

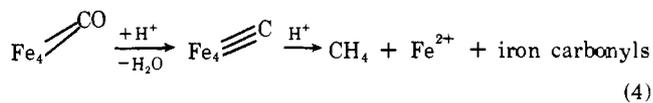
As mentioned above the yield of CH<sub>4</sub> is ~0.56 per cluster when pure HSO<sub>3</sub>CF<sub>3</sub> is employed, and it is increased to 0.82 per cluster when the reaction medium is 1:1 HSO<sub>3</sub>CF<sub>3</sub>-O(SO<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>. Neither concentrated HCl nor pure HSO<sub>3</sub>F produces volatile hydrocarbons, but concentrated H<sub>2</sub>SO<sub>4</sub> yields a trace of CH<sub>4</sub> along with SO<sub>2</sub>, CO<sub>2</sub>, CO, COS, and H<sub>2</sub>.

Two experiments were performed to test whether the methane originates from the coordinated carbon monoxide, or from an adventitious source. In the first of these, DSO<sub>3</sub>CF<sub>3</sub> was employed as reactant with the Fe<sub>4</sub> cluster, and infrared spectra of the methane-carbon monoxide fraction showed the presence of CD<sub>4</sub> and no indication of <sup>1</sup>H-containing methane. In the second experiment, the [Fe<sub>4</sub>(CO)<sub>13</sub>]<sup>2-</sup> was enriched such that 26% of the carbon monoxide contained the <sup>13</sup>C isotope. The reaction of this enriched metal carbonyl with HSO<sub>3</sub>CF<sub>3</sub> according to the procedure indicated above produced methane which was 25% <sup>13</sup>CH<sub>4</sub> as judged by quantitative infrared spectroscopy. These experiments convincingly show that the methane originates from carbon monoxide in the metal cluster, and therefore confirm eq 1.

Since H<sub>2</sub> is a product of the reaction, it was conceivable that methane might arise from a H<sub>2</sub> reduction rather than direct attack of H<sup>+</sup> on the metal cluster. To check this possibility the reaction was run under the uniform conditions outlined above but with the addition of 457 Torr of H<sub>2</sub>, which is 58 times greater than the H<sub>2</sub> produced in a typical run. The yield of CH<sub>4</sub> was 0.53 per cluster, which, within experimental error, is equal to the yield in the absence of added H<sub>2</sub>. Two isotopic experiments also demonstrate the lack of incorporation of dihydrogen into the product. When H<sub>2</sub> (344 Torr) was placed over the reaction mixture containing DSO<sub>3</sub>CF<sub>3</sub> in place of HSO<sub>3</sub>CF<sub>3</sub>, the only methane produced was CD<sub>4</sub> as judged by infrared spectroscopy (eq 2) and, when the reaction was run with D<sub>2</sub> over a reaction mixture containing HSO<sub>3</sub>CF<sub>3</sub>, only CH<sub>4</sub> was produced (eq 3). From these experiments it is clear that the hydrogen in the methane originates from H<sup>+</sup> and not from H<sub>2</sub> intermediate.

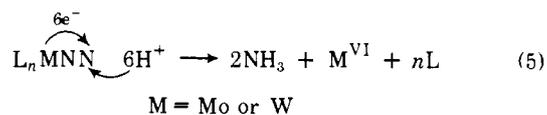


One possible mechanism is attack on the CO oxygen by protons to split off water, leaving a carbide which subsequently is attacked by H<sup>+</sup> to produce methane (eq 4). Any carbide



intermediate would have to display a different reactivity pattern from known carbides, because we have observed the conversion of [Fe<sub>6</sub>(CO)<sub>16</sub>C<sup>2-</sup>] into Fe(CO)<sub>15</sub>C in HSO<sub>3</sub>CF<sub>3</sub><sup>10</sup> without the production of CH<sub>4</sub>.

