NMR probe at 25 °C, and the kinetics were monitored. The same procedure was performed when measuring the effect of the methyl group in 1,3,2λ⁵-dioxaphospholanes **9** and **10**.

(d) $ZnCl_2$: k_2 Measurement for Epoxide Formation. To a clean, dry, purged (argon) 10-mm NMR tube that had been fitted with a septum was added 2.00 mL of 1,3,2λ⁵-dioxaphospholane **3** (0.46 mmol) and 0.50 mL of benzene-d_6 (NMR lock solvent). The tube was then cooled to −78 °C (dry ice/acetone bath), and 2.00 mL of a 0.23 M $ZnCl_2$ solution (in THF) was added (0.46 mmol). The tube was immediately placed in the NMR probe at −30 °C, and a ^{31}P NMR spectrum showed complete conversion of **3** to betaines **4a** and **4b** (δ 63.5 and 62.0 ppm). The probe was slowly warmed to 0 °C and at this temperature the disappearance of **4a** and **4b** and appearance of TPPO were monitored.

(e) $ZnCl_2$: k_2 Measurement for Hydride Migration. In a clean, dry argon-purged 10-mm NMR tube equipped with a septum was added 2.00 mL of 0.23 M 1,3,2λ⁵-dioxaphospholane **13** (in THF) and 0.50 mL of benzene-d_6 (NMR lock solvent). The tube was then cooled to −78 °C, and 2.00 mL of 0.23 M $ZnCl_2$ (in THF) was added. The tube was then placed in the NMR probe at −30 °C. The kinetics were subsequently monitored at 25 °C using the ^{31}P NMR resonance at δ 61.1 which is attributable to the requisite oxaphosphonium ion.

(f) Solvent Effects. The procedure was identical with that described in entry b, except 1,3,2λ⁵-dioxaphospholane **13** was prepared in toluene solvent (2.00 mL) to provide a solution for NMR study, which consisted of 2.00 mL of toluene, 2.00 mL of THF, and 0.50 mL of benzene-d_6 (NMR lock solvent).

Reaction of (*S*)-(−)-1,1-Diphenyl-1,2-propanediol with DTPP/LiBr. (*S*)-(−)-1,1-Diphenyl-1,2-propanediol (**11**) (0.500 g, 0.0022 mol) was added to a toluene solution (2.20 mL) of 1.0 M DTPP (0.0022 mol) in a 50-mL round-bottom flask. The solution was allowed to stir at ambient temperature for 3 h to permit complete conversion of (*S*)-(−)-**11** to the 1,3,2λ⁵-dioxaphospholane with DTPP. Afterward, oven-dried LiBr (0.250 g, 0.003 mol) was added. The mixture was allowed to stir for 24 h, and epoxide **7** (0.305 g, 66% isolated yield) was obtained by "rapid" chromatography using 4% ethyl acetate/96% hexanes as eluent. An optical rotation determination indicated inversion of stereochemistry at the stereocenter, and chiral shift ^1H NMR analysis with Eu(hfc)$_3$ indicated 96% ee.

Reaction of (*S*)-(−)-11 with DTPP/$ZnCl_2$. (*S*)-(−)-1,1-Diphenyl-1,2-propanediol (**11**) (0.700 g, 0.003 mol) was added to a toluene solution (3.00 mL) of DTPP (1 M, 0.003 mol) in a 25-mL, round-bottom flask. The solution was stirred for 3 h to effect formation of the requisite 1,3,2λ⁵-dioxaphosphospholane, and then $ZnCl_2$ (0.040 g, 0.0003 mol) was added to the dioxaphospholane at ambient temperature. The solution was allowed to stir for 16 h. Epoxide **7** was isolated by procedures described above, and an optical rotation determination coupled with a chiral shift ^1H NMR study showed retention of stereochemistry at the carbon stereocenter with 23% ee.

Reaction of (*R*)-(+)-7 with $ZnCl_2$: The Control. An anhydrous, toluene solution (1.20 mL) of (*R*)-(+)-**7** (0.210 g, 0.001 mol; 96% ee) was admixed with absolute ethanol (0.092 g, 0.002 mol), triphenylphosphine oxide (0.278 g, 0.0010 mol), and anhydrous $ZnCl_2$ (0.014 g, 0.0001 mol) under an argon atmosphere. The solution was allowed to stir under argon for 18 h, and then analysis by ^{13}C NMR spectroscopy indicated >75% conversion to 1,1-diphenyl-1-ethoxy-2-propanol (**8**), with the remaining product identified as unreacted epoxide **7**. The reaction mixture was purified by "rapid" chromatography using 4% ethyl acetate/96% hexanes as eluent, and **7** (0.018 g) was recovered. Subsequent optical rotation and chiral shift ^1H NMR experiments indicate that epoxide **7** displayed >95% ee, demonstrating that no epimerization of the chiral center has occurred upon interaction with $ZnCl_2$.

Methylation of 1,3,2λ⁵-Dioxaphospholane 3. Methyl trifluormethanesulfonate (0.34 g, 0.002 mol) was added (via syringe) to a solution of dioxaphospholane **3** in dichloromethane solvent (0.7 M, 3.00 mL, 0.0021 mol) under an argon atmosphere in a 10-mm NMR tube at −78 °C. The NMR tube was then placed in a preequilibrated NMR probe at −78 °C. The ^{31}P NMR spectrum is characterized by five distinct resonances; the major ones at δ 63.9 and 62.6 ppm were assigned to the regioisomeric oxyphosphonium salts on the basis of their similarities in the ^{31}P NMR shifts with **4a,b**.

Acknowledgment is made to the National Science Foundation (Grant CHE-87-20270) and the University of North Carolina's Research Council for support of this research. We are grateful to M & T Chemical Co. for samples of TPP.

Registry No. **3**, 104762-38-1; **9**, 104778-48-5; **10**, 118831-85-9; **13**, 96553-70-7; **15**, 96455-85-5; **19**, 49595-63-3; **27**, 104962-41-6.

