_2^-$) to the anions of 2,3-dimethylindole (**1a**$^-$) and 5-methoxy-3-methyl-2-phenylindole (**2a**$^-$) occurs in the stopped-flow time range. This reaction amounts to the transfer of dioxygen to an anionic enamine with the creation of a second anionic enamine (eq 16). Since both 4a-FlEtO$_2^-$ and **2b**$^-$ are products of reaction of oxygen with an enamine anion, it is logical to inquire as to the ability of **2b**$^-$ to transfer dioxygen



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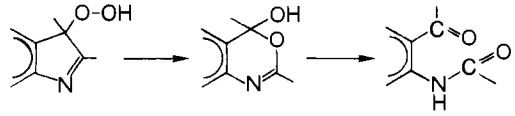
to a suitable ambident anion. In separate experiments, it was found that the rate of decomposition of **2b**$^-$ (9.1×10^{-4} s^{-1}) in *tert*-butyl alcohol is only slightly longer in the presence of the anion of 2,6-di-*tert*-butyl-4-methylphenol (9.8×10^{-4} s^{-1}). This, and the product analysis, in the presence and absence of 2,6-di-*tert*-butyl-4-methylphenol and 3,5-di-*tert*-butylcatechol (5×10^{-3} M) establish that dioxygen transfer from **2b**$^-$ to these ambident anions does not occur. It may be concluded from this experiment that the ability of 4a-FlEtO$_2^-$ to transfer an O_2 moiety is not due solely to the fact that the flavin peroxide anion is an enamine $^3O_2$ adduct. The presence of 2,6-di-*tert*-butyl-4-methylphenol anion did influence the product ratio obtained on decomposition of **2b**$^-$. Thus, the yield of **2d** was decreased from 92% to 80% and the yield of **2c** increased from 4% to 14%. With 3,5-di-*tert*-butylcatechol, the yield of **2d** was decreased to 46% and **2c**$^-$ increased to 51%. Apparently, the phenolate anions are capable of reducing the peroxide moiety of **2b**$^-$ to provide the tertiary alcohol (**2c**). A similar reduction of hydroperoxides to tertiary alcohols by FlEt$^-$ was reported previously.[2]

1b$^-$ and **2b**$^-$ undergo 2,3-indole bond rupture to yield acetamidoacetophenone (**1d**, eq 8) and benzamidoacetophenone (**2d**, eq 9). Oxidative ring cleavages through intermediate hydroperoxides (as in eq 8 and 9) are common in both organic[7] and enzymatic[8] reactions. A Hock rearrangement of the hydroperoxide (as in the hypothetic reaction of eq 17) is generally considered



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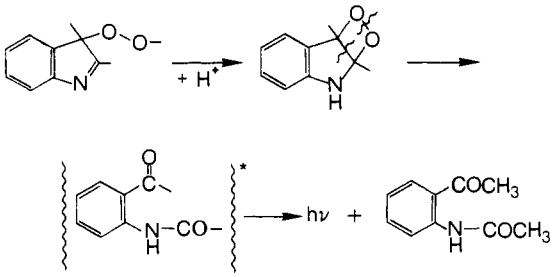
to be favored over one involving an intermediate dioxetane on the basis of the ring strain accompanying dioxetane formation.[9] However, the bond scissions accompanying the reactions of eq 8 and 9 have been shown[10] to provide chemiluminescence by the generation of excited **1d**$^-$ and **2d**$^-$ species. This requires that at least a portion of the 2,3 bond cleavage involves the intermediacy of dioxetane species (eq 18). However, the quantum yield for the conversion of **2b**$^-$ → **2d**$^-$ was found (Results) to be but 3.7×10^{-7}, so that the fraction of **2d**$^-$ that arises through a dioxetane intermediate may be miniscule.



