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Mechanistic and Synthetic Aspects of Amine Oxidations Promoted by 3-Methyl-5-ethyllumiflavinium Perchlorate

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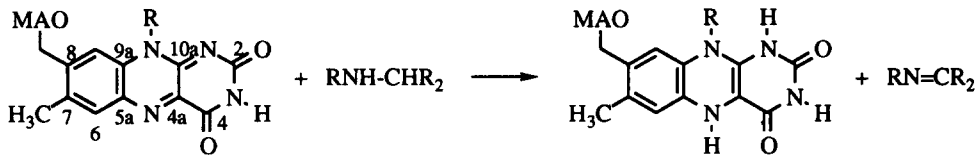
Abstract. Preparative and kinetic aspects of the chemistry of 3-methyl-5-ethyllumiflavinium perchlorate (**1**) with primary and secondary amines have been investigated. Reactions of **1** with primary and secondary amines leads to rapid production of modestly stable C4a-adducts. The rates of these processes, determined by stopped-flow kinetic methods, parallel amine nucleophilicities. The C4a-adducts undergo benzylamine promoted elimination reactions to produce N-benzylaldimine products with rates that parallel reactivity profiles expected for E_2-elimination processes. Finally, flavinium salt **1** serves as a catalyst for oxidations of primary and secondary amines under aerobic conditions. © 1997 Elsevier Science Ltd.

INTRODUCTION

Flavins are ubiquitous cofactors in enzyme catalyzed biological redox processes[1] and, as a result, have long gained and retained the attention of chemists seeking knowledge about their chemical and electronic properties.[2] Relevant to the studies discussed below is the function of flavin cofactors in a variety of enzymes which catalyze dehydrogenation reactions of their substrates. A specific example is found in the biological oxidation reactions of primary and secondary amines catalyzed by the monoamine oxidases (MAO-A and -B), two highly sequence homologous mammalian enzymes.[3] As depicted in Scheme 1, the chemical event in the MAO catalytic process involves oxidative conversion of an amine substrate to an imine product. The reduced flavin cofactor formed simultaneously is oxidized by molecular oxygen to regenerate the oxidized form of the enzyme while the imine product often undergoes hydrolysis to produce a carbonyl product.

The mechanistic role(s) played by the flavin cofactors in the biological dehydrogenation reactions has attracted much interest over the years. Although the family of oxidase enzymes that catalyze a host of similar oxidations (*e.g.* amine → imine by MAOs,[3] α-amino acid → α-imino acid by amino acid oxidases,[4] alcohols → ketones or aldehydes by alcohol oxidases,[5] and saturated CoA-esters → α,β-unsaturated CoA-esters by fatty acid dehydrogenases[6]) may well be evolutionarily related,[7] a number of different chemical mechanisms for the

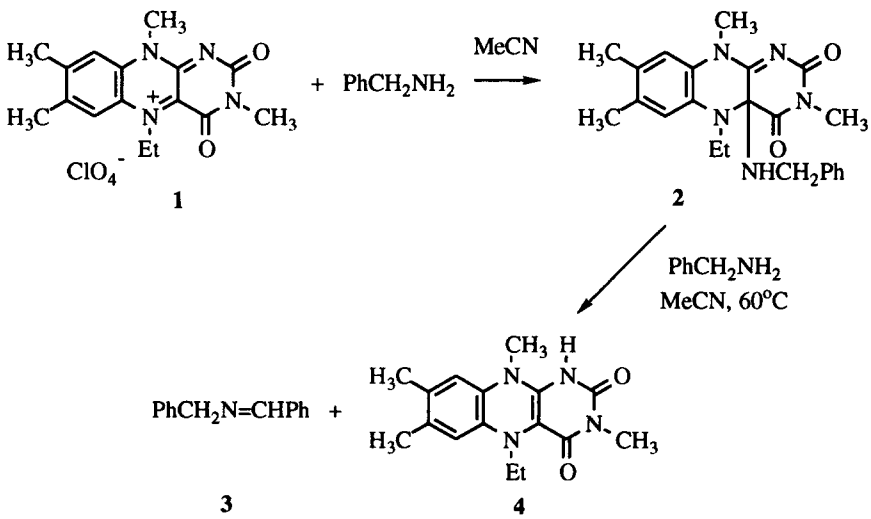
Scheme 1.



catalytic steps in these processes have become widely accepted. These include (1) a sequential electron-proton transfer route for MAO and alcohol oxidase catalysis, (2) a stepwise enolate anion generation, N5-flavin addition and elimination pathway for amino acid oxidases, and (3) a concerted α-deprotonation β-hydride transfer to N5-flavin scheme for fatty acid dehydrogenases.

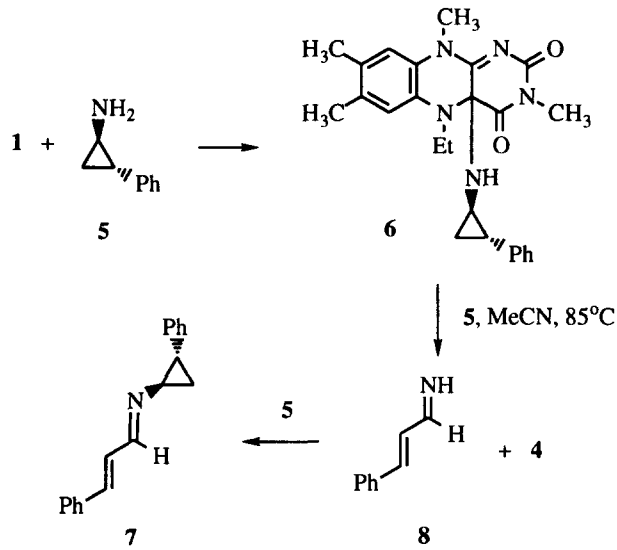
Our general interest in amine oxidation chemistry[8-10] has stimulated efforts which focus on the design and study of flavin chemical processes which could serve as mechanistic models for the pathways proposed for the biological dehydrogenation reactions.[11-14] The chemical mechanism(s) for MAO catalysis have, thus far, garnered our greatest attention. The results of our studies[11] of this problem have demonstrated that photochemical reactions of the flavin, 3-methyllumiflavin, with primary amines nicely model the sequential SET-proton transfer route suggested by Silverman[15] for MAO-promoted oxidative deamination reactions of amines. In addition, a model for the two-step polar mechanism, proposed earlier by Hamilton[16] for MAO-catalysis has arisen from our earlier efforts in this area. Specifically, we have shown that 3-methyl-5-ethyllumiflavinium perchlorate (**1**), an activated[17] flavin serving as a mimic for the FAD cofactor covalently linked at the MAO active site, undergoes reaction with the MAO-B substrate benzylamine to produce the C4a-adduct **2** cleanly (Scheme 2). Moreover, we noted that heating (60°C) the adduct **2** in the presence of benzylamine under anaerobic conditions leads to production of N-benzylbenzaldimine (**3**) along with dihydroflavin **4**.

Scheme 2.



