mentation and Biomedical Sciences Support Grants to the University of Colorado (DHHS) is gratefully acknowledged. T.H.K. also thanks the University of Colorado Council on Research and Creative Work for a faculty fellowship. We thank Dr. Sergio Penco of Farmitalia Carlo-Erba, Milan, Italy, for a gift of daunomycin, Drs. Makhluf Haddadin and Giorgio Gaudiano for many helpful discussions, and Mr. Martin Ashley for assistance with the NMR experiments.

Kinetics and Mechanism of Aliphatic Amine Oxidation by Aqueous $(batho)_2Cu^{II}$ †

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Abstract: The kinetics of oxidation of a large series of aliphatic amines by the "high-potential" oxidant $(batho)_2Cu^{II}$ (batho = 2,9-dimethyl-4,7-diphenyl-1,10-phenanthrolinedisulfonate) was studied under pseudo-first-order conditions (excess amine) in water or in 30% aqueous methanol (v/v) at 25 °C over the pH range 7–11. The oxidations follow bell-shaped pH–rate profiles, with the low-pH leg reflecting the fact that only the free amine base is subject to oxidation and the high-pH leg representing conversion of $(batho)_2Cu^{II}$ to an ineffective oxidant at high pH. The latter is thought to be $(batho)Cu^{II}(OH_2)OH$ on the basis of the observed effect of [batho] on rate at high pH, and curve fitting of the rate data yielded estimates of the unitless K_{eq} values governing this conversion. The variation in rate with degree of N-substitution and other structure–reactivity trends (such as the effect of ring size and the non-rate-retarding effect of 2,4,6-trimethyl substitution on $PhCH_2NR_2$) support a mechanism involving initial outer-sphere one-electron transfer, followed by proton transfer to the solvent, and then a rapid second one-electron oxidation to give imine/iminium product. Inner-sphere coordination of chelating amines shuts down the redox reaction, presumably as a consequence of displacement of the batho ligand(s) needed for high oxidant strength. Deuterium kinetic isotope effect (DKIE) measurements (i) comparing $PhCD_2N(CD_3)_2$ vs $PhCH_2N(CH_3)_2$ (intermolecular DKIE) and (ii) determining N-dealkylation preference in the case of $PhCH_2N(CH_3)CD_2Ph$ (intramolecular DKIE) suggest that the initial electron transfer is mainly rate-limiting. A rate comparison between erythro and threo diastereomers of 1,2-diphenyl-2-piperidinoethanol indicates a stereoelectronic preference for one-electron oxidation at nitrogen when held antiperiplanar to a β-hydroxyl. Stoichiometry studies using an excess of the Cu(II) oxidant reveal regioselective and chemoselective factors governing the overall amine-to-iminium oxidations.

Introduction

Mechanistic diversity in the chemical and enzymatic oxidation of amines is a subject of much current interest. The monooxygenase enzyme cytochrome P-450 achieves oxidative N-dealkylation via hydroxylation at C_α, followed by dissociation of the resulting carbinolamine. A mechanism involving abstraction of a hydrogen atom from C_α by a $(Fe{=}O)^{3+}$ species, followed by $HO^\bullet$ transfer from iron (the "rebound" step) was traditionally considered to rationalize the incorporation of O_2-derived oxygen into the aldehyde product.[1] However, considerations of measured isotope effects and redox potentials,[1-3] and observed suicide inactivation by cyclopropylamines,[4,5] led to a consensus that amine oxidation by cytochrome P-450 (and chemical model systems thereof) involves initial single-electron transfer (SET) to give an aminyl cation radical,[6-8] analogous to electrochemical oxidation of amines.[2] Initial SET is followed by (i) H^+ transfer from C_α and then back-transfer of $HO^\bullet$ from Fe(IV)OH to the resulting C_α radical intermediate or (ii) either H-atom transfer or, more likely, sequential H^+/e^- transfer giving imine/iminium, which is subsequently converted to carbinolamine by addition of the resulting Fe(III)-bound hydroxide.[3] SET oxidation of amines is also described for horseradish peroxidase (HRP),[9,10] which is supposed to be incapable of direct H-atom transfer on account of the inaccessibility of substrates to the "buried" iron center, and thus appears to oxidize "reducing substrates" via their association with the heme edge.[11] Although the C_α primary deuterium kinetic isotope effects for P-450 and HRP oxidation of amines differ considerably,[12,13] these have been rationalized on the basis of recent studies on the acidity of aminyl cation radicals[14] in terms of the presence (P-450) or absence (HRP) of a base to facilitate aminyl deprotonation.[6,8] The flavin-dependent mitochondrial monoamine oxidase (MAO) is also thought to dehydrogenate amines via a stepwise electron/proton/electron transfer mechanism.[15]

Two classes of copper-containing enzymes are known to oxidize amines. The so-called "copper amine oxidases" utilize a covalently bound quinone cofactor to achieve a pyridoxal-like transamination of primary amines to aldehydes, the role of copper being ascribed

† Presented in preliminary form at the 197th (Dallas, April 9–14, 1989, Abstr INOR 451) and 199th (Boston, April 22–27, 1990, Abstr INOR 165) National Meetings of the American Chemical Society.

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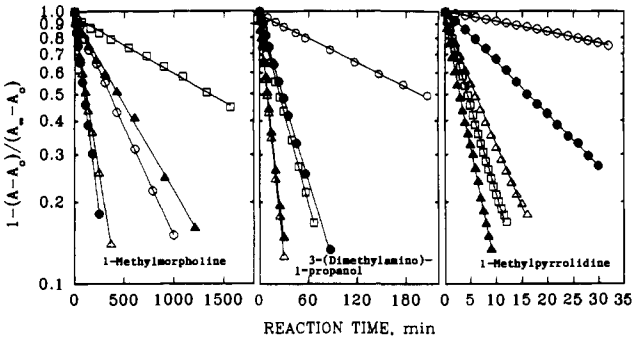

pH 7.0 (○); pH 8.0 (●); pH 9.0 (△); pH 10.0 (▲); pH 11.0 (□)

Figure 1. Pseudo-first-order kinetic plots for the oxidation of three amines by (batho)$_2$Cu^{II} in water (0.10 M phosphate buffer) at 25 °C at five different pH values; [amine]$_0$ = 0.05 M, [Cu(II)]$_0$ = 0.25 mM, [batho]$_0$ = 2.5 mM.

to the O_2-dependent reoxidation of the reductively aminated quinone cofactor.[16,17] The other class of copper enzymes is the so-called "blue" oxidases and includes laccase and the mammalian enzymes ceruloplasmin and ascorbate oxidase. These are all "high-potential" multinuclear (usually four coppers) enzymes which couple the SET oxidation of electron-rich substrates, especially catechols and *aromatic* diamines, to the reduction of dioxygen to water.[18] Although *aliphatic* amines are not usually thought of as substrates for these enzymes,[19] dehydrogenation of certain tertiary amine alkaloids to the corresponding iminium species has been reported[20] and appears to proceed via a mechanism involving one-electron oxidation at nitrogen followed by C_α deprotonation and then a second electron transfer.[20]

We recently reported[21] on a clarification of the mechanism of oxidation of "biological" buffers by the high-potential oxidant (batho)$_2$Cu^{2+} (batho = 2,9-dimethyl-4,7-diphenyl-1,10-phenanthrolinedisulfonate).[22] As this oxidant appeared to oxidize amines by an outer-sphere SET mechanism,[21] it appeared to represent an excellent model for the SET oxidation of aliphatic amines by the "blue" copper oxidases. The redox potential of (batho)$_2$Cu^{2+}, 0.62 V vs NHE,[23] puts it well in the range of the reported potentials of laccase (0.430–0.785).[24] One approach to elucidate oxidation mechanisms is through the use of structure–reactivity profiles coupled with isotope effect measurements. We felt that such characterization of the (batho)$_2$Cu^{2+} oxidant would be useful not only to provide a calibration for interpreting the nature of enzymatic amine oxidations which proceed via electron transfer but also in terms of the intrinsic mechanistic interest. Furthermore, our results could be compared to data obtained by Lindsay Smith on the oxidation of a large series of amines by $Fe(CN)_6^{3-}$,[25-27] a weaker outer-sphere oxidant (0.4 V vs NHE) with an overall negative rather than positive charge.