Electrochemical Models for Cytochrome P-450. N-Demethylation of Tertiary Amides by Anodic Oxidation

Larry R. Hall,† Reynold T. Iwamoto,‡ and Robert P. Hanzlik*,†

Departments of Medicinal Chemistry and Chemistry, University of Kansas, Lawrence, Kansas 66045-2506

Received July 20, 1988

Anodic oxidation of *N,N*-dimethylamides in acetonitrile/water (95:5) containing $NaClO_4$ gives the corresponding *N*-methylamides in high yields. *N*-Methyl-*N*-(hydroxymethyl)benzamide was isolated as an intermediate in the electrochemical N-demethylation of *N,N*-dimethylbenzamide and was characterized by GC/MS as its trimethylsilyl ether. Intramolecular kinetic deuterium isotope effects were measured for the anodic N-demethylation of *N*-methyl-*N*-trideuteriomethyl amides $RCON(CH_3)CD_3$, where R = $PhCH_2CH_2$, Ph, *p*-$O_2NC_6H_4$, and C_6F_5. The observed isotope effects were 2.16 ± 0.07, 2.78 ± 0.21, 2.10 ± 0.17, and 2.60 ± 0.15, respectively. The intermolecular isotope effect for anodic N-dealkylation of *N,N*-dimethylbenzamide was ca. 1.4–1.7. These isotope effects are much lower than those observed for cytochrome P-450 catalyzed N-demethylation of these compounds and are consistent with an ECE (electrochemical/chemical/electrochemical) mechanism involving aminium ion intermediates. These anodic oxidations are mild and highly reproducible and may have potential for synthetic application, particularly for the synthesis of metabolites.

The oxidative N-dealkylation of amines by cytochrome P-450 enzymes is a reaction of central importance in the biotransformation of a great many organic compounds, both endogenous and xenobiotic. The results of numerous studies of enzymic dealkylations,[1-7] as well as chemical[8-12] and photochemical[13,14] reactions that mimic this process,

† Department of Medicinal Chemistry.
‡ Department of Chemistry.

(1) Hanzlik, R. P.; Tullman, R. H. *J. Am. Chem. Soc.* **1982**, *104*, 2048–2050.
(2) Macdonald, T.; Karimulla, Z.; Burka, L. T.; Peyman, P.; Guengerich, F. P. *J. Am. Chem. Soc.* **1982**, *104*, 2050–2052.

0022-3263/89/1954-2446$01.50/0

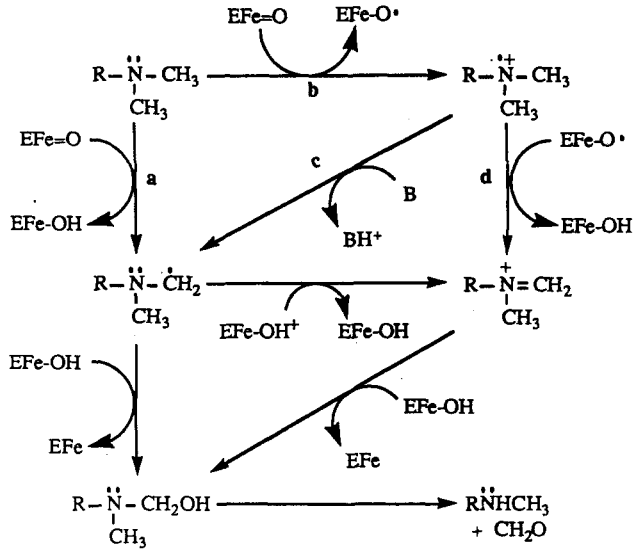


Figure 1. Mechanistic pathways for N-dealkylations of amines by cytochrome P-450 enzymes. Path a illustrates the "abstraction–recombination" mechanism, in which EFe=O represents the oxo-iron form of the hemoprotein and EFe is the ferric form of the enzyme (formally two equivalents lower in oxidation state than EFe=O). Pathway b illustrates the "aminium ion" mechanism; the electron acceptor is assumed to be the oxo-iron form of P-450 (EFe=O), and species B is a proton acceptor at the active site (possibly the oxygen of the one-electron-reduced form of EFe=O).

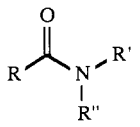
suggest the involvement of two limiting types of reaction mechanisms (Figure 1). These mechanisms are most often and perhaps best differentiated by their characteristic kinetic deuterium isotope effects (KDIEs).[4,7,8-12] In the first of these mechanisms (Figure 1, path a), hydrogen abstraction by the oxidant species is both the rate-limiting and product-determining step and is characterized by large KDIEs (≥7). The second (Figure 1, path b) involves an initial electron abstraction from the amine as the rate-limiting step, followed by either deprotonation of the resulting aminium ion (Figure 1, path c) or H-atom abstraction from the aminium ion (Figure 1, path d) as the product-determining step.[4,15] Deuteration has only a slight effect on the oxidation potentials of amines or their rates of reaction with one-electron oxidants.[8-10,16] Isotope effects on the product-determining follow-up steps vary somewhat depending on the particular reaction and conditions, but in general are also rather small (range ca. 1–3), and product ratios are often nearly statistical.[8-10,13,15]

Cytochrome P-450 catalyzed N-dealkylations of amines consistently show small KDIEs (ca. 1–2), even when measured by intramolecular competition.[4,17-22] In contrast, P-450-catalyzed O-dealkylations[23-25] and aliphatic C-hydroxylations[26-29] often show very large KDIEs (ca. 7–11), especially when measured by intramolecular competition.[30] These observations have been interpreted[4,5] to suggest that cytochrome P-450 initiates N-dealkylation by an electron-abstraction step, and O-dealkylation and aliphatic hydroxylation by an H-atom abstraction step. One extension of this logic is the prediction that raising the oxidation potential of an amine, e.g., by introduction of an electron-withdrawing substituent, should disfavor electron abstraction relative to H-atom abstraction and lead to large KDIEs for N-dealkylation in P-450 systems.

N,N-Disubstituted *amides*, which may be regarded as tertiary amines containing the strongly electron withdrawing acyl moiety, appeared especially attractive to us for testing this prediction. N-Dealkylation of amides by P-450 enzymes is well precedented,[31-35] but has received almost no attention from a mechanistic point of view. One interesting exception to this is a recent report by Shono et al.,[35] that the intramolecular KDIEs for N-dealkylation of *N*-methyl-*N*-(trideuteriomethyl)hydrocinnamide (**1b**) by liver microsomal cytochrome P-450 and by anodic oxidation were 1.75 and 1.80, respectively. While the latter value is in good agreement with the hypothesis outlined above, the former is not.