In our earlier work,[14] we also used the flavinium salt **1** in developing chemical models for MAO-inactivation promoted by cyclopropylamines, α-silylamines and hydrazines. In each case, reaction of the MAO-inactivator with **1** led to initial formation of a C4a-adduct which was followed by a secondary fragmentation process resulting in generation of a reactive intermediate of the type potentially involved in the formation of an irreversibly inhibited MAO. This is exemplified by MAO inactivation by *trans*-2-phenylcyclopropylamine (**5**) which is suggested[18] to be a consequence of 2-benzoylethylation of an active site cysteine thiol group. We observed that **5** reacts rapidly with flavinium salt **1** to yield a mixture of diastereomeric adducts **6**. The adduct then undergoes fragmentation when heated (85°C) in the presence of **5** to yield the aldimine **7**, a product of secondary reactions of the initially formed cinnamaldimine **8** (Scheme 3). If **8** were formed in the active site of MAO by a similar two-step mechanism, cystein thiol alkylation by Michael addition would lead to the same irreversibly inhibited MAO that is suggested to form in the inactivation by cyclopropylamine **5**.

Scheme 3.



The above results indicate that the chemical reactivity profiles observed for reactions of flavinium salt **1** with primary and secondary amines match those seen in the MAO catalytic and inactivation processes. Thus, the flavinium perchlorate represents a potential chemical model for the flavin cofactor present in these enzymes. As such, this substance could play a major role in the design of ideal mechanistic probes to elucidate the chemical mechanisms which operate in the biological reaction in which the MAOs (and perhaps other flavin oxidases)[19] participate. With these potential applications in mind, we recently embarked on a detailed study of the C4a-adduct formation and fragmentation reactions of **1** with a variety of primary and secondary amines. The immediate goals of this effort were (1) to determine how substituent and structural variations on the amine govern the rates of C4a-adduct formation, (2) to evaluate how amine substituents affect the rates of the ensuing C4a-adduct fragmentation reactions, and (3) to probe for conditions under which the flavinium salt **1** can itself serve as a catalyst for primary and secondary amine oxidations. The results of studies guided by these aims are presented below along with a discussion of their potential mechanistic and synthetic significance.

RESULTS AND DISCUSSION

C4a-Adduct Formation.

In our current investigation, we have demonstrated that the C4a-adduct forming reaction of benzylamine with the flavinium salt **1** (Scheme 2) is ubiquitous for a large number of primary and secondary amines. As the results accumulated in Table 1 show, substituted benzylamines, primary α-aminoacid esters, and secondary amines all react rapidly with **1** at 23°C in anhydrous acetonitrile to efficiently (82-99%) produce the corresponding flavin C4a-adducts. The adducts (in some cases, mixtures of diastereomers) are sufficiently stable to enable their isolation in >90% purity, but the adducts do decompose when exposed to light or elevated temperatures (>30°C) for long time (>10h) periods or under chromatographic conditions.

Characterization of the C4a-adducts was accomplished by use of UV-, ^{1}H NMR and ^{13}C NMR spectroscopic methods and by comparisons of these data with those accumulated previously for known amine-flavin C4a-adducts.[13-14] An example of this is found in the analysis of the ethyl glycinate derived adduct **15**. Reaction of flavinium salt **1** with this amino acid ester results in rapid and complete consumption of the flavinium salt characterized by the disappearance of its absorption bands at 420 and 550 nm and the appearance of a new band at 338 nm (ε = 7,940 $M^{-1}cm^{-1}$) associated with the C4a-adduct as well as other 4a,5-dihydroflavins (Figure 1). A variable concentration study (Figure 1) gave an equilibrium constant for adduct formation of *ca.* 5 x 10^4 demonstrating that the process is highly favorable in a thermodynamic sense.

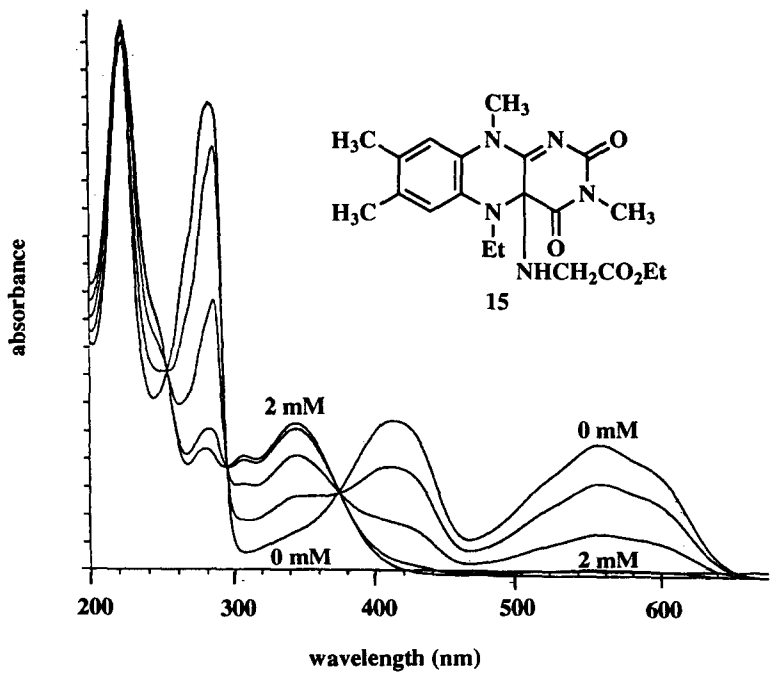


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Figure 1. UV-visible spectrometric monitoring of the reaction of flavinium salt **1** (0.1 mM) with ethyl glycinate (0, 0.05, 1.0, 1.5 and 2.0 mM) in MeCN at 23°C to produce C4a-adduct **15**. Spectra are recorded immediately (*ca.* 10s) after mixing.

The ^{1}H and ^{13}C NMR spectra of **15** contain resonances that are unique for C4a-adducts. For example, the coincident singlets at 6.95 ppm in the ^{1}H NMR spectrum and the methine carbon resonances at 117.1 and 125.7 ppm are characteristic of the respective H-6/H-9 and C-6/C-9 nuclei in 4a,5-dihydroflavins[13,14] (Figure 2).