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Since $^3O_2$ reacts with 1,5-dihydro-N^5-ethyl-3-methyllumiflavin (FlEtH) to provide 4a-FlEtO$_2$H, we may write the catalytic cycle of eq 19 wherein dihydroflavin acts as a dioxygenase catalyst. Tryptophane 2,3-dioxygenase is an iron porphyrn enzyme which combines with molecular oxygen in such a manner as to provide an active O_2 species.[11,12] Cobalt oxygen complexes [Co(salen)

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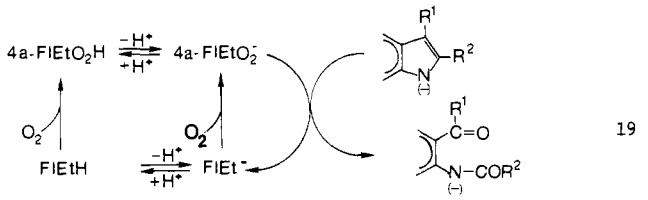
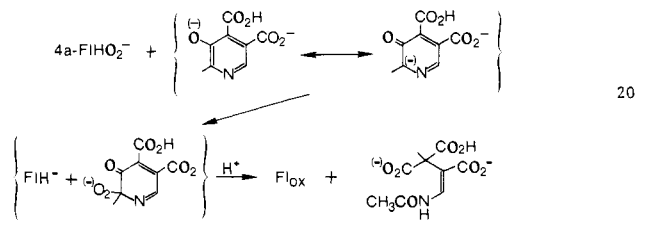


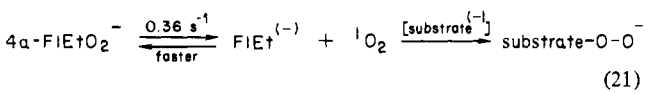
19

and Co(TPP)[13]] have also been shown to act as biomimetic indole dioxygenases. Considering the ease of dioxygen transfer from 4a-$FlEtO_2^-$ to substrate molecules which are ambident anions, it is surprising that 2-methyl-3-(hydroxypyridine)-5-carboxylic acid dioxygenase is the only recognized flavoenzyme dioxygenase responsible for the cleavage of a carbon–carbon double bond.[14] We suggest the mechanism is that shown in eq 20. The findings of the present and previous[1,2] studies of this series suggest the likelihood that other flavoenzyme dioxygenases exist.



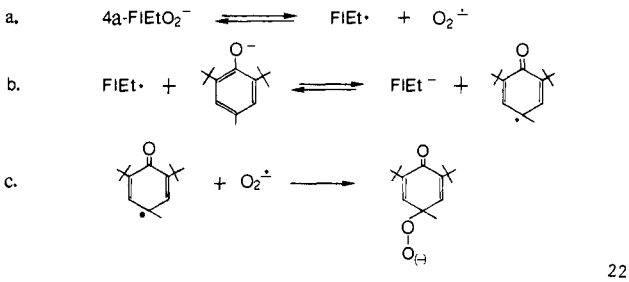
20

The kinetics for dioxygen transfer from 4a-$FlEtO_2^-$ to phenolate ions (Introduction) and to the indole anions **1a**$^-$ and **2a**$^-$ (Results) requires that 4a-$FlEtO_2^-$ undergoes an endothermic and reversible conversion into an intermediate (X of eq 5) and that dioxygenation occurs on trapping of this intermediate by substrate. The rate constant for the formation of X from 4a-$FlEtO_2^-$ has been determined to be 0.36 ± 0.01 s^{-1} with four substrates. The relative rate constants for reaction of X with these four substrates is provided in Table II. The identification of X is of prime concern. In the presence of the singlet oxygen traps, 2,5-dimethylfuran, and tetramethylethylene (second-order rate constants for reaction of both with $^1O_2$ in MeOH $\simeq 10^8$ M^{-1} s^{-1}),[15] there is no increase in the rate of 4a-$FlEtO_2^-$ disappearance over that anticipated from the spontaneous rate constant obtained in the absence of oxygen acceptor substrates. Thus, the sequence of eq 21 may be ruled out.