Because of the importance of this issue, we undertook to investigate the N-dealkylation of a *series* of deuterated amides, including **1b** under both enzymic and electrochemical conditions. Our initial attempts were thwarted, however, by our inability to observe *any* reaction with either **1b** or *N*-methyl-*N*-(trideuteriomethyl)benzamide (**2b**) under the conditions for anodic oxidation reported by Shono et al.[35] Thus we developed our own conditions for anodic oxidation of amides. In this paper we report a convenient method for electrochemical *mono*-N-deal-

(3) Agusto, O.; Beilan, H. S.; Ortiz de Montellano, P. R. *J. Biol. Chem.* **1982**, *257*, 11288–11295.
(4) Miwa, G. T.; Walsh, J. S.; Kedderis, G. L.; Hollenberg, P. F. *J. Biol. Chem.* **1983**, *258*, 14445–14449.
(5) Tullman, R. H.; Hanzlik, R. P. *Drug Metab. Rev.* **1984**, *15*, 1163–1182.
(6) Yamasaki, R. B.; Silverman, R. B. *Biochemistry* **1984**, *23*, 1322–1332.
(7) Burka, L. T.; Guengerich, F. P.; Willard, R. J.; Macdonald, T. L. *J. Am. Chem. Soc.* **1985**, *107*, 2549–2551.
(8) Lindsay-Smith, J. R.; Mead, L. A. V. *J. Chem. Soc., Perkin Trans. 2* **1973**, 206–210.
(9) Lindsay-Smith, J. R.; Masheder, D. *J. Chem. Soc., Perkin Trans. 2* **1976**, 47–51.
(10) Lindsay-Smith, J. R.; Sadd, J. S. *J. Chem. Soc., Perkin Trans. 2* **1976**, 741–747.
(11) Lindsay-Smith, J. R.; Nee, M. W.; Noar, J. B.; Bruice, T. C. *J. Chem. Soc., Perkin Trans. 2* **1984**, 255–260.
(12) Lindsay-Smith, J. B.; Mortimer, D. N. *J. Chem. Soc., Chem. Commun.* **1985**, 64–65 and 410–411.
(13) Lewis, F. D.; Simpson, J. T. *J. Am. Chem. Soc.* **1980**, *102*, 7593–7595.
(14) Sako, M.; Shimada, K.; Hirota, K.; Maki, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6034–6041.
(15) Nelsen, S. F.; Ippoliti, J. T. *J. Am. Chem. Soc.* **1986**, *108*, 4879–4881.
(16) Rosenblatt, D. H.; Davis, G. T.; Hull, L. A.; Forberg, G. D. *J. Org. Chem.* **1968**, *33*, 1649–1650.
(17) Elison, C.; Rapoport, H.; Laursen, R.; Elliott, H. W. *Science* **1961**, *134*, 1078–1079.
(18) Schmidt, H.-L.; Moller, M. R.; Weber, N. *Biochem. Pharmacol.* **1973**, *22*, 2989–2996.
(19) Thompson, J. A.; Holtzman, J. L. *Drug Metab. Dispos.* **1974**, *2*, 577–582.
(20) Nelson, S. D.; Pohl, L. R.; Trager, W. F. *J. Med. Chem.* **1975**, *18*, 1062–1065.
(21) Miwa, G. T.; Garland, W. A.; Hodshon, B. J.; Lu, A. Y. H.; Northrop, D. B. *J. Biol. Chem.* **1980**, *255*, 6049–6054.
(22) Yoo, J.-S. H.; Cheung, R. J.; Patten, C. J.; Wade, D.; Yang, C. S. *Cancer Res.* **1987**, *47*, 3378–3383.
(23) Guengerich, F. P. *J. Biol. Chem.* **1987**, *262*, 8459–8462.
(24) Al-Gailany, K. A. S.; Bridges, J. W.; Netter, K. J. *Biochem. Pharmacol.* **1975**, *24*, 867–870.
(25) Foster, A. B.; Jarman, M.; Stevens, J. D.; Thomas, P.; Westwood, J. H. *Chem.-Biol. Interact.* **1974**, *9*, 327–340.
(26) Dagne, E.; Gruenke, L.; Castagnoli, N. Jr. *J. Med. Chem.* **1974**, *17*, 1330–1333.
(27) Hjelmeland, L. M.; Aronow, L.; Trudell, J. R. *Biochem. Biophys. Res. Commun.* **1977**, *76*, 541–549.
(28) Shono, T.; Ohmizu, Y.; Toda, T.; Oshino, N. *Drug Metab. Dispos.* **1981**, *9*, 476–480.
(29) Hales, D. B.; Ho, B.; Thompson, J. A. *Biochem. Biophys. Res. Commun.* **1987**, *149*, 319–325.
(30) Foster, A. B. *Adv. Drug Res.* **1985**, *14*, 2–40.
(31) Low, L. K.; Castagnoli, N., Jr. In *Burger's Medicinal Chemistry*, 4th ed.; Wolff, M. E., Ed.; John Wiley & Sons: New York, 1980; Part I, pp 163–167.
(32) Jones, A. R. *Biochem. Pharmacol.* **1970**, *19*, 603–604.
(33) Wu, A.; Pearson, M. Lynn; Shekoski, D. L.; Soto, R. J.; Stewart, R. D. *J. High Resolut. Chromatogr.* **1979**, *2*, 558–562.
(34) Kestell, P.; Threadgill, M. D.; Gescher, A.; Gledhill, A. P.; Shaw, A. J.; Farmer, P. B. *J. Pharmacol. Exp. Ther.* **1987**, *240*, 265–270.
(35) Shono, T.; Tada, T.; Oshino, N. *J. Am. Chem. Soc.* **1982**, *104*, 2639–2641.



	R	R'	R''
a	1, $PhCH_2CH_2$–	CH_3	CH_3
b	2, Ph–	CH_3	CD_3
c	3, p-$O_2NC_6H_4$–	CD_3	CD_3
d	4, C_6F_5–	CH_3	H
e	5, H–	CH_3	CHO
f		CH_3	CH_2OCH_3
g		CH_3	CH_2OH

kylation of *N,N*-dimethylamides, as well as observations on the intermediates that are involved and the net overall kinetic deuterium isotope effects.