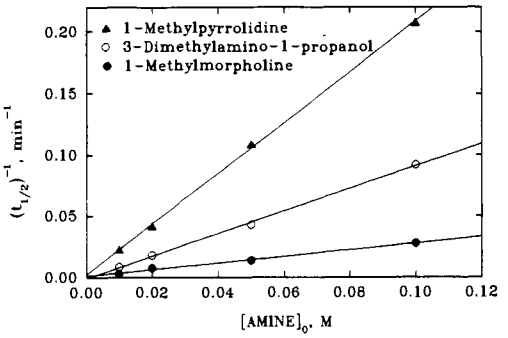

Figure 2. Dependence of $t_{1/2}$ values for the oxidation of three amines by (batho)$_2$Cu^{II} on the concentration of amine (in excess) in water (0.10 M phosphate buffer) at 25 °C; [Cu(II)]$_0$ = 0.25 mM, [batho]$_0$ = 2.5 mM.

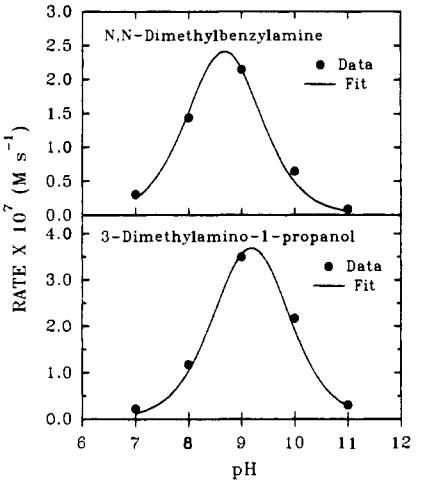

Figure 3. pH–rate profiles for the oxidation of two amines by (batho)$_2$Cu^{II} in 30% aqueous MeOH (top panel) or water (bottom panel) at 25 °C (0.10 M phosphate buffer); [amine]$_0$ = 0.05 M, [Cu(II)]$_0$ = 0.25 mM, [batho]$_0$ = 2.5 mM.

Table I. Effect of batho Concentration on Rate of Cu(II) Oxidation of $(CH_3)_2N(CH_2)_3OH$[a]

pH	[batho]$_0$ (mM)	$t_{1/2}$ (min)	$10^4 k_{obsd}$ (s^{-1})
6.88	1.0	440	0.26
	2.5	400	0.29
	5.0	410	0.28
8.00	1.0	50	2.31
	2.5	24	4.81
	5.0	20	5.78
10.83	1.0	108	1.07
	2.5	28.4	4.01
	5.0	16.8	6.88
11.74	1.0	580	0.20
	2.5	125	0.92
	5.0	71	1.63

[a] Reaction conditions: [amine]$_0$ = 0.05 M, [Cu(II)]$_0$ = 0.10 mM, 0.1 M potassium phosphate buffer, 25.0 °C.

Results and Discussion

General Kinetics Description. Our initial studies using (batho)$_2$Cu^{2+} in the oxidation of a limited series of amines[21] established that (i) the reaction is first-order in both Cu(II) and amine; (ii) the rate decreased with decreasing alkyl substitution on nitrogen and with the introduction of electron-withdrawing sub-

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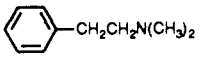
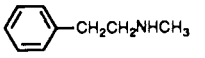
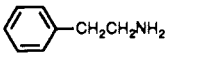
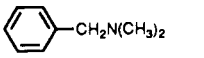
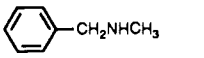
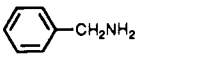
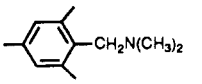
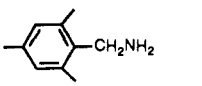
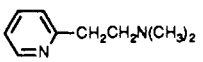
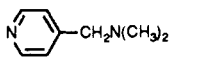
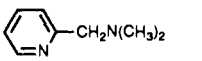
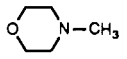
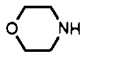
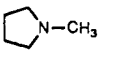
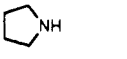
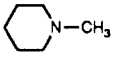
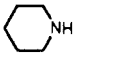
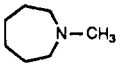
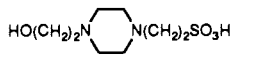
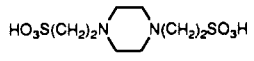
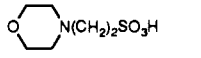
Table II. Second-Order Rate Constants of Amine Oxidation by $(batho)_2Cu^{II}$ [a]

	amines	pK_a (expt)[b]	pK_a (calcd)	10^3k (M^{-1} s^{-1})[h]
1		9.51	9.47	1020
2		10.17	9.94	253
3		9.84	9.54	9.93
4		9.06	9.00	120
5		9.82	9.57	33.5
6		9.60	9.44	1.12
7		9.51	9.31	394
8		9.58	9.43	3.49
9		9.16	9.00	39.1
10		7.63	7.89	3.76
11		8.16[c]		<0.5
12	$(CH_3)_2N(CH_2)_3OH$	9.61	9.69	206
13	$(CH_3)_2N(CH_2)_2OH$	9.42	9.39	131
14	$CH_3NH(CH_2)_2OH$	9.95		39.7
15	$H_2N(CH_2)_2OH$	9.55		1.02
16	$(CH_3)_2N(CH_2)_2OCH_3$	9.39	9.44	387
17	$H_2N(CH_2)_2OCH_3$	9.79		1.25
18	$CH_3(CH_2)_3N(CH_3)_2$	10.06	9.96	489
19		9.45[d]	9.18	13.3
20		8.33[e]		3.24
21		10.32[e]	10.22	2110
22		11.27[e]		385
23		10.38[f]	10.07	425
24		11.20[f]		88.2
25		10.56	10.49	5320
26		7.55[g]		234
27		6.80[g]		68.5
29		6.15[g]		7.01