(21)

For X = $FlEt^- + {}^3O_2$, k_2[indole$^-$] must (see eq 5) be greater than the observed rate constant for the reaction of 4a-$FlEtO_2^-$ under saturation by [indole$^-$], i.e., 0.36 s^{-1}. Saturation 95% in [**1a**$^-$] and [**2a**$^-$] can be calculated to occur at $\sim 5 \times 10^{-1}$ and $\sim 1 \times 10^{-1}$ M, respectively. At these concentrations of substrate, the values of k_2[indole$^-$] for reaction with oxygen may be calculated to be $\sim 5.5 \times 10^{-4}$ s^{-1} for [**1a**$^-$] and 8×10^{-5} s^{-1} for [**2a**$^-$]. Thus, the values of k_2[indole$^-$] are $\sim 10^{-3}$–10^{-4} times too small to allow X to represent solvent separated $FlEt^-$ and $^3O_2$. Similar evidence has ruled out triplet oxygen from being intermediate in the 4a-$FlEtO_2^-$ peroxidation of various phenols.[1,2] Evidence has been presented for the involvement of $O_2^{-}\cdot$ in the mechanism of tryptophan dioxygenase.[12] We originally favored a mechanism in which X consisted of $FlEt^- + O_2^{-}\cdot$ (eq 22).[1] One requirement for the validity of eq 22 is that substrates which undergo dioxygenation by 4a-$FlEtO_2^-$ must be able to reduce FlEt· by **1e**$^-$ transfer in the time period of the overall dioxygenation reaction.



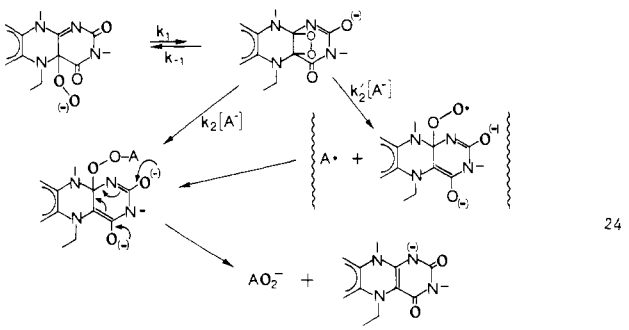
22

We have previously[1,2] shown this to be the case with the anions of the phenols 2,6-di-*tert*-butyl-4-methylphenol (eq 20), 9-hydroxy-10-ethoxyphenanthrene, and 9-hydroxy-10-methylphenanthrene. The present investigation has shown that the indole anions **1a**$^-$ and **2a**$^-$ also reduce FlEt· at a rate sufficiently great to allow the formation of the hydroperoxides **1b** and **2b** by combination of $O_2^{-}\cdot$ and indole radicals. It will be of interest to see if the ability of substrate to reduce FlEt· at a sufficient rate remains a requirement for dioxygenation by 4a-$FlEtO_2^-$. A mechanism which does not require the ambident anion substrate to react with a dioxygen moiety, but which involves a reaction with the flavin portion followed by combination with a dioxygen species, would explain why **1a**$^-$ could be a slightly better trap for X than is **2a**$^-$ but still provide a lower yield of dioxygen-transfer product. Be this as it may, the mechanism of eq 22 suffers, in that step c has been shown to be highly unlikely by the finding that $O_2^{-}\cdot$ as a potassium crown salt reduces the radical of 2,6-di-*tert*-butyl-4-methylphenol (in the same *t*-BuOH solvent employed in these studies) to yield $^3O_2$ and the phenolate anion.[16] Similar results have been obtained when employing $O_2^{-}\cdot$ in acetonitrile solvent.[17]

The nature of the intermediate X remains unknown. It may represent a complex of $^3O_2$ with $FlEt^-$. The reversibility of eq 23 has been established.[1] Alternatively, X may represent 4a,10a-

$$\text{4a-FlEtO}_2^- \rightleftarrows \text{FlEt}^- + {}^3O_2 \qquad (23)$$

or a 4,4a-dioxetane formed by internal cyclization of the peroxyanion moiety of 4a-$FlEtO_2^-$ (see ref 2). The mechanisms of eq 24 may be considered. Nucleophilic addition at an oxygen of a dioxetane with accompanying C–O bond scission has no precedent known to the authors. However, the carbonyl function at C(4) would facilitate the process by fulfilling the role of an electron sink. Nucleophilic attack upon the 4a,10a-dioxetane and upon an oxygen dihydroflavin complex differ by the extent of the covalent nature of the association of oxygen and dihydroflavin components. It should be noted that the 10a-alkylperoxy intermediate depicted in eq 24 differs in steric requirements from a 10a-(alkylperoxy)flavin, since the former arises from the latter by **2e**$^-$ reduction. Due to the C(4a)–C(4), double bond in the intermediate, there is far less steric crowding of the N^{10}-substituent. For this reason, our arguments[18] against peroxide migration from 4a to 10a in hydroperoxyflavins would not hold for the reactions of eq 23. One electron transfer from substrate to dioxetane