Experimental Section

General. Trideuteriomethyl iodide (>99% d_3) was from MSD Isotopes. *N,O*-Bis(trimethylsilyl)trifluoroacetamide (BSTFA) was obtained from Pierce. Other reagents were from Aldrich or Eastman Kodak; in some cases they were distilled or recrystallized before use. Melting points were determined by using a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ solution using Varian T-60 or FT-80 spectrometers; chemical shifts are reported vs internal Me_4Si. Silica gel GHLF plates from Analtech were used for thin-layer chromatography (TLC). TLC R_f values are on silica eluted with 5% MeOH in $CHCl_3$.

Gas Chromatography (GLC) and Mass Spectrometry (GC/MS). A Girdel series 300 capillary gas chromatograph equipped with a flame-ionization detector was used. Peak areas were integrated electronically. On another instrument, the flame detector was replaced by a Nermag R10-10b quadrupole mass spectrometer with a data system. Sample introduction was by split injection (GLC) or by use of a moving needle solids injector (GC/MS). GLC columns (obtained from J & W Scientific) and conditions were as follows: (A) 30 m × 0.25 mm fused silica, Durawax, 210 °C isothermal; (B) same as A but programmed at 5 °C/min from 200 to 230 °C (hold); (C) same as A but programmed at 5 °C/min from 150 to 210 °C (hold); (D) 30 m × 0.25 mm fused silica, DB-17, programmed at 5 °C/min from 150 to 230 °C (hold). The ionizing voltage was 70 eV, and selected-ion monitoring routines were used to measure isotope ratios. Isotope ratio data were analyzed as described previously.[36,37] Exact-mass measurements were made on a VG-ZAB-HS double-focusing mass spectrometer operated in the peak-matching mode.

Methyl(trideuteriomethyl)amine Hydrochloride. *N*-Benzylidenemethylamine (3.58 g, 30 mmol) and CD_3I (5 g, 34 mmol) were pipetted into a small (40 mL) stainless steel pressure cylinder, sealed, and heated to 100 °C for 24 h. After cooling to 45 °C (not lower to prevent the contents from solidifying), the cylinder was opened cautiously in a fume hood and the contents were poured into a 100-mL flask, along with rinsings of the cylinder (10% HCl, 5 × 5 mL). The reddish brown slurry was refluxed for 2 h and the resultant mixture placed in an addition funnel and dropped slowly onto NaOH pellets to liberate gaseous $CH_3(CD_3)NH$. The product was swept with a N_2 stream through a series of traps, each containing 4 mL of concentrated HCl in 50 mL of EtOH. Evaporation of the solution in the traps gave an 83% yield of $CH_3(CD_3)NH_2Cl$ as a white crystalline solid (mp 170–172 °C).

General Amide Synthesis. In a typical procedure, an acyl or benzoyl chloride (cf. **1**, **2**, **4**, or **5**; 3–8 mmol) and the appropriate amine hydrochloride (1.1 equiv) were placed in a 100-mL flask containing tetrahydrofuran (THF, 15–40 mL) and a magnetic stirring bar. A solution of 2 M NaOH (2.2 equiv) was added dropwise with stirring, and after 6 h at 25 °C, the THF was removed (rotovap) and the amide recovered by extraction with ethyl acetate. The following is a summary of the characteristics of the amides prepared this way.

***N,N*-Dimethylhydrocinnamide (1a)**: colorless oil (79% yield); R_f = 0.63; NMR δ 7.23 (s, 5 H, Ar H), 2.96 (m, 2 H, CH_2CO), 2.94 (s, 3 H, trans CH_3), 2.92 (s, 3 H, cis CH_3), 2.50 (m, 2 H, $ArCH_2$); GC/MS, GLC retention time using method A (see above) t_R(A) = 8.7 min, 178 (11, MH^+), 177 (89, M^+), 133 (10), 131 (10), 105 (50), 91 (100), 72 (87); exact mass 117.1153, calcd for $C_{11}H_{15}NO$ 177.1154.

***N*-Methyl-*N*-(trideuteriomethyl)hydrocinnamide (1b)**: 75% yield; NMR δ 7.23 (s, 5 H, Ar H), 2.94 (m, 2 H, CH_2CO), 2.92 (s, 1.5 H, trans NCH_3), 2.90 (s, 1.5 H, cis NCH_3), 2.49 (m, 2 H, $ArCH_2$); GC/MS, 181 (12, MH^+), 180 (92, M^+), 133 (11), 131 (13), 105 (47), 91 (100), 75 (92).

***N,N*-Bis(trideuteriomethyl)hydrocinnamide (1c)**: 84% yield; NMR δ 7.21 (s, 5 H, Ar H), 2.95 (m, 2 H, CH_2CO), 2.56 (m, 2 H, $ArCH_2$); GC/MS, 184 (9, MH^+), 183 (91), 133 (10), 131 (10), 105 (39), 91 (100), 78 (89).

***N*-Methylhydrocinnamide (1d)**: white crystalline solid (68% yield, recrystallized from MeOH); mp 61–62 °C; R_f = 0.52; NMR δ 7.21 (s, 5 H, Ar H), 5.69 (br s, 1 H, NH), 2.95 (m, 2 H, CH_2CO), 2.77 (s, 1.5 H, trans NCH_3), 2.71 (s, 1.5 H, cis NCH_3), 2.44 (m, 2 H, $ArCH_2$); GC/MS, t_R(A) = 13.1 min, 164 (13, MH^+), 163 (97, M^+), 162 (12), 133 (33), 131 (17), 105 (61), 91 (100), 86 (23), 77 (31), 58 (50); exact mass 163.0997, calcd for $C_{10}H_{13}NO$ 163.0993.

***N,N*-Dimethylbenzamide (2a)**: white crystalline solid (84% yield, recrystallized from ethyl acetate/hexane); mp 40.5–41.5 °C; R_f = 0.60; NMR δ 7.39 (s, 5 H, Ar H), 3.02 (br s, 6 H, NCH_3); GC/MS, t_R(B) = 5.25 min, 149 (25, M^+), 148 (71), 105 (100), 77 (76), 51 (72); exact mass 149.0835, calcd for $C_9H_{11}NO$ 149.0841.

***N*-Methyl-*N*-(trideuteriomethyl)benzamide (2b)**: 80% yield; NMR δ 7.40 (s, 5 H, Ar H), 3.02 (br s, 3 H, NCH_3); GC/MS, 152 (16, M^+), 151 (46), 105 (100), 77 (85), 51 (42).