[a] Reaction conditions: $[amine]_0$ = 0.05 M, 0.10 M phosphate buffer, $[Cu(II)]_0$ = 0.25 mM, $[batho]_0$ = 2.5 mM, 25 °C; **1–11** in 30% aqueous MeOH (v/v), λ = 478 nm; others in water, λ = 483 nm. [b] Measured at 25 °C, ion strength 0.15 M. [c] Fischer, A.; King, M. J.; Robinson, F. P. *Can. J. Chem.* **1978**, *56*, 3059. [d] Dean, J. A., Ed.; *Lange's Handbook of Chemistry*; McGraw-Hill: New York, 1979; 5–34. [e] Weast, R. C.; Astle, M. J.; Beyer, W. H., Ed.; *CRC Handbook of Chemistry and Physics*; 65th ed.; CRC Press Inc.: Boca Raton, FL, 1986; D-163. [f] Reference 28. [g] Sigma Chemical Co. 1988 Catalog, p 313. [h] **1–10**, **12**, **13**, **16**, **18**, **19**, **21**, **23**, and **25** were calculated with 5 pH values; **1–10** using $K_w = 6.04 \times 10^{-15}$, K = 2000, others using $K_w = 1.00 \times 10^{-14}$, K = 400.

stituents; and (iii) the rate increased with increasing pH up to about pH 10 and then decreased at higher pH. Using $[amine]_0 \gg [Cu(II)]_0$ as before, we now report clean pseudo-first-order kinetics for a wide range of amines (typical kinetic plots are shown in Figure 1) in most cases to more than 4 half-lives, though in certain cases complex kinetic behavior was seen in the late stages of the reaction. This could arise if intermediates formed during the reaction reduce $(batho)_2Cu^{2+}$ faster than does the parent amine by a margin which more than compensates for the large excess of parent amine. The first-order dependence in [amine] was independently demonstrated (some examples are shown in Figure 2).

We also checked to see what effect increasing ionic strength had on the rate. For 3-(dimethylamino)-1-propanol, the k_{obsd} for the disappearance of Cu^{2+} *decreased* from 3.63 to 2.96 × 10^{-4} s^{-1} upon addition of 1 M NaCl, using the experimental conditions of Tables I and II at pH 8.1, and k_{obsd} for *N*-methylpyrrolidine *decreased* from 1.26 to 1.12 × 10^{-3} s^{-1}. Although these differences are not large, they are consistent with a decrease rather than an increase in charge localization at the transition state. Very different effects were observed for ferricyanide oxidation of amines, where a high concentration of monocations, especially Cs^+, resulted in a large *increase* in rate.[25] These findings were rationalized in terms of the cations serving as "bridges" to facilitate electron transfer between the amines and the anionic oxidant $[Fe(CN)_6]^{3-}$.[25] Clearly, the *cationic* oxidant used in our study would not be expected to benefit from the presence of potentially "bridging" cations.

Manipulation of Rate Data. We previously explained the bell-shaped pH–rate profile (see Figure 3 for examples) in terms of the low-pH leg reflecting titration of the amine conjugate acid (only the neutral form of amine is oxidizable) and the high-pH leg reflecting a hydroxide-dependent conversion of the (batho)$_2$Cu^{2+} oxidant to a nonoxidizing species.[21] For the latter, we considered two possibilities: (i) a pentacoordinate (batho)$_2$CuOH$^+$ species and (ii) a tetracoordinate (batho)Cu(OH$_2$)OH species, with displacement of one batho ligand per copper, which might subsequently form the di-μ-hydroxy-bridged dimer, (batho)Cu(OH)$_2$Cu(batho)$^{2+}$. Displacement of batho is supported by our finding of an increased rate with increasing [batho] in the descending leg (high pH) but not the ascending leg (low pH) of the pH–rate profile. Illustrative data is given in Table I. The appropriate rate and equilibrium expressions and the resulting solution of the bimolecular rate equation from the pseudo-first-order k_{obsd}, taking into account appropriate stoichiometries, are given below.

$$R_3N + (batho)_2Cu^{2+} \xrightarrow{k} R_3N^{\cdot+} + (batho)_2Cu^{+} \quad (1)$$

$$(batho)_2Cu^{2+} + HO^- \rightleftharpoons (batho)Cu(OH_2)OH^+ + batho \quad (2)$$

Since $[Cu^{2+}]_t = [(batho)_2Cu^{2+}] + [(batho)Cu(OH_2)OH^+]$, $[batho]_t = 2[(batho)_2Cu^{2+}] + [(batho)Cu(OH_2)OH^+] + [batho]$, and $[R_3N]_0 = [R_3N] + [R_3NH^+] = [R_3N](1 + [H^+]/K_a)$, where K_a is the acid dissociation constant of the amine conjugate acid,

$$\text{rate} = -d[(batho)_2Cu^{2+}]/dt = k_{obsd}[(batho)_2Cu^{2+}]_t = k[(batho)_2Cu^{2+}][R_3N] = 2k[R_3N]_0\left(\frac{K_a}{K_a + [H^+]}\right)([batho]_t + K[HO^-] - ([batho]_t^2 + 2K[batho]_t[HO^-] + K^2[HO^-]^2 - 4[batho]_t[Cu^{2+}]_t + 4[Cu^{2+}]_t^2)^{1/2}] \quad (3)$$

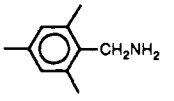
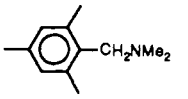
If dimerization of (batho)Cu(OH$_2$)OH$^+$ were very favorable under our reaction conditions, then one might expect the need to utilize the equilibrium expression of eq 4 instead of eq 2. In this case, the rate equation cannot be exactly solved, but by making the minor approximation that $[batho] \approx [batho]_0$, the data can be fit to eq 5, which predicts an approach to half-order dependence on $[Cu^{2+}]_t$ at high pH. To test this point, we measured the

$$2(batho)_2Cu^{2+} + 2HO^- \rightleftharpoons (batho)Cu(OH)_2Cu(batho)^{2+} + 2batho \quad (4)$$

$$\text{rate} = k[R_3N]_0\left(\frac{K_a}{K_a + [H^+]}\right)\left(\frac{-1 + \sqrt{1 + 8K'[HO^-]^2[batho]_0^2[Cu^{2+}]_t}}{4K'[HO^-]^2[batho]_0^2}\right) \quad (5)$$

dependence of rate on $[Cu^{2+}]_t$ at pH 11 for several amines (data not shown); we found that the rates could be fit by eq 3 and not by eq 5. Thus, dimerization of (batho)Cu(OH$_2$)OH$^+$ does not appear to be kinetically significant under our reaction conditions, and we therefore fit the whole of our rate data to eq 3.