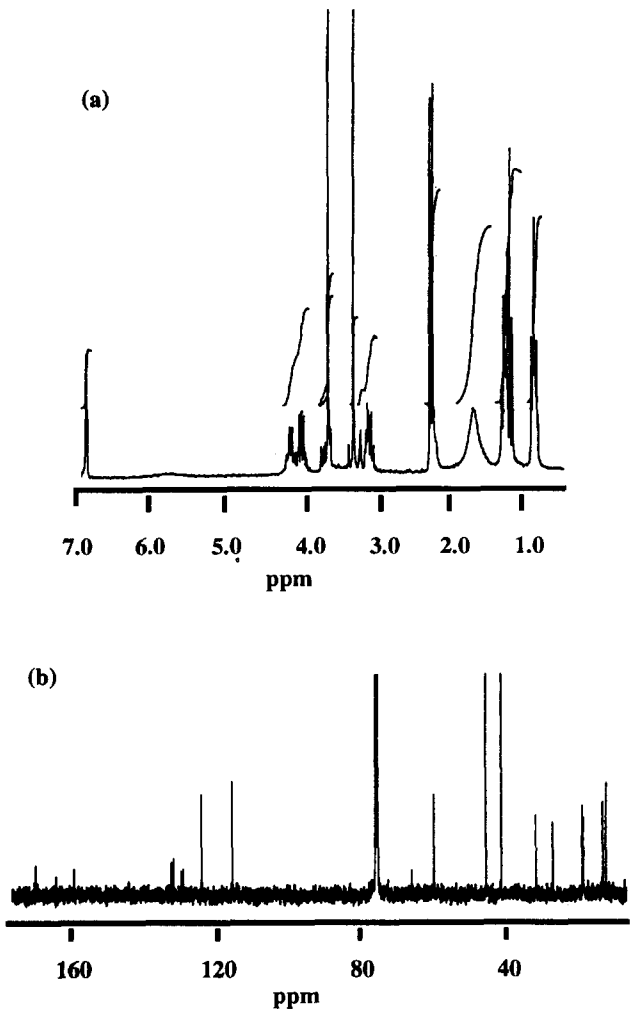
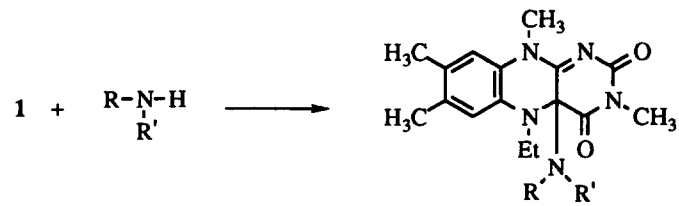


Figure 2. ^{1}H (spectrum a) and ^{13}C (spectrum b) NMR spectra of the ethyl glycinate derived C4a-adduct **15** in $CDCl_3$.

Table 1. C4a-Adduct Formation in the Reactions of Primary and Secondary Amines with Flavinium Salt 1.



Amine	C4a-Adduct	% Yield[a]	Rate Constants[b,c] ($M^{-1}s^{-1}$)x10^4	
			Decay of 1	Adduct Formation
$C_6H_5CH_2NH_2$	**2**	86	5.0	5.1
$C_6H_5CD_2NH_2$	**9**	91	4.3	4.3
4-CF_3-$C_6H_4CH_2NH_2$	**10**	99	2.4	2.5
4-NO_2-$C_6H_4CH_2NH_2$	**11**	86	2.9	2.8
4-MeO-$C_6H_4CH_2NH_2$	**12**	99	13.	13.
3,4-$(MeO)_2$-$C_6H_3CH_2NH_2$	**13**	90	22.	22.
3,4,5-$(MeO)_3$-$C_6H_2CH_2NH_2$	**14**	82	38.	38.
$EtO_2CCH_2NH_2$	**15**	85	—	—
$EtO_2CCHMeNH_2$	**16**	94	0.5	0.5
$MeO_2CCHPhNH_2$	**17**	99	—	—
$C_6H_5CH_2NHMe$	**18**	99	—	—
indoline	**19**	99	—	
6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline	**20**	99	—	—

(a) Preparative reactions run at 23°C in anhydrous MeCN with 5-10 molar excess of amine over **1**. C4a-Adduct yields are for material of > 90% purity; (b) Measured by stopped-flow methods for reaction of **1** (0.05-0.10 mM) and amines (>1 mM) at 25°C in MeCN. The rate constants for decay of **1** and formation of the C4a-adducts were determined by plotting the observed rate of decrease of the 558 nm band of **1** and the rate of increase of the *ca.* 342 nm bands of the adducts *vs.* amine concentration; (c) Entries marked _ indicates nt determined.

Stopped-flow kinetic methods were used to determine the rates of the C4a-adduct forming reactions of the flavinium salt **1**. Characteristics of the observations and analyses employed to derive the rate data given in Table 1 are the results obtained in our study of the addition reaction of benzylamine with flavinium salt **1** to generate the C4a-adduct **2**. In Figure 3 is portrayed time dependent UV-visible spectra recorded following rapid

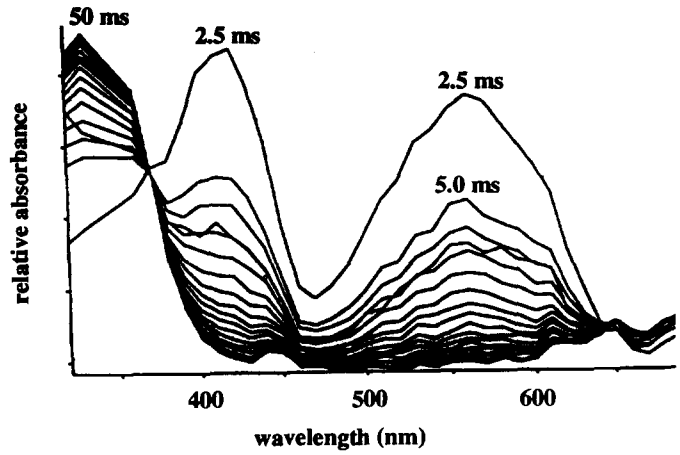


Figure 3. Time dependent UV-visible absorption spectra following stopped-flow admixture of flavinium salt (0.10 mM) and benzylamine (1.0 mM) in MeCN at 25°C. Each spectrum is recorded at 2.5 ms intervals following mixing over a 50 ms time interval.

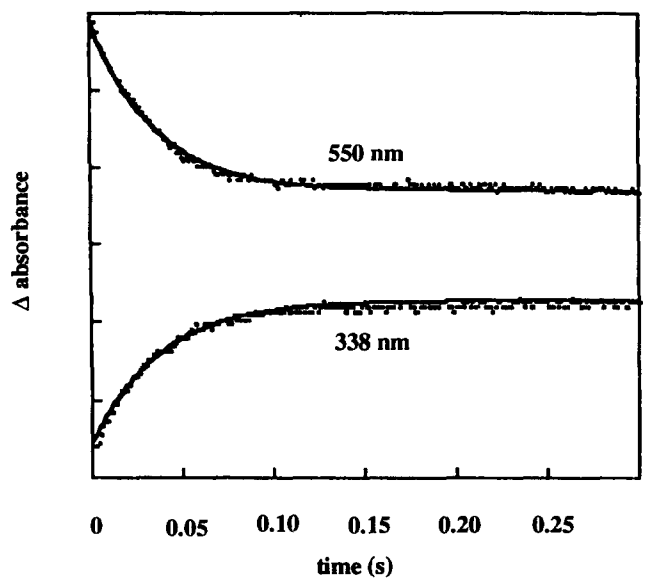


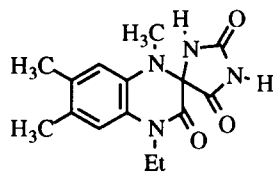
Figure 4. Plots of absorbance at 550 and 338 nm *vs.* time following mixing of flavinium salt **1** and benzylamine under the conditions described in Figure 3.

admixture of **1** with benzylamine (0.10 and 1.0 mM respective final concentrations) in anhydrous MeCN at 25°C. Analyses of the disappearing flavinium salt absorption at 558 nm and forming C4a-adduct absorption at 342 nm (Figure 4) show that these events are kinetically coupled. Plots of the observed rates *vs.* amine concentrations then provides the rate constants for flavinium salt decay and adduct formation given in Table 1.