The work of Chatt and co-workers<sup>11</sup> on the reduction of coordinated dinitrogen (eq 5) indicates that the necessary



equivalents for CO reduction may be supplied by a mononuclear complex of a metal such as Mo or W, which can easily reach a high oxidation state. In the iron series, however, it appears that a cluster is necessary to supply the six electrons required for the complete reduction of CO. Thus the mononuclear carbonyl Fe(CO)<sub>5</sub> in HSO<sub>3</sub>CF<sub>3</sub> produces the known ion [HFe(CO)<sub>5</sub>]<sup>+</sup>.<sup>12</sup> The three-iron cluster [Fe<sub>3</sub>(CO)<sub>11</sub>]<sup>2-</sup>

yields traces of CH<sub>4</sub> when treated with HSO<sub>3</sub>CF<sub>3</sub>, and as described above a good yield of methane was obtained from the four-iron cluster.

It is probable that the reaction of metal carbonyl clusters with the surface of hydrated metal oxides is analogous to the homogenous reaction reported here.<sup>13</sup> A closer comparison of the two reactions will be possible when the role of dihydrogen is delineated in the heterogenous reaction.

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## Tandem Directed Metalation Reactions. Short Syntheses of Polycyclic Aromatic Hydrocarbons and Ellipticine Alkaloids

Sir:

Directed metalation of aromatic substrates<sup>1</sup> is an increasingly important strategy for the regiospecific synthesis of highly substituted benzene derivatives,<sup>2</sup> heterocycles,<sup>2b,c,3</sup> and natural products.<sup>4</sup> The rapidly growing list of functionalities capable of promoting and stabilizing ortho metalation which includes oxazolines,<sup>3a,5</sup> imidazolidine,<sup>6</sup> CH=NR,<sup>2a,4a,7</sup> CONR,<sup>3l,4b,f,g,8,9</sup> CSNR,<sup>3c</sup> CONR<sub>2</sub>,<sup>2b,3b,4c,d</sup> CH(OMe)<sub>2</sub>,<sup>4i</sup> OCH<sub>2</sub>OMe,<sup>3d,4e,h</sup> OCH(Me)OEt,<sup>3k</sup> CH<sub>2</sub>SMe,<sup>10</sup> CH<sub>2</sub>O<sup>-</sup>,<sup>3e,f</sup> NCOR,<sup>3h</sup> N≡C,<sup>3i</sup> and halo and methoxy ArCr(CO)<sub>3</sub><sup>3j</sup> offers attractive and, at times, highly advantageous solutions to preparative problems not readily achieved by classical (usually electrophilic) chemistry. We report on the new concept of tandem directed metalation (Scheme 1) involving ortho-lithiated tertiary benzamide (1) and benzyl alkoxide (3) intermediates which provides rapid access to polycyclic anthraquinones and unusual heterocyclic benzoquinones (Table 1). We delineate the scope of this one-pot aromatic ring construction reaction and demonstrate its utility for the synthesis of carcinogenic polycyclic aromatic hydrocarbons (PAH's)<sup>11</sup> and chemotherapeutic ellipticine alkaloids (6).<sup>12</sup> Both classes of compounds currently constitute lively and urgent areas of study.<sup>13,14</sup>