Table III. Second-Order Rates (10^3k, M^{-1} s^{-1}) for Oxidation of Various Groupings of Amines by (batho)$_2$Cu^{II} at 25.0 °C

primary amines	secondary amines	tertiary amines
$PhCH_2CH_2NH_2$	$PhCH_2CH_2NHMe$	$PhCH_2CH_2NMe_2$
9.93	253	1020
$PhCH_2NH_2$	$PhCH_2NHMe$	$PhCH_2NMe_2$
1.12	33.5	120
		
3.49		394
$HOCH_2CH_2NH_2$	$HOCH_2CH_2NHMe$	$HOCH_2CH_2NMe_2$
1.02	39.7	131

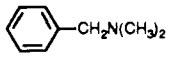
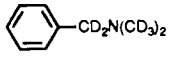
Kinetic constants obtained for 28 amines are listed in Table II. For the first 11 entries, containing phenyl or pyridine groups, the solvent used was 30% aqueous methanol, whereas H_2O was used for the remaining amines. Amine pK_a values were measured by potentiometric titration,[28] or in some cases were available in the literature (as noted in the table footnotes). Computer simulation of pH rate profile data obtained on 18 compounds (entries 1–10, 12, 13, 16, 18, 19, 21, 23, and 25) was then performed according to eq 3. Values of the second-order rate constant k were varied to obtain a best fit with the experimentally determined pK_a values, with the constraints of iteration to a *single* value of K, for each of the two solvent systems used. The resultant values of K were 2000 for 30% aqueous methanol and 400 for water. With these optimal values of K, the rate data were then refitted, this time allowing for variation in the pK_a. The best fit second-order k values along with the "kinetic" pK_a values obtained from the fitting routine and the experimentally determined pK_a values are all listed in Table II. The kinetic pK_a values calculated from the fitting routine are, with three exceptions, seen to be lower than the experimental pK_a values, in some cases by as much as 0.2 to 0.3 pH unit. The cause of these discrepancies is not immediately obvious, but differences between kinetically determined and experimentally measured pK_a values have been observed over the years in many studies. For the remainder of the amines, rate data was obtained at a single pH (8.1); the best fit value of K obtained above was then used in conjunction with the experimental pK_a values to obtain the second-order k's listed in Table II.

Structure–Activity Analysis. In order to facilitate an assessment of the effect on rate of increasing substitution on nitrogen, pertinent second-order k's have been grouped in Table III. The data confirms the general trend primary < secondary < tertiary. Adding two *N*-methyl groups to the primary amines results in a fairly constant average rate acceleration of about 110-fold, whereas adding one methyl group to the secondary amine (compare also entries 19 vs 20, 21 vs 22, and 23 vs 24) results in an average 4-fold rate acceleration. Clearly, the first *N*-methyl has a greater effect than the second, as expected from reactivity–selectivity considerations. The slower rates observed for the benzyl and hydroxyethyl series relative to the phenethyl series are consistent with the expected rate-retarding effect of electron-withdrawing substituents on oxidation at nitrogen. The rates observed for the tertiary amines are about 2 orders of magnitude faster than those observed by Lindsay Smith for oxidation by ferricyanide under similar conditions,[25-27] a finding consistent with the differing redox potentials (0.62 for (batho)$_2$Cu^{2+} and 0.4 for ferricyanide). In fact, primary amines are essentially inert to oxidation by ferricyanide,[25] and thus our observed oxidation of primary amines, albeit slow, is itself good evidence of the lower selectivity of (batho)$_2$Cu^{2+} as an oxidant compared to ferricyanide.

Interestingly, the 2,4,6-trimethyl substitution in the benzyl series results in *faster* rates (~3-fold for both primary and tertiary

(28) Rosenblatt, D. H.; Hull, L. A.; De Luca, D. C.; Davis, G. T.; Weglein, R. C.; Williams, H. K. R. *J. Am. Chem. Soc.* **1967**, *89*, 1158.

Table IV. Rate Data for $(batho)_2Cu^{II}$ Oxidation of *N,N*-Dimethylbenzylamine and Its Perdeutero Derivative[a]

	10^4k_{obsd} (s^{-1})								
	pH 6.0	pH 7.0	pH 8.1	pH 9.0	pH 10.0	pH 11.0	pK_a	k (M^{-1} s^{-1})	k_H/k_D[b]
	0.30	1.22	5.78	5.50	2.60	0.43	9.06	0.120	1.88
	0.14	0.54	2.63	2.99	1.44	0.25	9.36	0.0637	

[a] Reaction conditions: $[amine]_0$ = 0.05 M, $[Cu(II)]_0$ = 0.25 mM, $[batho]_0$ = 2.5 mM, 0.1 M potassium phosphate buffer, 25.0 °C, 30% MeOH. [b] From the curve-fitted second-order k values.

systems; Table III), consistent with an overriding polar effect (electron-donating) rather than steric effect of the ortho methyls. In contrast, we observed that 2,4,6-trimethyl substitution *retards* the alkaline $KMnO_4$ oxidation of benzylamine by a factor of 9 at 30 °C.[29] Permanganate oxidation of primary amines is thought to proceed by hydride or hydrogen-atom abstraction from C_α,[30] which should be sterically slowed by the ortho methyls. We have found that 2,4,6-trimethyl substitution also slows the rate of oxidation of benzylamine by CuCl/pyridine/O_2, a reaction which appears to proceed via coordination of the nitrogen to copper.[31] The dominant polar effect of 2,4,6-trimethylation seen in the case of oxidation by $(batho)_2Cu^{2+}$ is instead consistent with a rate-limiting outer-sphere oxidation at nitrogen for this oxidant.

The rate data listed in Table II, entries 21, 23, and 25, shows the effect of ring size on the oxidation of cyclic tertiary amines; the five- and seven-membered ring systems have rates that are 5 and 12.5 times faster than the six-membered ring system (note that the pK_a values are nearly identical). A similar phenomenon was previously observed by Lindsay Smith for ferricyanide oxidations (though the differences are greater for this more selective oxidant).[26] This has been attributed to conformational energy differences associated with the rehybridization of the nitrogen atom from sp^3 to sp^2 that occurs upon one-electron oxidation to the aminyl cation radical.[32]

Effect of Amine Coordination to Copper. The rate data included in Table II permits an assessment of the effect of coordination ability of the amine on the rate of oxidation by Cu(II). The 32-fold slower rate of the (4-pyridyl)methyl compound relative to the benzyl compound (entries 10 vs 4) is reflective of the greater electron-withdrawing effect for the former. The failure of the (2-pyridyl)methyl compound (entry 11) to undergo oxidation (an upper limit of the rate constant has been estimated) is then interpreted in terms of direct bidentate coordination to Cu(II), apparently with displacement of one or both of the batho ligands. The loss of batho would eliminate the basis of the unusually high oxidizing strength of Cu(II), thus explaining the absence of an observed redox reaction. The 26-fold slower rate of the (2-pyridyl)ethyl relative to the phenethyl system (entries 9 vs 1) is too large to be rationalized alone on the basis of the increased electron-withdrawing effect two carbons away from nitrogen. We believe that there must additionally be partial coordination of the (2-pyridyl)ethyl compound to the Cu(II), with an accompanying lowering in potential. *In the general case*, although our experimental data does not rule out the possibility that some type of interaction of amine with the Cu(II) center facilitates electron transfer, any such coordination cannot be so strong as to result in loss of batho ligand. At the same time, the data is wholly consistent with an outer-sphere one-electron-transfer mechanism.