A review of the rate data given in Table 1 reveals several interesting features of the C4a-adduct forming reactions. As expected, α-deuterium substitution in benzylamine has almost no effect on the rate of addition to **1**. In contrast, arene ring substituents have a patterned impact upon the kinetics of this process. The differential effects of electron withdrawing (rate decrease) and donating (rate increase) group substitution on addition rates are consistent with intuition about the nucleophilicity of the benzylamines and the polar mechanism for the process. Finally, the slow rate of the ethyl alanate-flavinium salt reaction dramatizes how remote substituents can control the rates of C4a-adduct formation.

C4a-Adduct Elimination Reactions.

In earlier efforts,[14] studies of C4a-adduct fragmentation reactions provided important information about possible mechanistic pathways that could be operable in a number of different MAO-inactivation reactions. In addition, we demonstrated that the benzylamine derived C4a-adduct **2** undergoes decomposition at elevated temperatures (60-80°C) in the presence of benzylamine leading to generation of the aldimine derivative **3** (Scheme 2) along with the known[20] flavin decomposition products **21** and **22**. The initial aim of our continuing study of this process was to develop conditions under which the C4a-adducts are cleanly converted to the products of net amine oxidative deamination. Accomplishment of this goal would enable a detailed kinetic investigation of the elimination reaction as well as an exploration of the synthetic potential of a catalytic sequence involving flavin adduct formation and elimination steps for converting amines to their oxidation products.



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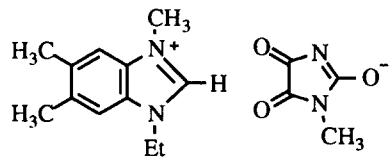

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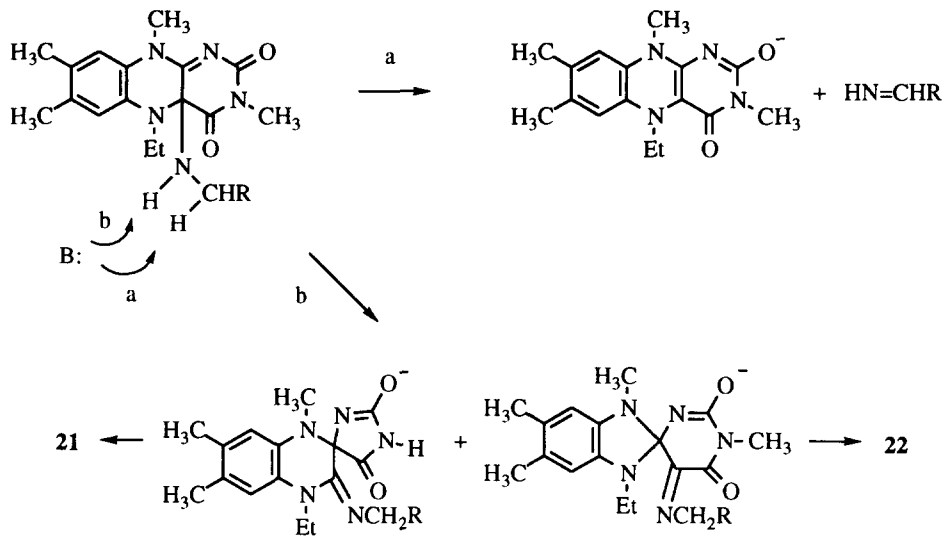
Mechanistic reasoning leads to the proposal that benzylamine promotes elimination of the C4a-adduct **3** by abstraction of an α-CH proton in concert with departure of the hydroflavin anion **23** (Scheme 4). In contrast, fragmentation to form the spirocyclic and benzimidazolium products **21** and **22** most likely involves abstraction of an NH-proton followed by or simultaneous with migration of the C4-carbonyl (→ **21**) or N5-center (→ **22**) (Scheme 4). If so, the relative yields of the elimination *vs.* decomposition products might be sensitive to the base used to induce the process and, perhaps, to the temperature of the reaction. An exploratory survey of various reaction conditions, in which the nature of the base (*e.g.* KOtBu, 2,6-lutidine, LDA) and temperature are varied, showed that the conversion of C4a-adduct **2** to aldimine **3** occurs in a quantitative yield (*i.e.*, none of **21** and **22** are formed) when benzylamine is the base and the reaction is conducted in MeCN at 22°C under anaerobic conditions.

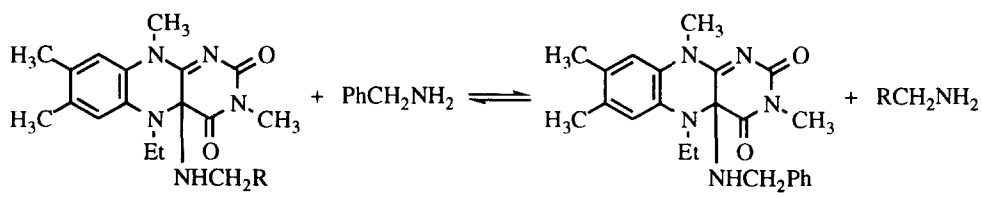
Having developed conditions to promote the elimination process, the C4a-adducts **10-14** were then reacted with benzylamine as base to produce the corresponding N-benzylaldimine products. However, several issues needed to be resolved first before the results of these reactions could be unambiguously interpreted. Firstly, although the large equilibrium constants (*ca.* 10^4) for C4a-adduct formation suggest that amine exchange reactions (Scheme 5) would be slow, the requirements of our analyses necessitated that we demonstrate that this exchange is not competitive with the elimination reactions.

Scheme 4.



Secondly, we noted in our earlier work[13] that when the elimination reaction of C4a-adduct **2** with benzylamine was conducted under non-anaerobic conditions a greater than quantitative yield of N-benzylbenzaldimine was observed. This phenomenon was attributed to reoxidation of the 4a,5-dihydroflavin coproduct **4** and its ready reaction in the presence of excess benzylamine to produce the starting adduct **2**. The occurrence of this pathway in benzylamine promoted elimination reactions of adducts **10-14** would complicate product distributions and kinetic analyses.

Scheme 5.



Results obtained from experimentation show that the processes outlined above do not interfere with the elimination reactions of C4a-adducts. For example, reaction of the benzylamine derived flavin-adduct **2** with p-methoxybenzylamine in the dark under strictly anaerobic conditions at 23°C leads to clean production of a single product characterized as N-(p-methoxybenzyl)benzaldimine **24** (Scheme 6). ^{1}H NMR analysis of the reaction mixture failed to reveal the presence of N-(p-methoxyphenyl)p-methoxybenzaldimine which would have been generated if the amine exchange or dihydroflavin oxidation processes had intervened. Likewise, reactions of the C4a-adducts **10-14** derived from arene ring substituted benzylamines under the elimination conditions (10 molar excess of $PhCH_2NH_2$, MeCN, 42°C, deoxygenated) in each case afforded a single N-benzyl-arylaldimine product **25-29** in yields ranging from (80-99%) (Table 2).