Table I. Synthesis of Anthraquinones by Tandem Directed Metalation

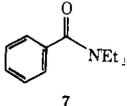
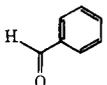
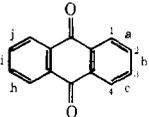
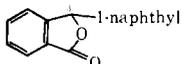
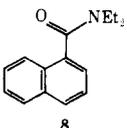
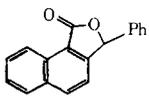
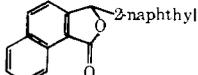
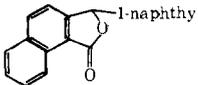
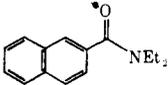
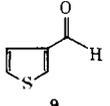
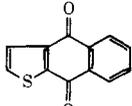
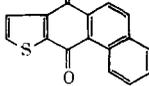
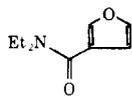
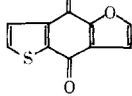
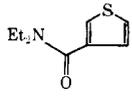
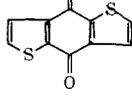
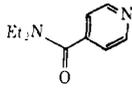
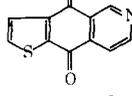
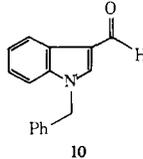
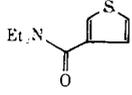
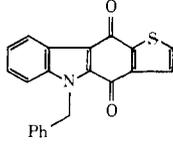
entry	amide	aldehyde	product	yield, %	mp, °C (lit. mp) <sup>a</sup>
1				43	284 (287)
2	7	2-MeOC <sub>6</sub> H <sub>4</sub> CHO	1-methoxyanthracene-9,10-dione	10	168-169 (170)
3	7	4-MeOC <sub>6</sub> H <sub>4</sub> CHO	2-methoxyanthracene-9,10-dione	28	192-193 <sup>b</sup>
4	7	4-MeC <sub>6</sub> H <sub>4</sub> CHO	2-methylanthracene-9,10-dione	15	184 (177-179)
5	7	1-naphthaldehyde	benz[a]anthracene-7,12-dione	44	165-166 (166-167)
				20	132-133 (137)
6	7	2-naphthaldehyde	benz[b]anthracene-5,12-dione	39	283 (284-285)
			Benz[a]anthracene-7,12-dione	5	
			3-(2-naphthyl)-phthalide	22	140-141 <sup>b</sup>
7	7	9-phenanthraldehyde	Dibenz[a,c]anthracene-9,14-dione	41	179-180 (181-183)
			3-(5-phenanthryl)phthalide	24	162-164 <sup>b</sup>
8	3,4-diOMe-C <sub>6</sub> H <sub>3</sub> CONEt <sub>2</sub>	PhCHO	3-Phenyl-4,5-dimethoxyphthalide	74	81 <sup>b</sup>
9		PhCHO		81	164-166 <sup>b</sup>
10	8	2-naphthaldehyde	Dibenz[a,i]anthracene-7,14-dione	10	225-226 (229)
				70	148 <sup>b</sup>
11	8	1-naphthaldehyde	Dibenz[a,h]anthracene-7,14-dione	10	249-249.5(248-249)
				81	166(170.5-171) <sup>c</sup>
12		2-naphthaldehyde	dibenz[a,i]anthracene-7,14-dione	2	225-226 <sup>d</sup>
			dibenz[b,i]anthracene-6,13-dione	2	>300 (388-398)
13		7		35	225 (227-228) <sup>e</sup>
14	9	8		37	205 (199-201) <sup>f</sup>
15	9			24	250 <sup>b</sup>
16	9			77	252-253 (258-260) <sup>e</sup>
17	9			20	192-193 <sup>b</sup>
18				67	211-212 <sup>b</sup>

Table I (Continued)

entry	amide	aldehyde	product	yield, %	mp, °C (lit. mp) <sup>a</sup>
19	<b>10</b>	<b>7</b>		44	172-173 (178.5-179.5) <sup>g</sup>
20	<b>10</b>	<b>8</b>		20	227-228 <sup>b</sup>
21				26 76 40	196-197 <sup>b</sup> 245 <sup>b</sup> 268 <sup>b</sup>
			11a, R = CH <sub>2</sub> OMe b, R = Me c, R = CH <sub>2</sub> Ph		

<sup>a</sup> Except where noted otherwise, melting points refer to values quoted in or traced from ref 16. <sup>b</sup> New compound; analytical and spectral data are in full accord with the structure. <sup>c</sup> L. F. Fieser and G. W. Kilmer, *J. Am. Chem. Soc.*, **61**, 862 (1939). <sup>d</sup> Identical (melting point, mixture melting point, UV and NMR spectra) with the sample in entry 10. <sup>e</sup> D. W. H. MacDowell and J. C. Wisowaty, *J. Org. Chem.*, **37**, 1712 (1972). <sup>f</sup> M. S. Newman and K. G. Ihrman, *J. Am. Chem. Soc.*, **80**, 3652 (1958). <sup>g</sup> V. I. Shvedov, G. N. Kurilo, and A. N. Grinev, *Khim. Geterotsikl. Soedin.*, 1079 (1972); *Chem. Abstr.*, **77**, 139712s (1972).