Kinetic Isotope Effects. Deuterium kinetic isotope effects (DKIE) on *aromatic* amine oxidations have been determined using *N,N*-dimethylaniline, the intermolecular DKIE being assessed using $PhN(CD_3)_2$ vs $PhN(CH_3)_2$ and the intramolecular DKIE being assessed using $PhN(CH_3)(CD_3)$. For the oxidation of *aliphatic* amines by ferricyanide, Lindsay Smith resorted to the use of *N,N*-dimethylbutylamine and its α,α-dideuterio derivative.[26] In a similar vein, we chose to use *N,N*-dimethylbenzylamine and *N,N*-dibenzylmethylamine for obtaining inter- and intramolecular DKIE information. Comparison of the rates for $PhCD_2N(CD_3)_2$ and for $PhCH_2N(CH_3)_2$, with correction for differing pK_a values as shown in Table IV, gives a k_H/k_D ratio of 1.88. This is a "mixed" primary intermolecular DKIE, since the intrinsic k_H/k_D for debenzylation and demethylation may differ. However, the determination of the yield of the two possible secondary amine products indicated similar partial rate factors of 0.46 for debenzylation and 0.54 for demethylation (0.27 per methyl group). We could have measured a "homogeneous" primary DKIE using either $(CH_3)_3N$ or $(PhCH_2)_3N$; however, the primary DKIEs obtained for these two amines would be expected to differ from each other on account of differing positions of the transition state for oxidation at methyl vs oxidation at benzyl. The systems for which we measured kinetic isotope effects were chosen on the basis of the structural similarity to the series of amines (Table II) for which we obtained kinetic data. Suffice it to say that the k_H/k_D value of 1.88 is indicative of a transition state for oxidation which involves little C–H bond breaking, consistent with initial one-electron oxidation at nitrogen as being mainly rate-limiting. Our DKIE is greater than the value of 1.04 obtained for the ferricyanide oxidation of n-Bu_2NCH_3 vs n-Bu_2NCD_3,[26] though the latter value was not corrected for possible changes in product profile which would reduce the k_H/k_D in the event of a partial rate-limiting role of C–H bond breaking.

Through a determination of the yield of the various possible secondary amine products arising from $PhCH_2N(CH_3)CD_2Ph$, we obtained partial rate factors of 0.40 for loss of $PhCH_2$, 0.12 for loss of $PhCD_2$, and 0.48 for loss of CH_3. This is indicative of a "product" DKIE (intramolecular k_H/k_D) of 3.3 for debenzylation, a value which was confirmed by measuring the yields of PhCHO and PhCDO. This is very similar to the "product" DKIE of 3.6 obtained for the ferricyanide oxidation of n-Bu_2NCD_3.[26] Both of these "product" DKIE values are 2–3 times smaller than those observed for mechanisms involving C_α–H bond breaking via a symmetrical transition state.[30] This means either that loss of the C_α proton involves a substantially asymmetric transition state or that one-electron oxidation of the benzylic radical to the benzylidene iminium product is partially rate-limiting.

Stereoelectronic Effects. When the facile oxidation of HEPES and *N,N*-dimethylethanolamine by $(batho)_2Cu^{2+}$ was first reported,[22] we considered the possibility that the β-heteroatom substitution in these amines was facilitating oxidation via a concerted oxidative cleavage mechanism (eq 6). When we found, however, that oxidations by $(batho)_2Cu^{2+}$ were quite general, it no longer appeared necessary to consider any special type of mechanism. In fact, we found (Table II) that *N,N*-dimethyl-*propanol*amine, which cannot undergo the eq 6 mechanism, reacted *faster* than its C_2 homologue (compare entries 12 vs 13), consistent with a weakening of the rate-retarding electron-withdrawing effect of oxygen. Nonetheless, in a series of papers on

$$:XCH_2CH_2NR_2 \xrightarrow{-e^-} :XCH_2^{\bullet} + CH_2{=}NR_2^+ \quad (:X = R'O, R'_2N) \qquad (6)$$

(29) Amine oxidations by $KMnO_4$ were conducted under pseudo-first-order conditions ($[KMnO_4]_0$ = 1.0 mM, $[amine]_0$ = 40 mM) in 30% aqueous CH_3CN, which was 0.5 M in KOH at 30.0 °C. The reduction of Mn(VII) was followed at 522 nm. A first-order plot of the absorbance change was linear to 4 half-lives. The $t_{1/2}$ values for benzylamine and its 2,4,6-trimethyl derivative were 36 and 321 s (average of two runs).

(30) Wei, M.-M.; Stewart, R. *J. Am. Chem. Soc.* **1966**, *88*, 1974.

(31) Tang, W.; Sayre, L. M. Manuscript in preparation.

(32) Lindsay Smith, J. R.; Masheder, D. *J. Chem. Soc., Perkin Trans. 2* **1976**, 47.

Table V. *dl-erythro-* and *dl-threo*-2-(1-Piperidino)-1,2-diphenylethanol Oxidation by (batho)$_2$Cu^{II} [a]

amines	10^4k_{obsd} (s^{-1}) (pH) 6.9	7.9	8.9	9.9	10.9	k (M^{-1} s^{-1}) [b]
erythro	3.85	15.8	18.4	3.96	0.584	0.237
threo	1.88	5.32	6.04	1.51	0.144	0.0685

[a] Reaction conditions: [amine]$_0$ = 0.05 M, 0.10 M Cs_2CO_3 buffer, [Cu^{II}]$_0$ = 0.25 mM, [batho]$_0$ = 2.5 mM, 25 °C, in 50% aqueous MeOH (v/v). [b] Calculated by using $K_w = 4.35 \times 10^{-15}$, K = 3400.

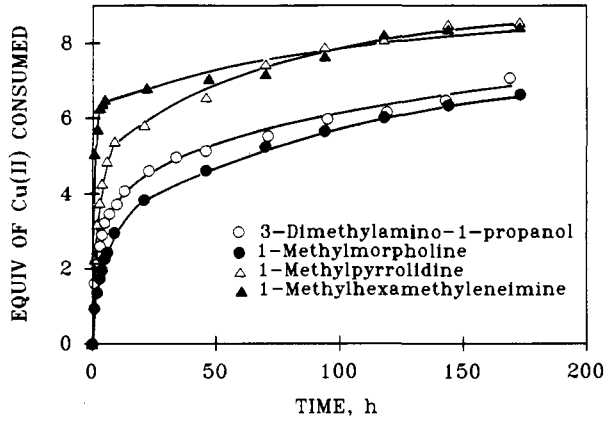


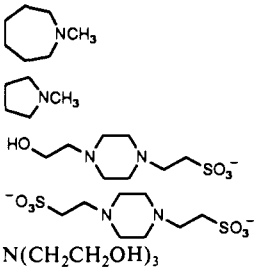
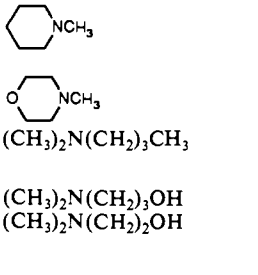
Figure 4. Time plots for consumption of (batho)$_2$Cu^{II} (in excess) by four amines in water at 25 °C; see the Experimental Section for reaction conditions.

the photoinduced SET oxidation of amines,[33] Whitten and co-workers observed that a β-heteroatom can provide stereoelectronic assistance to oxidation at nitrogen *even when cleavage occurs in a subsequent step.*[34] Apparently, the proper positioning of a lone pair on a β-heteroatom disposed antiperiplanar to the nitrogen undergoing oxidation provides a "frontier orbital" (hyperconjugative) facilitation of HOMO ionization. This was ascertained through rate comparisons between threo and erythro diastereomers that contain large groups (e.g., 1,2-diaryl substitution) to provide steric control of conformational preference.