Scheme 6.

$$\mathbf{2} + p\text{-}(CH_3O)C_6H_4CH_2NH_2 \xrightarrow[23^\circ C]{MeCN} p\text{-}(CH_3O)C_6H_4CH_2N{=}CHC_6H_5$$

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The relative rates of the C4a-adduct (**2**, **10-12**) eliminations given in Table 2 were estimated by use of parallel reactions conducted for equivalent time periods in which conversions (low) to product are assumed to reflect rates. Exact rate constants for eliminations of **2**, **11**, and **14** (Table 2) were determined by measuring the time dependent evolution of the respective aldimine products **3**, **26**, and **14**.

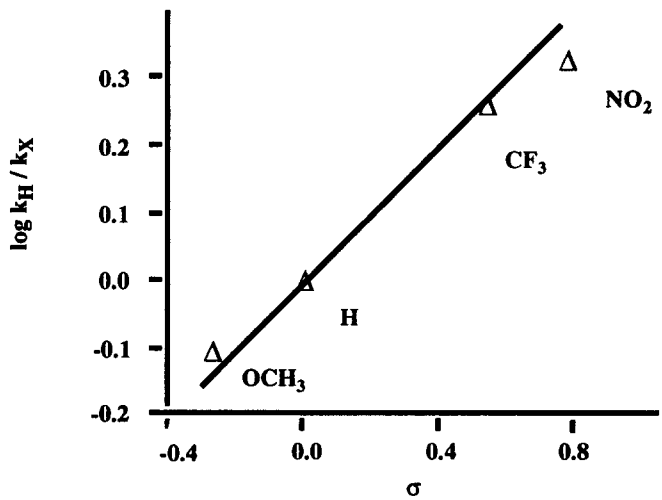
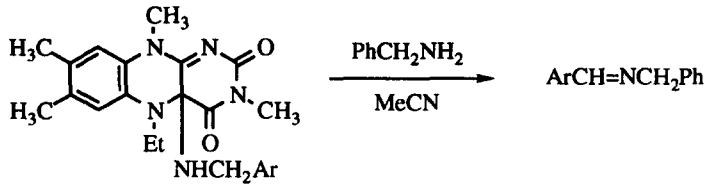


Figure 5. A linear free energy plot of the relative rates (k_H/k_X) of elimination of p-X-$C_6H_4CH_2NH_2$ derived C4a-adducts **2**, **10-12** (from Table 2) *vs.* sigma.

Table 2. Benzylamine Promoted C4a-Adduct Elimination Reactions.



Ar	C4a-Adduct	Aldimine	% Yield[a]	Estimated Relative Rate[b]	Absolute Rates ($M^{-1}s^{-1}$)[c,d]
C_6H_5	**2**	**3**	99	1.0	430
4-(CF_3)-C_6H_4	**10**	**25**	80	1.8	—
4-(NO_2)-C_6H_4	**11**	**26**	96	2.1	870
4-(MeO)-C_6H_4	**12**	**27**	92	0.8	—
4,5-$(MeO)_2$-C_6H_3	**13**	**28**	84	—	—
3,4,5-$(MeO)_3$-C_6H_2	**14**	**29**	99	—	88

(a) Preparative reactions in MeCN at 38°C under deoxygenated argon; (b) Determined by ^1H NMR methods based on the percent conversion to product for parallel fixed time (42 min) reactions at 38°C; (c) For reaction of 0.032 mM C4a-adduct with 0.32 mM benzylamine at 40°C in CD_3CN with ^1H NMR analysis for product formation conducted periodically over a 15-20 h period. Observed rate constant obtained from a plot of ln [C4a-adduct remaining] *vs.* time; (d) Entries marked _ indicates nt determined.

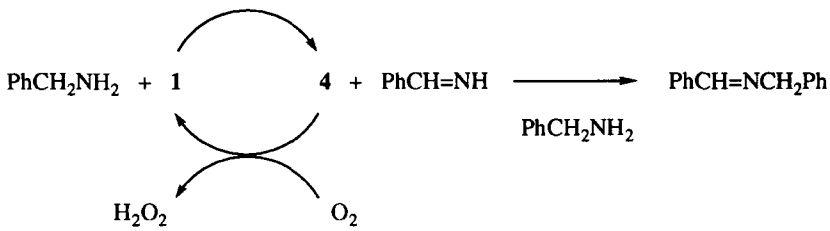
The observations made demonstrate that base induced elimination reactions of C4a-adducts derived from the addition of benzylic amines to the flavinium perchlorate **1** occur efficiently under mild (weak base, low temperature) conditions. The effects of aryl ring substituents on the rates of this process, reflected in a ρ = +0.79 (derived from the linear free energy treatment shown in Figure 5), are reminiscent of those recorded for E_2-elimination of 2-phenethyl substrates ($ArCH_2CH_2X$) where electron withdrawing groups on the arene ring enhance rates.[21]

When viewed as a whole, the studies described above provide a firm foundation for understanding the steps of a mechanism for flavin induced amine oxidation which may mimic that involved in the catalytic function of the monoamine oxidases. Moreover, the effort has provided information about how substituents might be used to control the relative rates of the addition and elimination steps of the polar mechanism and, as such, to increase the lifetime of a C4a-adduct which might serve as an intermediate in the enzymatic redox process.

Flavinium Salt Catalysis of Amine Oxidations.

The parallel between the amine oxidation chemistry of flavinium perchlorate **1** and the MAOs is not limited to their possible mechanistic similarities. As pointed out above, MAO-catalyzed conversions of primary and secondary amines to the corresponding imine products involves two major stages. In the first, the amine substrate is oxidized and the flavin cofactor of the enzyme is reduced to form a 1,5-dihydroflavin. The catalytic cycle is then completed by molecular oxygen induced conversion of the reduced enzyme to its active oxidized form with concommitment production of hydrogen peroxide. The initial hint that the flavinium salt **1** could participate in a similar catalytic cycle arose during the course of our study of the elimination reaction of C4a-adduct **2**.[13] When care was not taken to eliminate all oxygen from the mixture containing **2** and benzylamine, a greater than stoichiometric yield of aldimine was formed. This result suggested that the 1,5-dihydroflavin **4**, co-formed in the elimination reaction, undergoes rapid oxidation to produce the starting flavinium cation which then adds benzylamine to reform the starting adduct **2** (Scheme 7).

Scheme 7.



In order to determine if this phenomenon is general, *i.e.*, if amine oxidations can be catalyzed by the flavinium salt **1**, the reactions of several primary and secondary amines with catalytic amounts of **1** under aerobic conditions were explored. Solutions (MeCN) of **1** and the benzylamines listed in Table 3 in *ca.* 1:13 molar ratios were stirred at temperatures between 22-36°C under an air atmosphere. In all cases, C4a-adducts formed rapidly and quantitatively followed by slower conversion to the aldimine products. As the data in Table 3 show, multiple turnover of the amine by the flavinium salt does occur leading to high yielding production of the amine oxidation products.