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(11) Feigelson, P.; Brady, F. O. "Molecular Mechanisms of Oxygen Activation"; Hayaishi, O., Ed.; Academic Press: New York, 1974; p 87.
(12) Hirata, F.; Hayaishi, O. *J. Biol. Chem.* **1975**, *250*, 5960.
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(15) See references in Wasserman, H. H., Murray, R. E., Eds. "Singlet Oxygen"; Academic Press: New York, 1979.
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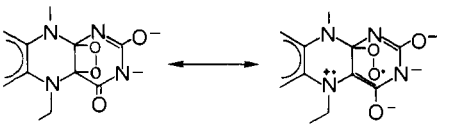
(17) Sawyer, D., private communication.
(18) Miller, A.; Bruice, T. C. *J. Chem. Soc., Chem. Commun.* **1979**, 896. Bruice, T. C.; Miller, A. *Ibid*, **1980**, 693.

intermediate followed by coupling of substrate and 10a-dihydroflavin peroxide radicals (eq 24) is the covalent counterpart of the superoxide mechanism of eq 22 or the reaction of substrate with a complex composed of FlEt· and O_2^{-}·. We know of no precedent in the literature for **1e**$^-$ reduction of a dioxetane accompanied by C–O bond scission. However, as in the nucleophilic addition mechanism, the C(4) carboxyl group may serve as an electron sink and the dioxetane itself may possess a radical character (eq 25).



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Acknowledgment. This work was supported by grants from the National Institutes of Health and National Science Foundation. T.C.B. gratefully acknowledges support as a Guggenheim Fellow.

Communications to the Editor

Synthesis and X-ray Structural Characterization of the $[Rh_{22}(\mu_3\text{-}CO)_7(\mu\text{-}CO)_{18}(CO)_{12}]^{4-}$ Anion Containing a Large Close-Packed Cluster with an ABAC Sequence of Compact Layers

Sir:

During our studies on the rhodium carbonyl cluster compounds of high nuclearity containing fragments of metal lattices, we have isolated and structurally characterized the anions $[Rh_{13}H_{5-n}(CO)_{24}]^{n-}$ (n = 2, 3),[1,2] $[Rh_{14}(CO)_{25}]^{4-}$,[3] $[Rh_{14}H(CO)_{25}]^{3-}$,[4] and $[Rh_{15}(CO)_{27}]^{3-}$.[3] We now wish to report the synthesis and X-ray characterization of the new $[Rh_{22}(CO)_{37}]^{4-}$ anion.

This anion was first observed as a minor byproduct in the synthesis of $[Rh_{15}(CO)_{27}]^{3-}$,[3] where it was sometimes present in the sodium fraction of the alkali metals salts. It has now been synthesized by refluxing for 4–6 h under nitrogen mixtures of $Rh_4(CO)_{12}$ and NaOH in 2-propanol in the ratio of one OH^- for every 5–5.5 Rh atoms. A mixture of brown products is formed from which the $[Rh_{22}(CO)_{37}]^{4-}$ anion can be separated, after filtration, evaporation to dryness in vacuo, and dissolution in water, by fractional precipitation of the sodium salts. After separation of an eventual first fraction at 2.5% NaCl concentration (which contains another new species, namely, the $[Rh_{14}(CO)_{26}]^{2-}$ anion[5]), addition of NaCl up to 9% causes the separation of $Na_4[Rh_{22}(CO)_{37}]$ in tiny brown crystals with a metallic appearance.[6] The yields are rather low, 1–10% depending on experimental conditions. The corresponding bulky cation salts can be obtained by metathesis in alcohols.