We compared the propensity of the erythro and threo isomers of 1,2-diphenyl-2-piperidinoethanol to undergo oxidation by (batho)$_2$Cu^{2+} in buffered methanol, where the pH was maintained using 0.1 M Cs_2CO_3 and the required amount of added CF_3CO-OH. Computer fitting of the data shown in Table V to eq 3 using the experimentally determined pK_a values of 8.92 (erythro) and 8.80 (threo) and allowing free variation in K yielded a best fit to the k values shown, with K = 3400. The 3.5-fold greater rate for the erythro diastereomer is consistent with a preferred antiperiplanar orientation of oxygen and nitrogen as enforced by the preferred transoid (as opposed to gauche) disposition of the vicinal phenyl groups. Curiously, this rate difference is equal to the 3–4 greater reactivity of erythro compared to threo observed by Whitten and co-workers for photoinduced oxidation of related β-heteroatom-substituted amines.[34]

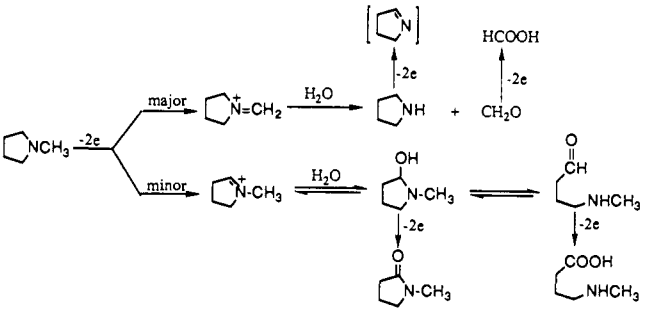
Stoichiometry and Product Studies. Although the comparative rate data presented in Table II is indicative of the electronic effects governing what we believe to be an initial one-electron oxidation at nitrogen, we have so far said nothing about the overall mechanism leading to products of N-dealkylation. We approached the latter question in two ways: by measuring the number of equivalents of (batho)$_2$Cu^{2+} reduced by 1 equiv of various amines and, in some cases, through direct product analysis. In the former case, a time plot for the reduction of 10 equiv of (batho)$_2$Cu^{2+} by 1 equiv of amine was obtained, and the number of equivalents consumed at the inflection, to the closest whole integer, was noted by inspection (see the examples in Figure 4). The results are provided in Table VI. Hegetschweiler and Saltman previously reported that HEPES is able to reduce 6 equiv of Cu^{2+},[22] and we confirmed this result as well as finding the same behavior for PIPES. We additionally found that the simple five- and seven-membered cyclic *N*-methyl tertiary amines also consumed 6 equiv of Cu^{2+}, whereas the corresponding six-membered ring and all simple acyclic tertiary amines examined consumed 4 equiv of Cu^{2+}.

Table VI. Stoichiometry of Cu(II) Reduced by Tertiary Amines

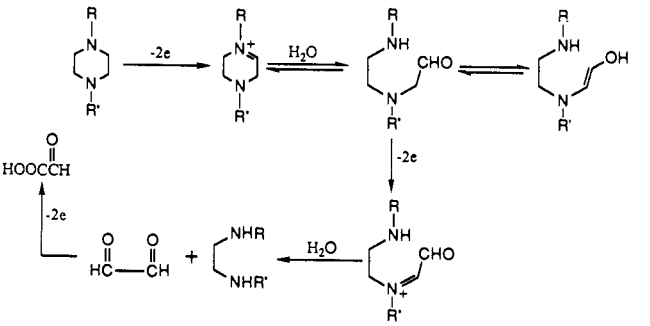
amines which consume 6 equiv of Cu(II)	amines which consume 4 equiv of Cu(II)
	
$CH_3N(CH_2CH_2OH)_2$ [a]	

[a] Consumed most closely 5 equiv of Cu(II) during rapid phase of Cu(II) depletion.

Scheme I



Scheme II



Our explanation of these results is provided in eq 7 and Schemes I and II. The acyclic tertiary amines consume 2 equiv of Cu^{2+} in achieving N-dealkylation to a secondary amine and an aldehyde, the latter then consuming 2 equiv of Cu^{2+} upon oxidation to carboxylic acid (eq 7). In independent experiments we confirmed

$$R_2NCH_2R' \xrightarrow{-2e} R_2\overset{+}{N}{=}CHR' \xrightarrow{H_2O} R_2NH + R'CH{=}O \xrightarrow{-2e} R'COOH \quad (7)$$

that formaldehyde and butyraldehyde consume 2 equiv of Cu^{2+} during the time course of the rapid Cu^{2+} depletion (first 10 h), whereas the secondary amines are oxidized very slowly. The consumption of 6 equiv of Cu^{2+} by *N*-methylpyrrolidine (Scheme I) is rationalized on the basis of using 4 equiv to achieve oxidative

(33) Lee, L. Y. C.; Ci, X.; Giannotti, C.; Whitten, D. G. *J. Am. Chem. Soc.* **1986**, *108*, 175.
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N-demethylation to a secondary amine and eventually HCOOH, and an additional 2 equiv in achieving dehydrogenation of pyrrolidine to 1-pyrroline (identified by comparison to an authentic sample). The heightened reactivity of the secondary amine in this case is explained on the basis of ring size as discussed above, a conclusion which we confirmed by independently demonstrating that pyrrolidine consumes 2 equiv of Cu^{2+} in the rapid phase of the stoichiometry experiments (data not shown). Presumably the analogous situation holds in the case of the seven-membered ring, whereas the secondary six-membered ring (piperidine) was shown to be oxidized too slowly to compete during the same time frame. In competition with N-demethylation is ring oxidation, a pathway which, as shown in Scheme I, would alone result in the consumption of 4 equiv of Cu^{2+}. The operation of this pathway was confirmed through our isolation of 1-methyl-2-pyrrolidinone (not quantified) in the oxidation of *N*-methylpyrrolidine. However, it appears that ring oxidation is a minor pathway in this case, since otherwise one would have expected the overall consumption to be closer to 4 rather than 6 equiv of Cu^{2+}.

The consumption of 6 equiv of Cu^{2+} in the oxidation of HEPES and PIPES is understood in terms of double oxidative cleavage of a single ethylene edge (Scheme II). This yields, after two two-electron oxidations, an N,N'-disubstituted ethylenediamine derivative (which being a secondary amine would undergo only very slow further oxidation) and glyoxal, the latter consuming 2 additional equiv of Cu^{2+} in being oxidized to glyoxylic acid. The consumption by glyoxal of only 2 equiv of Cu^{+} during the rapid phase of Cu^{2+} depletion and the relative inertness of glyoxylic acid were independently confirmed, though we made no attempt to verify production of glyoxylic acid in these reactions. The preference for the second two-electron oxidation occurring at the same ethylenediamine edge as the first is understood in terms of the well-known ease of oxidation of α-amino carbonyl compounds, explained on the basis of equilibration of this functionality with an enol–enamine tautomer,[35] as shown in Scheme II. It is clear that if the second two-electron oxidation occurred on the *other* ethylenediamine edge, then one would generate *two* α-amino aldehyde functions, which should then result in the consumption of 8 rather than 6 equiv of Cu^{2+}.