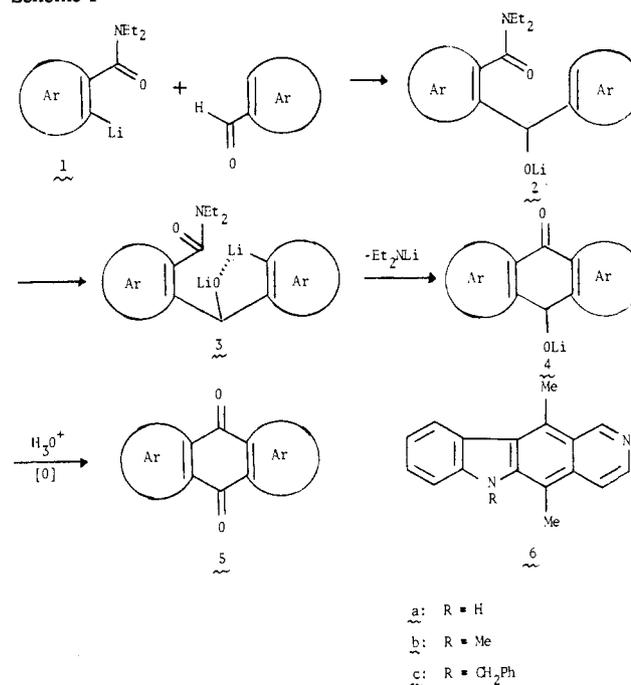
Metalation (1.0 equiv of *sec*-BuLi, 1.0 equiv of TMEDA, Et<sub>2</sub>O, -78 °C, 1 h) of *N,N*-diethylbenzamide (**7**) gave the yellow-orange ortho-lithiated species **1** which, upon sequential treatment at -78 °C with benzaldehyde (1.0 equiv) and *sec*-BuLi (1.25 equiv) and allowing the reaction mixture to warm to room temperature overnight (12 h), afforded anthraquinone in 43% yield. Table I illustrates representative anthraquinones and heterocyclic benzoquinones obtained by this procedure. Alkoxy and alkyl groups in the benzaldehyde reactant are poorly tolerated and give low yields of anthraquinones (entries 2-4), whereas alkoxy-substituted benzamides afford (after treatment with TsOH)<sup>2b</sup> only phthalide products (entry 8). The reaction of **7** with 1- and 2-naphthaldehyde and 9-phenanthraldehyde provides polycyclic anthraquinones in modest yields (entries 5-7). Entry 6 shows the preference for the formation of a linear rather than an angular anthraquinone system. 1-*N,N*-Diethylnaphthamide undergoes reaction with benzaldehyde and 2-naphthaldehyde to give (after TsOH) mainly phthalide derivatives (entries 9 and 10). 2-*N,N*-Diethylnaphthamide is a poorer substrate providing the two possible anthraquinones in low yields (entry 12).

Some of the condensed anthraquinones (entries 5, 7, 11, and 12) were reduced (aluminum tricyclohexoxide, cyclohexanol)<sup>15</sup> to the corresponding hydrocarbons,<sup>16</sup> thus completing short syntheses which compete favorably with reported methods for these carcinogenic PAH's.<sup>15,16</sup>

Knowledge concerning the facile abstraction of the 2 proton in furan,<sup>17</sup> thiophene,<sup>17</sup> and *N*-substituted indole<sup>18</sup> derivatives stimulated tandem directed metalation reactions on these systems. Thus treatment of ortho-lithiated benz- and 1-naphthamides with thiophene-3-aldehyde gave 4,9-dihydro-naphtho[2,3-*b*]thiophene-4,9-dione and its 7,8-benzo analogue, respectively (entries 13 and 14). Furthermore, condensation of the same thiophene aldehyde with metalated furan-3, thiophene-3, and pyridine-4<sup>19</sup> amides afforded the easily isolable diheterocyclic benzoquinones (entries 15-17). Combination of *N*-benzylindole-3-aldehyde (**10**) with ortho-lithiated aromatic and heteroaromatic amides smoothly gave condensed indolobenzoquinone systems (entries 18-20). Most of these compounds have been accessible only by tedious and inefficient routes.