***N,N*-Bis(trideuteriomethyl)benzamide (2c)**: 80% yield; R_f = 0.57; NMR δ 7.41 (s, 5 H, Ar H); GC/MS, 155 (18, M^+), 154 (40), 105 (100), 77 (67), 51 (32).

***N*-Methylbenzamide (2d)**: white crystalline solid (69% yield); mp 58–61 °C; R_f = 0.45; NMR δ 7.83 (m, 2 H, Ar H), 7.40 (m, 3 H, Ar H), 6.85 (br s, 1 H, NH) 3.03 (s, 1.5 H, trans NCH_3), 2.93 (s, 1.5 H, cis CH_3); GC/MS, t_R(B) = 7.7 min, 135 (24.1, M^+), 134 (41.5), 105 (84.8), 77 (100), 51 (32.2); exact mass 135.0680, calcd for C_8H_9NO 135.0684.

***N,N*-Dimethyl-*p*-nitrobenzamide (3a)**: pale yellowish crystalline solid (76% yield, recrystallized from ethyl acetate/hexane); mp 92–93.5 °C; R_f = 0.55; NMR δ 8.28 (d, J = 8.8 Hz, Ar H), 7.67 (d, J = 8.8 Hz, Ar H), 3.01 (br s, 6 H, NCH_3); GC/MS, t_R(D) = 18.0 min, 194 (32, M^+), 193 (91), 177 (10), 150 (100), 120 (20), 104 (88), 92 (45), 76 (78), 50 (51); exact mass 194.0686, calcd for $C_9H_{10}N_2O_3$ 194.0691.

***N*-Methyl-*N*-(trideuteriomethyl)-*p*-nitrobenzamide (3b)**: 69% yield; NMR δ 8.28 (d, J = 8.8 Hz, Ar H), 7.67 (d, J = 8.8 Hz, Ar H), 3.03 (br s, 3 H, NCH_3); GC/MS, 197 (27, M^+), 196 (77), 180 (7), 150 (100), 120 (16), 104 (65), 92 (25), 76 (50), 50 (32).

***N*-Methyl-*p*-nitrobenzamide (3d)**: white crystalline solid (69% yield, recrystallized from MeOH); mp 212–214 °C; R_f = 0.39; NMR δ (CF_3CO_2H, peaks relative to $CHCl_3$ at 7.26 ppm) 8.80 (d, J = 10 Hz, Ar H), 8.40 (d, J = 10 Hz, Ar H), 8.0 (br s, 1 H, NH), 3.30 (br s, 3 H, NCH_3); GC/MS, t_R(D) = 24.9 min, 180 (30, M^+), 179 (60), 164 (8), 163 (26), 150 (100), 133 (17), 120 (42), 104 (60), 93 (35), 76 (48); exact mass 180.0515, calcd for $C_8H_8N_2O_3$ 180.0534.

***N,N*-Dimethylpentafluorobenzamide (4a)**: colorless oil (78% yield); R_f = 0.68; NMR δ 3.17 (s, 3 H, trans NCH_3), 3.01 (s, 3 H, cis NCH_3); GC/MS, t_R(C) = 4.25 min, 239 (19, M^+), 220 (42), 195 (100), 167 (38), 117 (24), 72 (18); exact mass 239.0362, calcd for $C_9H_6F_5NO$ 239.0370.

***N*-Methyl-*N*-(trideuteriomethyl)pentafluorobenzamide (4b)**: 83% yield; NMR δ 3.07 (s, 1.5 H, trans NCH_3), 2.88 (s, 1.5 H, cis NCH_3); GC/MS, 242 (16, M^+), 223 (39), 195 (100), 167 (27), 117 (16), 75 (11).

***N*-Methylpentafluorobenzamide (4d)**: white crystalline solid (47% yield, recrystallized from ethyl acetate/hexane); mp 95–96 °C; R_f = 0.53; NMR δ 6.95 (br s, 1 H, NH), 3.10 (s, 1.5 H, trans NCH_3), 3.00 (s, 1.5 H, cis NCH_3); GC/MS, t_R(C) = 9.5 min, 225 (18, M^+), 206 (25), 195 (100), 167 (42), 117 (41); exact mass

(36) Hanzlik, R. P.; Hogberg, K.; Moon, J. B.; Judson, C. M. *J. Am. Chem. Soc.* **1985**, *107*, 7164–7167.
(37) Hanzlik, R. P.; Schaefer, A. R.; Moon, J. B.; Judson, C. M. *J. Am. Chem. Soc.* **1987**, *109*, 4926–4930.

225.0209, calcd for $C_8H_4F_5NO$ 225.0213.

***N*-Formyl-*N*-methylhydrocinnamide (1e).** *N*-Methylhydrocinnamide (**1d**, 100 mg, 0.61 mmol) was placed in a clean, dry, screw-cap culture tube (13 × 100 mm) containing anhydrous benzene (1 mL) and *N,N*-diformylacetamide[38] (210 mg, 1.83 mmol), a stir bar was added, and the mixture was sealed and heated by immersing the bottom 1 cm of the tube in a 130 °C oil bath for 48 h. (Caution: the heating and subsequent cooling were carried out behind a safety shield.) The material was applied to a silica gel column (10 g) and eluted with $CHCl_3$ to afford 32 mg of **1e** as a colorless oil (still containing traces of **1d** by TLC): R_f = 0.46; t_R(A) = 13.5 min; NMR δ 9.21 (s, 1 H, CHO), 7.23 (s, 5 H, Ar H), 3.09 (s, 3 H, NCH_3), 2.98 (m, 4 H); MS, 191 (25, M^+), 163 (3), 132 (13), 131 (12), 105 (31), 104 (100), 91 (50), 77 (19), 60 (56); exact mass 191.0945, calcd for $C_{11}H_{13}NO_2$ 191.0943.