Lastly, our results comparing the mono-, bis-, and tris-β-hydroxyethyl tertiary amines indicate that oxidative C_α–C_β cleavage of these β-oxy-substituted amines provides no special encouragement for oxidation, as alluded to above. Our finding that triethanolamine consumes 6 equiv of Cu^{2+} can be rationalized in two ways: (i) initial two-electron oxidative C–C cleavage yielding CH_2O and $(HOCH_2CH_2)N{=}CH_2^+$, the latter subsequently hydrolyzing to a secondary amine and CH_2O followed by oxidation of the two formaldehydes to HCOOH (2 × 2e) or (ii) initial 2e oxidative N-dealkylation to a secondary amine and $HOCH_2CHO$, the latter subsequently undergoing four-electron oxidation, first to glyoxal and then to glyoxylic acid. The finding that *N*,*N*-dimethylethanolamine consumes only 4 equiv of Cu^{2+} is then indicative of preferential oxidative N-demethylation in this compound. Finally, *N*-methyldiethanolamine was found to consume very close to 5 equiv of Cu^{2+}, suggesting that only when there is a 2-fold statistical "edge" does oxidation at *N*-β-hydroxyethyl compete equally with oxidation at *N*-methyl.

Conclusion

We have presented a kinetics and mechanism study on the oxidation of aliphatic amines by the high-potential mononuclear Cu(II) oxidant, $(batho)_2Cu^{II}$. Structure–reactivity data supports a mechanism involving an essentially outer-sphere initial one-electron oxidation at nitrogen, followed by loss of a proton to the solvent, where the first step is mainly rate-limiting. Strong coordination of amines to the copper (i.e., through chelation) prevents rather than aids oxidation, apparently on account of displacement of the batho ligand, which in turn lowers the Cu(II) oxidation potential. The reactivity trends parallel, to a large extent, those seen by Lindsay Smith using ferricyanide as the oxidant, except that $(batho)_2Cu^{II}$ is a less selective oxidant and, unlike ferricyanide, is converted to a ineffective oxidant at high pH. The Cu(II) and Fe(III) oxidants also respond differently to the effect of solvent ions. We found that the oxidation of amines by Cu(II) reflects a stereoelectronic preference equal to that observed by Whitten in the photoinduced oxidation of amines. Stoichiometry studies on tertiary amines are consistent with an overall two-electron oxidation of amine to imine (or iminium), which can be followed by a second two-electron oxidation when the resulting secondary amine is particularly susceptible to oxidation (e.g., pyrrolidine but not piperidine), as well as by oxidation of the released aldehyde. Our results provide general structure–reactivity information which should be useful in interpreting the reactivity trends of aliphatic amine oxidation by "electron-transfer" enzymes. Oxidation of lower potential amines by various "blue" copper oxidases may be found to be more common than is usually considered and could conceivably occur physiologically.

Experimental Section

General Methods and Materials. All ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian XL-200 Fourier transform spectrometer, using tetramethylsilane as the internal standard. UV–visible spectra were obtained using a Perkin-Elmer Lambda 3B spectrophotometer equipped with a temperature-controlled multiple-cell compartment. Mass spectra were recorded on a Kratos MS25RFA spectrometer. Melting point were obtained using a Thomas-Hoover apparatus and are uncorrected. All solvents, reagents, and organics were the most pure available from commercial sources. The following tertiary amines were obtained from Aldrich Chemical Co.: *N*,*N*-dimethylbenzylamine, *N*,*N*-dimethylethanolamine, 3-(dimethylamino)-1-propanol, 1-methylmorpholine, 1-methylpyrrolidine, and 1-methylpiperidine.

Previously unreported spectral data are given below for tertiary amines which were prepared from commercial primary or secondary amines by methylation using the standard HCHO–HCOOH method.[36] ***N*,*N*-Dimethyl-*n*-butylamine**: ^1H NMR δ 0.92 (t, 3 H, J = 7.1 Hz, CH_3), 1.31–1.48 (m, 4 H, CH_2), 2.21–2.28 (m, 8 H, CH_3N and CH_2N); bp 93–34 °C (lit.[36] bp 94 °C). **2-[(Dimethylamino)methyl]pyridine**: ^1H NMR δ 2.30 (s, 6 H, NCH_3), 3.59 (s, 2 H, CH_2N), 7.19 (dd, 1 H, J = 5.7 and 7.5 Hz, Py C_5-H), 7.37 (d, 1 H, J = 7.5 Hz, Py C_3-H), 7.65 (t, 1 H, J = 7.5 Hz, Py C_4-H), 8.58 (d, 1 H, J = 5.7 Hz, Py C_6-H); bp 61–62 °C (4 mm) (lit.[37] bp 74–75 °C (7 mm)). **4-[(Dimethylamino)methyl]pyridine**: ^1H NMR δ 2.25 (s, 6 H, NCH_3), 3.43 (s, 2 H, CH_2N), 7.26 (d, 2 H, J = 6.0 Hz, Py C_3/C_5-H), 8.55 (d, 2 H, J = 6.0 Hz, Py C_2/C_6-H); bp 86–87 °C (11 mm) (lit.[37] bp 86–87 °C (11 mm)). 1-Methylhexamethyleneimine: ^1H NMR δ 1.59 (s, 8 H, CH_2), 2.35 (s, 3 H, NCH_3), 2.54 (t, 4 H, NCH_2); bp 139–140 °C (lit.[38] bp 140 °C). ***N*,*N*-Dimethyl-(2-methoxyethyl)amine**: ^1H NMR δ 2.27 (s, 6 H, NCH_3), 2.49 (t, 2 H, J = 5.5 Hz, CH_2N), 3.37 (s, 3 H, OCH_3), 3.47 (t, 2 H, J = 5.5 Hz, CH_2O); bp 101–103 °C (lit.[39] bp 101–103 °C).

Previously unreported physical/spectral data are given below for amines which we prepared according to the cited references. 2-[2-(Dimethylamino)ethyl]pyridine, prepared from the base-mediated addition of dimethylamine to 2-vinylpyridine:[40] bp 88–89 °C (5 mm); ^1H NMR δ 2.31 (s, 6 H, NCH_3), 2.72 (t, 2 H, J = 7 Hz, Py-CH_2), 2.97 (t, 2 H, J = 7 Hz, NCH_2), 7.16 (m, 2 H, Py C_3-H and C_5-H), 7.63 (t, 1 H, J = 6 Hz, Py C_4-H), 8.56 (d, 1 H, Py C_6-H). 2,4,6-Trimethylbenzylamine, prepared by $LiAlH_4$ reduction[41] of mesitonitrile:[42] bp 99–101 °C (6 mm) (lit.[43] bp 98.5–100 °C (6 mm)); ^1H NMR δ 1.18 (s, 2 H, NH_2), 2.24 (s, 3 H, CH_3), 2.34 (s, 6 H, CH_3), 3.80 (s, 2H, NCH_2), 6.83 (s, 2 H, Ar). *N*,*N*-Dimethyl-(2,4,6-trimethylbenzyl)amine, prepared from condensation of dimethylamine with 2,4,6-trimethylbenzyl chloride in benzene:[44] bp 107–108 °C (10 mm) (lit.[44] bp 107–108 °C (10 mm)); ^1H NMR δ

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2.21 (s, 6 H, NCH_3), 2.24 (s, 3 H, CH_3), 2.34 (s, 6 H, CH_3), 3.34 (s, 2 H, CH_2N), 6.82 (s, 2 H, Ar).