Under similar reaction conditions, flavinium salt **1** (3 mM) serves as a catalyst for oxidations of secondary amines (40 mM). As exemplified by the transformations of indoline (**32**) to indole (**33**) and of 6,7-dimethoxy-1,2,3,4-tetrahydroquinoline (**34**) to its dihydro analog **35** (Scheme 8), secondary amines are readily oxidized by use of catalytic **1** and sacrificial O_2. A control reaction of **32** carried out in the absence of **1** did not lead to production of detectable quantities of indole.

Summary.

Reactions of primary and secondary amines with the flavinium salt **1** in many ways model the processes occurring in monoamine oxidase catalyzed amine oxidations. Consequently, the results of the present study provide a clearer picture of the detailed mechanistic steps in one possible mechanism for these enzymatic redox reactions. In addition, the substituent effects on the rates of C4a-adduct formation and elimination, delineated in this work, may find utility in the design of substrates constructied to probe the MAO-catalytic mechanism.

Finally, the multiple turnovers seen in the flavinium salt catalyzed oxidations of primary and secondary amines not only mimic MAO catalysis but they also suggest strategies for efforts aimed at developing new catalysts for amine and related oxidations.

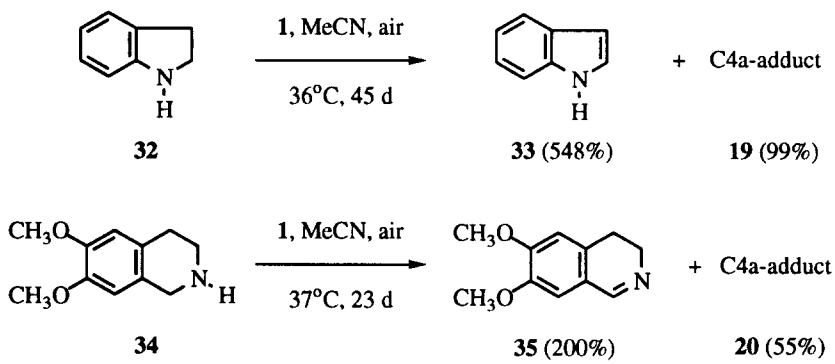
Table 3. Flavinium Salt **1** Catalyzed Primary Amine Oxidation

$$p\text{-}X\text{-}C_6H_4CH_2NH_2 \xrightarrow[MeCN,\ air]{\mathbf{1}\ (catalytic)} p\text{-}X\text{-}C_6H_4CH_2N{=}CHC_6H_4\text{-}p\text{-}X$$

Amine X=	Temperature (°C)	Time (d)	Percent Yields[a] Aldimine	Spirocycle **21**	C4a-Adduct
H	22	4	180 (**3**)	27	83 (**2**)
H	22	12	950 (**3**)	90	0
CF_3	36	3	327 (**30**)	31	65 (**10**)
MeO	36	3	235 (**31**)	32	59 (**12**)

a) Reaction conducted using *ca.* 1:13 molar ratios of **1** (3 mM) and amine (40 mM) under an air atmosphere. Products yields, determined by ^1H NMR analysis, are based on starting flavinium salt.

Scheme 8.



EXPERIMENTAL SECTION

General. ^1H NMR spectra were recorded at 200, 400 and 500 MHz and ^{13}C NMR were recorded at 50 MHz. NMR spectra were obtained by using $CDCl_3$ solutions unless otherwise noted and chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. ^{13}C NMR resonances were assigned by use of the DEPT technique to determine number of attached hydrogens. Mass spectral data were recorded by using either electron impact (EI) or chemical ionization (CI) techniques. The intensities of infrared bands are denoted as w=weak, br=broad, s=strong, m=medium. Thin layer chromatography (TLC) was performed on 0.25 mm silca or alumina plates. The compounds were visualized by exposure to iodine vapor or uv-light (254 nm). Preparative TLC was performed on 20 x 20 cm x 2 mm silica-gel plates. Column chromatography was performed on flash grade silica gel (230-400 mesh), Florisil (100-200 mesh), or neutral alumina (80-200 mesh).

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. All distillations were performed under a dry N_2 or Argon atmosphere unless otherwise noted. All solvents were distilled prior to use and dried if necessary unless otherwise noted. Ethyl ether and tetrahydrofuran were distilled over sodium and benzophenone. All new compounds were obtained as oils in >95% purity (NMR) unless otherwise noted.

Reaction of Flavinium Perchlorate Salt 1 with Benzylamine. General Procedure for the Preparation C4a-Adducts. To a solution of flavinium salt **1**[20,22] (6 mg, 0.014 mmol) in anhydrous CH_3CN (1 mL) under N_2 at 25°C was added benzylamine (6 mg, 0.060 mmol). This resulted in an instantaneous color change from deep purple to yellow/green. The mixture was concentrated *in vacuo* followed by trituration with $CHCl_3$. The combined $CHCl_3$ triturates were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was washed thoroughly with hexane-ether at 25°C to provide C4a-adduct **2**[13] (6 mg, 0.012 mmol) as a light yellow solid in 86% yield. Note: decompostion of the C4a-adduct occurs on exposure to heat, O_2, and light.

Spectroscopic data for adducts **2**, **9** and **18** matched those reported previously.[13,14] Spectroscopic properties for other amine-flavin C4a-adducts prepared in a similar manner are as follows:

10: ^1H NMR: 0.88 (t, J = 7.1, 3H, N-5-CH_3), 1.73 (br s, 1H, NH), 2.25 (s, 3H, C-7-CH_3), 2.30 (s, 3H, C-8-CH_3), 3.13 (m, 2H, N-5-CH_2), 3.34 (s, 3H, N-10-CH_3), 3.47 (s, 3H, N-3-CH_3), 3.62 (ABq, J = 14.4, 5.3 Hz, 2H, PhCH_2), 6.89-7.57 (m, 6H, C6-H, C9-H and Ph); ^{13}C NMR: 13.2 (N-5-CH_3), 19.5 (C-7-CH_3), 19.7 (C-8-CH_3), 28.0 (N-10-CH_3), 32.6 (N-3-CH_3), 45.5 (N-5-CH_2), 46.4 (C4a-CH_2), 66.4 (CF_3), 68.6 (C4a), 117.0 (C-6), 125.3 (C-9), 125.0, 128.0, 128.8, and 142.9 (C4a-Ph), 131.2 (C-5a), 131.3 (C-7), 133.0 (C-8), 134.0 (C-9a), 155.7 (C-10a), 160.6 (C-2), 167.3 (C-4); IR: ($CHCl_3$) 1724 (m), 1641 (s), 1580 (s), 1323 (s) cm^{-1}; EIMS: *m/z* (relative intensity) 473 (14), 416 (6), 387 (9), 299 (100), 271 (74), 257 (63), 230 (18), 214 (31), 186 (21), 174 (76), 159 (63); HRMS: *m/z* 473.2052 ($C_{24}H_{26}O_2N_5F_3$ requires 473.2039).