Electrochemical Experiments. All solvents were HPLC grade, and the anhydrous $NaClO_4$ was recrystallized before use. HPLC grade methanol was dried by refluxing over and distilling from Mg turnings. The potentiostat (Model 173), programmer (Model 175), and electrometer probe (Model 178) were from Princeton Applied Research and were used with a high-impedance X-Y recorder from Houston Instruments. Most electrochemical experiments were conducted in a three-compartment cell with glass frits separating the compartments. The central compartment contained the platinum working electrode while one side compartment contained a Pt auxiliary electrode and the other contained a saturated calomel reference electrode (SCE). $E_{1/2}$ values of substrates were measured by using 1–5 mM solutions in acetonitrile (MeCN) containing 10 mM nBu_4NBF_4 which had been dried over molecular sieves.

Controlled-potential electrolyses were carried out in a three-compartment cell by using a wire mesh Pt working electrode (surface area ca. 3 cm^2) with 0.5–5.0 mM amide substrate and 10 mM $NaClO_4$. Constant-current electrolyses were initially carried out in a magnetically stirred one-compartment cell with two Pt-foil electrodes ca. 1 cm square separated by 1 cm. However, because of the formation of complex product mixtures, some components of which were chlorinated, later experiments were done in a two-compartment cell with the anode and cathode separated by a glass frit.

Electrochemical oxidations were worked up by evaporation to dryness under vacuum. The residues were dissolved in water (10 mL) and extracted with ethyl acetate (3 × 3 mL) which was dried (anhydrous $MgSO_4$) and evaporated to near dryness under vacuum in preparation for analysis by GLC or GC/MS. Alternatively, the residue from the extract was dissolved in THF/0.1 N HCl (1:1) and refluxed for 30 min. After evaporation of the THF, the ethyl acetate extractable hydrolysis products were analyzed as described above.

Isolation of Intermediate 2g. Amide **2a** was electrolyzed under standard conditions (10 mM substrate and 0.1 M $NaClO_4$ in MeCN containing 5% H_2O) until 2 F of electricity was consumed. An equal volume (10 mL) of water was added and the solution concentrated to 2 mL at room temperature in vacuo. This solution was passed through a C-18 solid phase extraction cartridge (500 mg, Analytichem), which was then washed with water (6 mL) and air-dried by using an aspirator. The column was then washed with ether (2 mL). The ether was dried (anhydrous Na_2SO_4) and treated with 50 μL of BSTFA, heated in a screw-cap tube at 60 °C for 24 h, and concentrated to 0.2 mL for GC/MS analysis (conditions C). Under these conditions, three peaks were observed: unchanged **2a**, 76%, t_R = 10.7 min; demethylated product **2d**, 9%, t_R = 15.5 min; **2g**-TMS, 15%, t_R = 11.8 min. MS for the trimethylsilyl (TMS) ether of **2g**: 237 (19, M^+), 222 (8), 192 (11), 135 (11), 118 (15), 105 (100), 77 (53), 73 (21). A similar pattern was seen when d_6-amide **2c** was used, except that the following mass spectrum was obtained for the d_5 analogue of **2g**-TMS: 242 (18, M^+), 227 (6), 224 (8), 195 (18), 138 (11), 121 (19), 105 (100), 77 (38), 73 (23).

Results

In order to confirm that dimethylamides would have much higher oxidation potentials than the corresponding *N,N*-dimethylamines, the $E_{1/2}$ values of compounds **1a–5a** and *N,N*-dimethylbenzylamine were measured. The results, reported in Table I, amply illustrate the electron-withdrawing influence of various acyl substituents relative to alkyl or aryl substituents.

Table I. Potentials for Anodic Oxidation of Substrates in Acetonitrile

compound	$E_{1/2}$,[a] V vs SCE
$PhCH_2NMe_2$	0.82 ± 0.02
$PhNMe_2$	1.01 ± 0.02
p-$O_2NC_6H_4NMe_2$	1.28 ± 0.02
$PhCH_2CH_2CONMe_2$ (**1a**)	1.95 ± 0.01
$PhCONMe_2$ (**2a**)	2.04 ± 0.01
p-$O_2NC_6H_4CONMe_2$ (**3a**)	>2.5
$C_6F_5CONMe_2$ (**4a**)	>2.5
$HCONMe_2$ (**5a**)	2.29 ± 0.01

[a] Measured on 1–5 mM solutions of substrates in dry MeCN containing 10 mM nBu_4NBF_4 by using Pt electrodes (mean ± SD, n = 4).

In our first effort at anodic oxidation of amides, we attempted to reproduce the conditions reported by Shono et al.[35] for oxidation of **1b**. However, we found that a 5 mM solution of **1a** in methanol containing 0.01–0.1 M $NaClO_4$ had an anodic limit of 1.1–1.2 V vs SCE and the reported potential of 2.0 V vs SCE could not be obtained. Controlled-potential electrolysis at 1.1–1.2 V consumed 4 F of electricity in 14 min, but left **1a** unchanged. Even after 120 min under these conditions, neither **1a** nor **2a** was oxidized.

Reasoning that electrolysis of methanol might be limiting the reaction, we examined the electrolysis of **1a** in various mixtures of acetonitrile and methanol. With a 95:5 mixture of MeCN/MeOH containing 10 mM $NaClO_4$, it was possible to carry out controlled-potential electrolysis at 2 V (vs SCE), and electrolysis of **1a** for 72 min consumed 22 F of electricity. The reaction solution was evaporated under vacuum and the residue partitioned between ethyl acetate and water. Analysis of the organic extract by capillary GC/MS revealed the presence of two products in a 3:1 ratio, in addition to unreacted **1a**. The major product was the monodemethylated amide **1d**, as shown by GC/MS comparison to an authentic standard. The minor product had a mass spectrum consistent with the structure *N*-formyl-*N*-methylhydrocinnamide (**1e**). This was supported by the following additional observations. The molecular ion of the minor product from anodic oxidation of deuterated amide **1b** showed mass shifts of both 1 amu and 3 amu corresponding to $PhCH_2CH_2CON(CDO)CH_3$ and $PhCH_2CH_2CON(CHO)CD_3$, respectively. Treatment of the minor product with THF/0.1 N HCl (1:1) at 50 °C for 1 h converted it into a mixture of **1d** (major product) and cinnamic acid (minor product); these conditions did *not* hydrolyze **1a** or **1d** to cinnamic acid. Finally, the minor product was identical by GC/MS and ^1H NMR with an authentic sample of **1e** prepared by independent synthesis.