N,N-Dimethylbenzylamine-d_8 was prepared by the $LiAlD_4$ reduction[45] of N,N-dimethylbenzamide-d_6 in dry ether: bp 180-182 °C (743 mm); ^1H NMR δ 7.31 (s, 5 H, Ph); ^{13}C NMR (^{13}C-^2H couplings) δ 45.4 (sp, J = 23 Hz, NCD_3), 64.4 (p, J = 22 Hz, CD_2), 127.0 (s, C-4), 128.2 (s, C-3 and C-5), 129.1 (s, C-2 and C-6), 138.9 (s, C-1); EIMS (40 eV) m/z 143 (M^+, 10), 107 ([M - $2CD_3$]$^+$, 13). N,N-Dimethylbenzamide-d_6 was prepared[46] by heating a mixture of benzoyl chloride and N,N-dimethylformamide-d_7 (Aldrich) at 150 °C for 4 h, followed by extraction of the reaction mixture with ether, evaporation of the ether layer, and fractional distillation under reduced pressure: bp 135-137 °C (15 mm); ^1H NMR δ 7.39 (s, 5 H, Ph).

N,N-Dibenzylmethylamine-α,α-d_2 was prepared[47] by reduction of N-methyl-N-benzylbenzamide[48] with $LiAlD_4$ in dry ether: bp 135-136 °C (4 mm); ^1H NMR δ 2.15 (s, 3 H, NCH_3), 3.94 (s, 2 H, CH_2N), 7.23-7.36 (m, 10 H, Ph); EIMS (40 eV) m/z 213 (M^+, 8).

dl-erythro-2-(1-Piperidino)-1,2-diphenylethanol and *dl-threo*-2-(1-piperidino)-1,2-diphenylethanol were prepared according to the published procedure[49] in 56% and 51% yields, respectively.

Kinetics. Buffer solutions were prepared weekly in doubly distilled water. A solution of the $(batho)_2Cu^{II}$ complex was prepared using the appropriate quantities of $CuSO_4$ and batho. A solution of the amine was prepared separately in phosphate buffer, and the pH was adjusted to the desired value with KOH. Following equilibration of 2.9 mL of the latter solution in the spectrometer at 25 °C, 0.1 mL of $(batho)_2Cu^{II}$ solution was added, and the cuvette was shaken. The reactions were followed by monitoring the formation of $(batho)_2Cu^{I}$ spectrophotometrically at 483 nm (water),[23] 478 nm (30% aqueous MeOH), or 474 nm (50% aqueous MeOH). To complete the reduction of Cu(II) and to determine the infinity absorbance, 5 μL of 10% sodium dithionite solution was added. The pH values were obtained at 25.0 °C using a Fisher Accumet Model 810 meter. The "apparent" pH values in 30% and 50% aqueous MeOH (v/v) were converted to operational pH values by subtraction of 0.04 and 0.10, the appropriate values of "δ" for these same solvent mixtures.[50] The pK_w values used for these same solvent mixtures were 14.219 and 14.362, respectively.[51]

Determination of Stoichiometry. The number of equivalents of Cu(II) reduced per equivalent of the various amines was determined by adding 0.1 mL of an aqueous or methanolic solution of 0.02 mmol of amine to a mixture of 2 mL of an aqueous solution of 0.2 mmol of $(batho)_2Cu^{II}$, 1 mL of 0.30 M KH_2PO_4, and 1 mL of 0.60 M KOH and keeping the resulting mixture in the dark at 25 °C. Aliquots were removed at periodic intervals over a 7-day period and diluted by a factor of 150 with water for determination of A_{483}.

Product Analysis. To a solution of batho (3.34 g, 5.90 mmol) and 0.74 g (2.95 mmol) of $CuSO_4$ in 10 mL of water was added a solution of 1.5 mmol of amine in 5 mL of 0.3 M potassium phosphate buffer at pH 8. After remaining at 25 °C for 24 h, the reaction mixture was brought to pH 12.5 and extracted with five 10-mL portions of ether. The ether layer was back-extracted with three 15-mL portions of 10% HCl and then treated with a slight excess of 2,4-DNP reagent, and the resulting (2,4-dinitrophenyl)hydrazone was removed by filtration, dried, and weighed for determination of the yield of aldehyde products. A weighed amount of fumaric acid disodium salt was added to the aqueous layer (containing the amine products in HCl salt form), which was then evaporated to dryness in vacuo and analyzed by ^1H NMR spectroscopy. The yield of amine product was determined by integration relative to the fumaric acid singlet. Both the aldehyde and amine were analyzed by ^1H NMR for determination of the product distribution in the case of the N,N-dibenzylmethylamine-α,α-d_2 reaction.

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Registry No. 1, 1126-71-2; **2**, 589-08-2; **3**, 64-04-0; **4**, 103-83-3; **5**, 103-67-3; **6**, 100-46-9; **7**, 34274-10-7; **8**, 40393-99-5; **9**, 6304-27-4; **10**, 38222-85-4; **11**, 43071-19-8; **12**, 3179-63-3; **13**, 108-01-0; **14**, 109-83-1; **15**, 141-43-5; **16**, 3030-44-2; **17**, 109-85-3; **18**, 927-62-8; **19**, 109-02-4; **20**, 110-91-8; **21**, 120-94-5; **22**, 123-75-1; **23**, 626-67-5; **24**, 110-89-4; **25**, 1192-95-6; **26**, 7365-45-9; **27**, 5625-37-6; **29**, 4432-31-9; $(batho)_2Cu^{II}$, 14875-92-4; D_2, 7782-39-0; *dl-erythro*-2-(1-piperidino)-1,2-diphenylethanol, 19640-37-0; *dl-threo*-2-(1-piperidino)-1,2-diphenylethanol, 19640-36-9.

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Effect of Transition-Metal Complexation on the Stereodynamics of Persubstituted Arenes. Evidence for Steric Complementarity between Arene and Metal Tripod

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Abstract: The stereodynamics in 1,4-dimethoxy-2,3,5,6-tetraethylbenzene (**5**), 1,4-bis(methoxymethyl)-2,3,5,6-tetraethylbenzene (**6**), and 1,4-dineohexyl-2,3,5,6-tetraethylbenzene (**7**) and their respective tricarbonylchromium complexes, **5(Cr)**, **6(Cr)**, and **7(Cr)**, have been studied by variable-temperature NMR techniques. Barriers to rotation about the sp^2-sp^3 bonds for **5-7** and **5(Cr)-7(Cr)** have been determined using the Gutowsky-Holm approximation to be 7.7, 9.4, 11.2, 6.6, 8.9, and 11.8 kcal/mol, respectively. Unlike previous studies in this area, the stereodynamics of the arene do not change demonstrably upon metal complexation. This observation is attributed to a lock-and-key complementarity between the metal tripod and the arene. The possibility of correlated dynamics between the metal tripod rotation and the ethyl group rotation is discussed.

The use of transition-metal complexation as a method for studying the stereodynamics of alkylbenzenes has recently been demonstrated.[1] This method desymmetrizes a π system (e.g., an arene) by rendering the faces of the π system nonequivalent. The utility of the method is limited by the degree to which the presence of the metal disturbs the parent compound's stereodynamics. These limits can be probed through systems where the symmetry allows one to observe the stereodynamics of both the free and the metal-complexed arene. Investigations of this type

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