11: ^1H NMR: 0.88 (t, J = 7.1 Hz, 3H, N-5-CH_3), 2.23 (s, 3H, C-7-CH_3), 2.31 (s, 3H, C-8-CH_3), 3.10-3.25 (m, 2H, N-5-CH_2), 3.36 (s, 3H, N-10-CH_3), 3.43-3.70 (m, 2H, C4a-CH_2), 3.51 (s, 3H, N-3-CH_3), 6.96 and 6.98 (s, 1H, H-6), 7.08 and 7.10 (s, 1H, H-9), 7.50 (br d, J = 8.5 Hz, 2H, C4a-Ph), 8.17 (br d, J = 8.5 Hz, 2H, C4a-Ph); ^{13}C NMR: 13.2 (N-5-CH_3), 19.5 (C-7-CH_3), 19.8 (C-8-CH_3), 28.0 (N-10-

CH_3), 32.6 (N-3-CH_3), 45.0 (N-5-CH_2), 46.5 (C4a-CH_2), 77.2 (C4a), 117.0 (C-6), 125.4 (C-9), 128.3, 128.6, 128.7, 129.3, 146.7, (C4a-Ph), 131.0 (C-5a), 133.2 (C-8), 134.2 (C9a), 155.6 (C10a), 160.7 (C-2), 167.0 (C-4); IR: ($CHCl_3$) 2932 (w), 1726 (m), 1665 (s), 1560 (s), 1518 (s), 1344 (s), 1282 (m), 1108 (w) cm^{-1}; EIMS *m/z* (relative intensity) 450 (M^+, 0.1), 356 (21), 316 (31), 299 (100), 271 (66); HRMS: *m/z*. 450.20098 ($C_{12}H_{26}N_6O_4$ requires 450.2016).

12: ^1H NMR: 0.88 (t, J = 7.1 Hz, 3H, N-5-CH_3), 2.00 (br s, NH), 2.25 (s, 3H, C-7-CH_3), 2.29 (s, 3H, C-8-CH_3), 3.12 (m, 2H, N-5-CH_2), 3.32 (s, 3H, N-10-CH_3), 3.47 (dd, J = 14.1, 3.0, 2H, C4a-CH_2), 3.49 (s, 3H, N-3-CH_3), 3.71 (s, 3H, OCH_3), 6.66 - 6.79 (m, 4H, C4a-Ph), 6.90 (s, 1H, H-6), 7.01 (s, 1H, H-9); ^{13}C NMR: 13.2 (N-5-CH_3), 19.5 (C-7-CH_3), 19.7 (C-8-CH_3), 28.0 (N-10-CH_3), 32.6 (N-3-CH_3), 45.8 (N-5-CH_2), 46.3 (C4a-CH_2), 55.2 (OCH_3), 68.8 (C4a), 113.5, 129.0, 130.6, 139.0 (C4a-Ph), 117.0 (C-6), 125.2 (C-9), 131.4 (C-5a), 158.7 (C-10a), 160.9 (C-2), 170.0 (C-4); IR: ($CHCl_3$) 1670 (s), 1590 (s) cm^{-1}. EIMS *m/z* (relative intensity) 435 (M^+, 0.2), 420 (8), 328 (3), 316 (5), 299 (42), 271 (13), 255 (15), 175 (8), 136 (41), 121 (100); HRMS *m/z* 435.2264 ($C_{24}H_{29}O_3N_5$ requires 435.2271).

13: ^1H NMR: 0.88 (t, J = 7.1 Hz, 3H, N-5-CH_3), 1.98 (br s, 1H, NH), 2.24 (s, 3H, C-7-CH_3), 2.26 (s, 3H, C-8-CH_3), 3.14 (m, 2H, N-5-CH_2), 3.33 (s, 3H, N-10-CH_3), 3.47 (s, 3H, N-3-CH_3), 3.50-3.69 (m, 2H, C4a-CH_2), 3.62 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 6.24 (s, 1H, C4a-Ph), 6.46 (dd, J = 8.0, 1.2 Hz, 1H, C4a-Ph), 6.64 (d, J = 8.0 Hz, 1H, C4a-Ph), 6.89 (s, 1H, H-6), 7.03 (s, 1H, H-9); ^{13}C NMR: 13.3 (N-5-CH_3), 19.5 (C-7-CH_3), 19.7 (C-8-CH_3), 28.0 (N-10-CH_3), 32.6 (N-3-CH_3), 45.9 (N-5-CH_2), 46.3 (C4a-CH_2), 55.4 (OCH_3), 55.9 (OCH_3), 64.7 (C4a), 110.6, 110.8, 111.2, 119.1, 120.0 and 123.3 (C4a-Ph), 116.9 (C-6), 125.4 (C-9), 131.2 (C-5a), 132.7 (C-7), 133.7 (C-8 and C-9a), 148.7, 160.8 (C-2), 167.7 (C-4); IR: ($CHCl_3$) 3450 (br), 3000 (m), 1675 (s), 1563 (s), 1500 (w), 1425 (w), 1463 (w), 1338 (w), 1288 (w), 1125 (s) cm^{-1}; EIMS: *m/z* (relative intensity) 465 (M^+, 0.2), 450 (0.7), 315 (13), 299 (42), 271 (100), 214 (4), 151 (71), 136 (46); HRMS: *m/z* 465.2396 ($C_{25}H_{31}O_4N_5$ requires 465.2376).

14: ^1H NMR: 0.89 (t, J = 7.1 Hz, 3H, N-5-CH_3), 2.25 (s, 3H, C-7-CH_3), 2.26 (s, 3H, C-8-CH_3), 3.07-3.21 (m, 2H, N-5-CH_3), 3.34 (s, 3H, N-10-CH_3), 3.45 (m, 2H, C4a-CH_2), 3.51 (s, 3H, N-3-CH_3), 3.65 (s, 6H, OCH_3), 3.74 (s, 3H, OCH_3), 6.03 (s, 1H, C4a-Ph), 6.60 (s, 1H, C4a-Ph), 6.91 (s, 1H, H-6), 7.05 (s, 1H, H-9); ^{13}C NMR: 13.4 (N-5-CH_3), 19.3 (C-7), 19.6 (C-8-CH_3), 29.3 (N-10 CH_3), 32.6 (N-3-CH_3), 46.3 (N-5-CH_2 and C4a-CH_2), 55.8 (OCH_3), 56.3 (OCH_3), 60.8 (OCH_3), 64.6 (C4a), 104.7 (Ph), 106.3 (Ph), 117.0 (C-6), 125.5 (C-9), 131.6 (C-5a), 132.7 (C-7), 137.5 (C-8 and C9a), 153.0 (Ph), 153.8 (Ph), 155.7 (C-10a), 160.6 (C-2), 167.4 (C-4); IR: ($CHCl_3$) 2939 (w), 1722 (m), 1668 (s), 1565 (s), 1505 (m), 1462 (m), 1422 (m), 1330 (w), 1281 (w), 1236 (w), 1127 (s) cm^{-1}; EIMS: *m/z* (relative intensity) 495 (M^+, 0.1), 480 (0.9), 375 (10), 300 (54), 285 (10), 271 (100), 257 (15), 214 (16), 197 (41), 186 (25), 166 (34); HRMS: *m/z* 495.2490 ($C_{26}H_{33}O_5N_5$ requires 495.2482).