Studies by Ross et al.[39] have shown that current density is a variable that can influence the outcome of anodic oxidation reactions. In order to study its role in the anodic oxidation of **1a**, we used a single-chambered electrolysis cell having two Pt electrodes, each 1 cm × 1 cm. Electrolysis of **1a** (0.5–5.0 mM) in methanol containing 0.1 M $NaClO_4$ for 1.6 min at a current density of 0.1 A/cm^2 resulted in the appearance (after *non*hydrolytic workup and GC/MS analysis) of five products, including **1d**, **1e**,

(38) Gramain, J. C.; Remuson, R. *Synthesis* **1982**, 264–266.

(39) Rudd, E. J.; Finkelstein; Ross, S. D. *J. Org. Chem.* **1972**, *37*, 1763–1767.

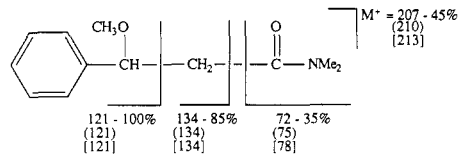


Figure 2. Mass spectral fragmentation of amide 6. The numerical data give the mass and relative intensities (% of base peak) for the major ions of the material derived by anodic oxidation of **1a**, **1b** (parentheses), and **1c** (brackets), respectively.

Table II. Isotope Effects of Anodic Oxidation of *N,N*-Dimethylamides[a]

amide	concn, mM	isotope effect, k_H/k_D	conversion at end
1b	5.0	2.16 ± 0.07	
1a/1c	5.0	1.70 ± 0.03[b]	
2b	5.0	2.78 ± 0.21[c]	
	5.0	2.86 ± 0.10[c]	
2a/2c	0.25	1.46 ± 0.05	5%/30s
	5.0	1.61 ± 0.11	7%/3 min
	100	1.69 ± 0.06	5%/35 min
	5.0[d]	1.43 ± 0.03	7%/2 min
	5.0[e]	5.97 ± 0.06	1%/30 min
2b	5.0[c]	3.28 ± 0.24	1%/30 min
3b	5.0	2.10 ± 0.17	
4b	5.0	2.60 ± 0.15	

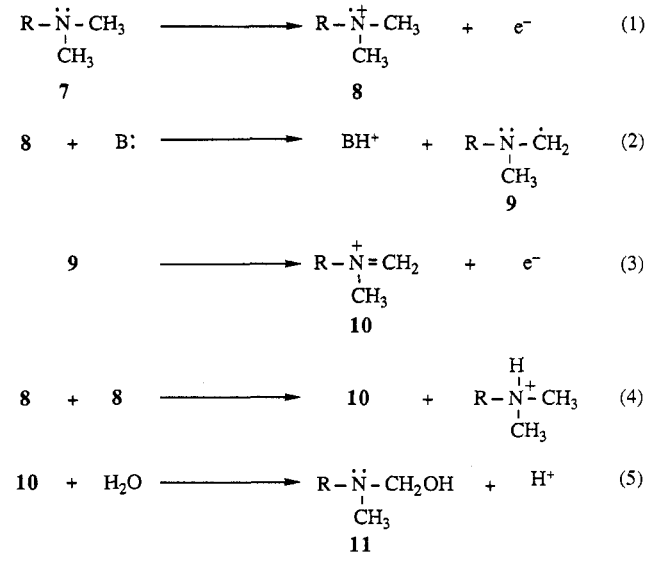
[a] Anodic oxidations of substrates at stated concentration in $MeCN/H_2O$ (95:5) containing 10 mM $NaClO_4$ were carried out by controlled-potential electrolysis at 2.0 V vs SCE. Values reported are the mean ± SD of four separate experiments. [b] Measured after <5–7% total oxidation of substrate. [c] Results of duplicate sets of four experiments conducted 6 months apart. [d] Same conditions as *a* above except for addition of 100 mM $HClO_4$. [e] Same conditions as *a* above except for addition of 100 mM Et_4NOH.

and the methoxymethyl amide **1f** (which is the intermediate reported[35] by Shono et al.). After 3.2 min, 2 F of electricity had passed and there were six product peaks (**1d**, **1e**, **1f**, and three unidentified), and after 30 min of electrolysis, GC/MS analysis revealed at least 25 product peaks, many of which contained one or two chlorine atoms. Thus it was obvious that many secondary reactions involving solvent- and/or electrolyte-derived intermediates were occurring. To avoid this, a two-chambered electrolysis cell was used in which a glass frit separated the anode and cathode (each Pt, 1 cm × 1 cm). Now the formation of chlorinated products was not observed, but the oxidation of **1a** still produced a mixture. In this case, one of the major products was the *benzylic* methoxylation product $PhCH(OCH_3)CH_2CONMe_2$ (**6**). This was confirmed by analysis of the shifts in the mass spectra of the corresponding products formed by anodic oxidation of **1a**, **1b**, and **1c** (Figure 2).

Acetonitrile and methanol are notoriously difficult solvents to dry, and we were concerned that adventitious water might be affecting our results. To examine this, we simply changed our solvent to acetonitrile/*water* (95:5), keeping other conditions the same but returning to the three-chambered cell and controlled-potential rather than controlled-current electrolysis. Under these conditions, we observed that amides **1a–4a** were cleanly oxidized to their corresponding monodesmethyl derivatives.

Because of the *apparent* simplicity of the reactions, these conditions were used to investigate the isotope effects on the anodic oxidation of *N,N*-dimethylamides 1–4. The results are reported in Table II. The *intra*molecular isotope effects observed with **1b–4b** show a modest preference for removal of hydrogen over deuterium ($2.2 < k_H/k_D < 2.8$). Under conditions of *inter*molecular competition (i.e., **1a/1c** and **2a/2c**), the observed isotope effects were significantly smaller ($1.4 < k_H/k_D < 1.7$). This result was independent of substrate concentration from 0.25 to 100 mM.

Scheme I



Because anodic N-dealkylation involves proton generation,[40,41] the effects of added acid and base were investigated. As shown in Table II, addition of 0.1 M $HClO_4$ had no observable effect on the net rate of oxidation, the product profile, or the isotope effects associated with the anodic oxidation of *N,N*-dimethylbenzamide. On the other hand, addition of 0.1 M tetraethylammonium hydroxide caused major changes in the reaction. The limiting anodic potential that could be achieved decreased from >2 V to ca. 1.1–1.2 V, the overall rate of amide oxidation decreased dramatically, and the product distribution changed from exclusively *N*-methylbenzamide under acidic or neutral conditions to a 3:1 mixture of *N*-methylbenzamide and benzamide in the presence of base. The apparent isotope effects also increased substantially, but since this could be an artifact due to the secondary N-dealkylation of the initially formed N-methylbenzamide, the significance of this result is questionable.