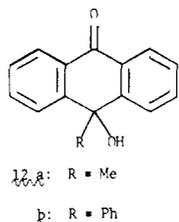
A one-step construction of the ellipticine alkaloid skeleton

Scheme I



was achieved by using *N*-substituted indole-3-aldehydes with lithiated *N,N*-diethylisonicotamide (entry 21).<sup>20</sup> Sequential treatment of the *N*-methylenemethoxyquinone **11a** with excess MeLi, 47% HI in MeOH, and SnCl<sub>2</sub> in HOAc-HCl-THF (5:1:5)<sup>21</sup> without isolation of intermediates gave ellipticine (**6a**) (overall 40% yield).<sup>22</sup> The same reaction sequence on the *N*-methyl- (**11b**) and *N*-benzylquinones (**11c**) provided the corresponding ellipticine derivatives **6b** (62%) and **6c** (40%).<sup>23</sup>

The proposed mechanism (Scheme I) for the reaction, in particular, the formation of dianion **3**, is supported by independent tandem metalation of **7** with acetophenone and benzophenone under identical reaction conditions to yield the hydroxyanthracenones **12a** (17%) and **12b** (15%).<sup>24</sup> The generation of simple ortho-lithiated benzyl alkoxide species corresponding to **3** has been documented.<sup>3e,f,25</sup> The low yields



of anthraquinones in the reaction of **7** with alkoxy and methyl benzaldehydes (entries 2–4, 8) points to complications due to competitive metalation directed by  $\text{CONEt}_2$  and  $\text{CH}_2\text{O}$ -groups and steric effects in the cyclization, **3**  $\rightarrow$  **4**. The aerial oxidation step, **4**  $\rightarrow$  **5**, is well precedented.<sup>26,27</sup>

Outside of the specific application presented here, the concept of tandem directed metalation may have broader significance in organic synthesis.<sup>28</sup>

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## Determination of Rotational Correlation Time from Perturbed Angular Correlations of $\gamma$ Rays: Apomyoglobin Reconstituted with $^{111}\text{Indium(III)}$ Mesoporphyrin IX<sup>1</sup>

Sir:

Currently popular methods for determining macromolecular rotational correlation time,  $\tau_{\text{rot}}$ , each possess major drawbacks. Fluorescence depolarization (FD)<sup>2</sup> and depolarized light scattering<sup>3</sup> require transparent media. Electron paramagnetic resonance (EPR) "spin labeling"<sup>4</sup> and FD require introduction of an artificial reporter group, linked by one or more flexible bonds to the macromolecule. EPR line-shape analysis is complicated by inhomogeneous (nitrogen hyperfine coupling) broadening, nitrogen nuclear relaxation, and g-tensor nonaxial symmetry.<sup>5</sup> NMR relaxation time analysis is complicated by competing relaxation pathways,<sup>6,7</sup> internuclear distance uncertainty,<sup>8</sup> pulse imperfections, and multiexponential relaxation.<sup>9,10</sup>

In contrast, time-resolved emission anisotropy from a perturbed  $\gamma$ - $\gamma$  angular correlation (PAC) experiment can provide direct determination of  $\tau_{\text{rot}}$ ,<sup>11–16</sup> in opaque media (even in vivo<sup>17</sup>), at  $10^{-12}$  M, without flexible and/or bulky reporter groups. Unfortunately, previous PAC determinations of  $\tau_{\text{rot}}$  have been complicated by multiple  $\tau_{\text{rot}}$  processes.<sup>14–16</sup> In this communication, we report the PAC results from the successful reconstitution of indium-111 mesoporphyrin IX, In-MPP (see ref 18 for synthesis), into apomyoglobin by the procedure of Srivastava<sup>19</sup> to give a singly labeled protein with unique conformation and chemical form.<sup>20</sup>

The crystal and molecular structure of the closely related tetraphenylporphyratoindium(III) chloride<sup>21</sup> strongly suggests that In-MPP-myoglobin should be isostructural with the Fe(II) heme in deoxy-myoglobin or deoxyhemoglobin, because the indium atom is displaced above the mean porphyrin plane by the same distance (0.6 Å) as is Fe(II) in the native proteins.