The characteristic IR spectrum of the sodium salt in THF (Figure 1) shows bands at 2020 (vs), 2010 (sh m), 1990 (vw), 1940 (w), 1880–1860 (m br), 1815 (sh m), 1803 (ms), and 1765 (w) cm^{-1}, which are possibly in accord with the X-ray structure. However, the spectrum in other solvents such as MeCN changes markedly in the bridging CO stretching region, showing bands at 2015 (vs), 1925 (w br), 1860 (sh), 1850 (ms br), 1835 (m sh), and 1805 (m br) cm^{-1}, suggesting that the anion in solution can adopt carbonyl stereochemistries different from that of the solid state depending on the solvent. This hypothesis seems to be confirmed by preliminary results from ^{13}C NMR spectroscopy.[7]

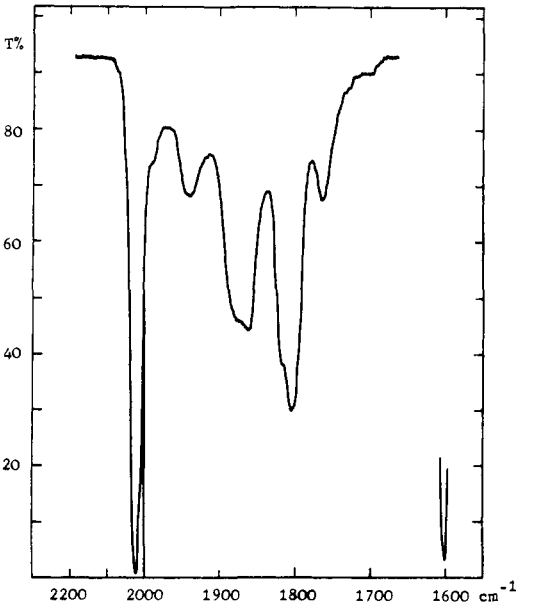
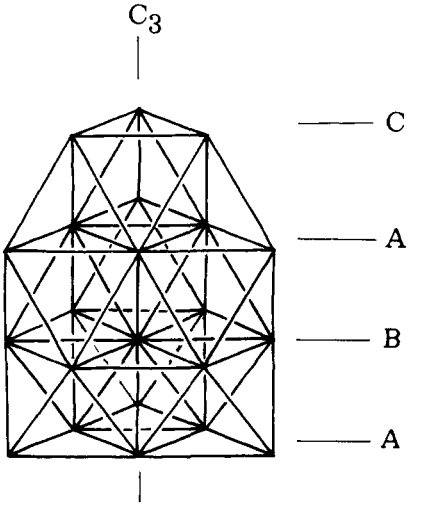


Figure 1. IR spectrum of $Na_4[Rh_{22}(CO)_{37}]$ in THF solution.

Scheme I



Studies on the $^{13}C\{^{103}Rh\}$ INDOR and ^{103}Rh NMR spectra are in progress. No hydride signal can be detected in the ^1H NMR spectrum from τ −50 to +58 either at room temperature or at −90 °C.

(1) Albano, V. G.; Ceriotti, A.; Chini, P.; Ciani, G.; Martinengo, S.; Anker, W. M. *J. Chem. Soc., Chem. Commun.* **1975**, 860.
(2) Albano, V. G.; Ciani, G.; Martinengo, S.; Sironi, A. *J. Chem. Soc., Dalton Trans.* **1979**, 978.
(3) Martinengo, S.; Ciani, G.; Sironi, A.; Chini, P. *J. Am. Chem. Soc.* **1978**, *100*, 7096.
(4) Ciani, G.; Sironi, A.; Martinengo, S. *J. Organomet. Chem.* **1980**, *192*, C-42.
(5) Martinengo, S.; Ciani, G.; Sironi, A., to be published.
(6) In the fractional crystallization of the sodium salts, the required NaCl concentration is reached by dropping in, while stirring, the proper amount of a concentrated NaCl solution. The solution is then left to crystallize 3–4 h or more before filtration of every fraction. If the relative band intensities in the bridging COs region of the IR spectrum are not as in Figure 1, the product should be redissolved and the fractional precipitation repeated.
(7) Martinengo, S.; Heaton, B. T., unpublished results.

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