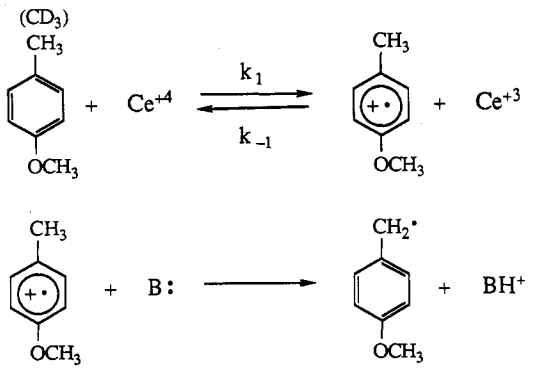
Discussion

The cytochrome P-450 catalyzed dealkylation of amides **1b–5b** is very efficient and shows large intramolecular KDIEs (k_H/k_D) ranging from 4 to 7.[42] These reactions proceed via isolable *N*-methyl-*N*-hydroxymethyl intermediates such as **1g**.[42] Under the conditions described above, anodic oxidation of *N,N*-dimethylamides **1a–4a** generates cleanly the corresponding *N*-monomethyl amides. As in the enzymic process, an isolable *N*-methyl-*N*-hydroxymethyl intermediate is involved, but the overall intramolecular KDIEs are much smaller (Table II). Thus, while the enzymic and anodic N-dealkylations are superficially similar, even to the point of involving a common intermediate, their mechanisms must differ substantially.

The anodic oxidation of *amines* has traditionally been thought to proceed via an ECE (electrochemical/chemical/electrochemical) mechanism represented by steps 1, 2, 3, and 5 of Scheme I. The characteristic absence of large

(40) O'Donnell, J. F.; Mann, C. K. *J. Electroanal. Chem.* **1967**, *13*, 157–162.
(41) Ross, S. D.; Finkelstein, M.; Rudd, E. J. *Anodic Oxidation*; Academic: New York, 1975; Chapter 9.
(42) Unpublished results; manuscript in preparation.

Scheme II



*inter*molecular KDIEs on this process suggests that step 1 in Scheme I is both isotopically insensitive and rate limiting. The characteristically low *intra*molecular KDIEs on this process have been rationalized by postulating that aminium ions like **8** are strong acids and hence not very discriminating in loss of H^+ vs D^+ in step 2. Recent measurements have shown, however, that aminium ions are not strongly acidic.[15] This finding led to the proposal[15] that, rather than undergoing deprotonation, aminium ions such as **8** would undergo hydrogen atom transfer disproportionation as shown in step 4 of Scheme I, and that a more likely overall mechanism for anodic oxidation of *amines* would consist of steps 1, 4, and 5. In the context of this mechanism, the observed low intramolecular KDIEs might be explicable in terms of the low (homolytic) dissociation energies of C(α)–H bonds in aminium ions[15] and the reactivity of aminium ions as hydrogen-abstraction reagents. These circumstances would favor an early transition state for C–H bond breaking and thus a low KDIE.

The anodic oxidation of *amides* also involves cation radical intermediates,[39,41,43,44] although electron removal requires a higher potential than for amines (Table II). It would seem reasonable that this step (i.e., step 1 of Scheme I, R = acyl) would be substantially rate limiting and isotopically insensitive as it is with amines. This would be consistent with the failure of added strong acid, a product of step 2, to influence the overall rate or outcome of the anodic oxidation of *N*,*N*-dimethylbenzamide (Table II). It is also consistent with the fact that the low intramolecular isotope effect observed for anodic oxidation of **2b** (k_H/k_D = 2.8) is reduced even further when measured by using the intermolecular approach with **2a**/**2c** (k_H/k_D = 1.4–1.7). These observations imply that, at least for *N*,*N*-dimethylbenzamide oxidation, step 1 is almost totally rate limiting, and that there is a substantial commitment of **8** to go on to product and not back to **7**. Once **8** deprotonates, radical **9** is presumably oxidized in a rapid step to cation **10**, the precursor of the carbinolamide **11** and the final N-dealkylated amide.

If the above interpretation is correct, it shows an interesting parallel to the one-electron oxidation of methylbenzene derivatives. In particular, an analogous example of "commitment" occurs in the case of the Ce^{4+}-mediated oxidation of *p*-methoxytoluene to *p*-methoxybenzyl acetate (Scheme II).[45] In this case, the intermolecular KDIE is 3.5 in the absence of added cerous ion, but as the initial concentration of the latter is increased by adding cerous sulfate, the opportunity for back-reaction (i.e., $k_{-1}[Ce^{3+}]$ in Scheme II) increases, thus decreasing the "commitment" of the cation–radical to the deprotonation reaction; correspondingly the observed intermolecular isotope effect increases from 3.5 to a limiting value of 6.2.

In conclusion, the anodic oxidation of amides shows many mechanistic parallels to the more thoroughly studied anodic oxidation of amines. With amides, the intramolecular KDIEs on the overall process are somewhat larger than with amines, but the lowered intermolecular KDIEs and the absence of an effect of added acid suggest that initial one-electron oxidation is almost totally rate limiting overall. These conclusions appear to support our original hypothesis that comparisons of KDIEs for N-dealkylation of amides vs their amine analogues would provide a good method for differentiating electron-abstraction vs hydrogen-abstraction mechanisms for enzymic N-dealkylations. Results of our application of this approach to cytochrome P-450 systems will be reported separately.

Acknowledgment. Financial support for this work was provided in part by grants from the National Institutes of Health (GM-31910 and RR-5606). L.R.H. is a predoctoral trainee of the National Institutes of Health (GM-07775).

(43) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4624–4628.
(44) Ross, S. D.; Finkelstein, M.; Rudd, E. J. *J. Org. Chem.* **1972**, *37*, 2387–2391.
(45) Baciocchi, E.; Rol, C.; Mandolini, L. *J. Am. Chem. Soc.* **1980**, *102*, 7598–7600.