15: ^1H NMR: 0.84 (t, J = 7.3 Hz, 3H, N-5-CH_3), 1.18 (t, J = 7.1 Hz, 3H, ester-CH_3), 1.26 (q, J = 7.1 Hz, 2H, ester-CH_2), 1.68 (br s, 1H, NH), 2.23 (s, 3H, C-7-CH_3), 2.27 (s, 3H, C-8-CH_3), 3.12 (q, J = 7.3 Hz, N-5-CH_2), 3.32 (s, 3H, N-10-CH_3), 3.66 (s, 3H, N-3-CH_3), 4.03 (m, 2H, NHC$\underline{H}_2$); ^{13}C NMR: 13.2 (N-5-CH_3), 14.1 (ester-CH_3), 19.5 (C-7-CH_3), 19.8 (C-8-CH_3), 28.0 (N-10-CH_3), 32.6 (N-3-CH_3), 42.3 (ester-CH_2), 46.6 (N-5-CH_2), 61.0 (NHCH_2), 67.2 (C4a), 117.1 (C-6), 125.7 (C-9), 130.7 (C-5a), 131.3 (C-7), 133.4 (C-8), 134.0 (C9a), 161.0 (C-2), 166.1 (C-2), 171.7 (ester C=O); IR: ($CHCl_3$) 3420 (br s), 1742 (m), 1719 (m), 1677 (s), 1575 (s), 1557 (s), 1282 (m), 1203 (w), 1160 (w) cm^{-1}; UV-vis (CH_3CN)

λ_{max} = 338 (ε = 7940 $M^{-1}cm^{-1}$), 279, 223 nm; EIMS *m/z* (relative intensity) 401 (M^+, 9), 299 (85), 271 (100), 214 (47), 186 (30), 171 (22), 103 (19); HRMS *m/z* 401.2062 ($C_{20}H_{27}O_4N_5$ requires 401.2063).

16: ^1H NMR: (mixture of isomers) 0.86 (t, *J* = 6.0 Hz, 3H, N-5-CH_3), 1.00-1.31 (m, 6H, alanine-CH_3), 2.21 (br s, 1H, NH), 2.24 (s, 3H, C-7-CH_3), 2.27 (s, 3H, C-8-CH_3), 3.00-3.11 (m, 2H, N-5-CH_2), 3.26 (major) (s, 3H, N-10-CH_3), 3.34 (minor) (s, 3H, N-10-CH_3), 3.38 (minor) (s, 3H, N-10-CH_3), 3.65 (major) (N-3-CH_3), 3.66 (minor) (N-3-CH_3), 3.70 (minor) (N-3-CH_3), 3.81-4.27 (m, C4a-CH_2, ala-CH-N, ala-OCH_2), 6.85-7.05 (m, 2H, H-6, H-9); ^{13}C NMR: 13.1 (N-5-CH_3), 14.0 (ala-CH_3), 14.2 (ala-CH_3), 19.4 (major) (C-7-CH_3), 19.5 (minor) (C-7-CH_3), 19.7 (major) (C-8-CH_3), 20.2 (minor) (C-8-CH_3), 27.9 (major) (N-10-CH_3), 28.4 (minor) (N-10-CH_3), 32.6 (N-3-CH_3), 46.2 (N-5-CH_2), 46.3 (C4a-CH_2), 47.6 (major) (ala-CHN), 48.8 (minor) (ala-CHN), 61.0 (major) (ala-OCH_2), 62.0 (minor) (ala-OCH_2), 66.9 (C4a), 117.0 (major) (C-6), 117.1 (minor) (C-6), 125.4 (minor) (C-9), 125.7 (major) (C-9), 131.0 (major) (C5a), 131.2 (minor) (C-5a), 133.1 (C-8), 133.6 (C9a), 153.0 (C10a), 161.9 (C-2), 166.5 (minor) (C-4), 170.5 (major) (C-4), 175.6 (O=CO); IR: ($CHCl_3$) 3416 (br m), 1733 (m), 1679 (s), 1661 (s), 1568 (s), 1556 (s), 1279 (m), 1160 (m) cm^{-1}; UV-vis (CH_3CN) λ_{max} = 338 (ε = 7920 $M^{-1}cm^{-1}$), 279, 223 nm; EIMS *m/z* (relative intensity) 415 (M^+, 8), 316 (23), 299 (100), 270 (58), 256 (24), 213 (39), 185 (26), 171 (23); HRMS *m/z* 415.2229 ($C_{21}H_{29}N_5O_4$ requires 415.2220).

17: ^1H NMR: (mixture of isomers) 0.86 (t, *J* = 7.1 Hz, 3H, N-5-CH_3), 2.10 (major) (s, 3H, C-7-CH_3), 2.20 (major) (C-8-CH_3), 2.26 (minor) (C-7-CH_3), 2.29 (minor) (C-8-CH_3), 3.08-3.24 (m, 2H, N-5-CH_2), 3.25 (major) (s, 3H, N-10-CH_3), 3.27 (minor) (s, 3H, N-10-CH_3), 3.42 (minor) (s, 3H, N-3-CH_3), 3.63 (major) (s, 3H, N-3-CH_3), 3.64 (minor) (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 4.63 (major) (m, 1H, CHN), 5.05 (minor) (d, *J* = 8.1 Hz, 1H, CHN), 6.74-7.38 (m, 7H, H-6, H-9, Ph); ^{13}C NMR: 13.1 (major) (N-5-CH_3), 13.2 (minor) (N-5-CH_3), 19.3 (minor) (C-7-CH_3), 19.6 (major) (C-7-CH_3), 19.7 (C-8-CH_3), 27.9 (N-10-CH_3), 32.2 (minor) (N-3-CH_3), 32.7 (N-3-CH_3), 46.3 (major) (N-5-CH_2), 46.5 (minor) (N-5-CH_2), 52.4 (major) (CHN), 56.2 (minor) (CHN), 57.4 (major) (C4a), 58.7 (minor) (C4a), 116.8 (major) (C-6), 117.2 (minor) (C-6), 125.6 (C-9), 125.7, 126.8, 127.1 (minor), 127.3 (major), 127.8 (minor), 127.9 (major), 128.1 (minor), 128.8 (major) and 138.0 (C4a-Ph), 131.0 (C5a), 132.8 (C-7), 133.7 (C-8), 133.8 (C9a), 156.0 (C10a), 162.0 (C-2), 166.0 (C-4), 171.9 (O=CO); IR: ($CHCl_3$) 2944 (w), 1789 (w), 1731 (s), 1669 (s), 1558 (m), 1496 (m), 1455 (m), 1386 (m), 1264 (m), 1210 (m), 1171 (m), 1096 (m) cm^{-1}; EIMS *m/z* (relative intensity) 463 (M^+, 0.2), 356 (25), 316 (53), 299 (100), 270 (65), 256 (34), 213 (15), 106 (11); HRMS *m/z* 463.2214 ($C_{25}H_{29}N_5O_4$ requires 463.2219).

19: ^1H NMR: (mixture of isomers) 0.97 (t, *J* = 7.1 Hz, 3H, N-5-CH_3), 2.05 (minor) and 2.14 (major) (s, 3H, C-7-CH_3), 2.08 (minor) and 2.16 (major) (s, 3H, C-8-CH_3), 2.92-3.18 (m, 4H, N-5-CH_2, indoline-CH_2), 3.22 (s, 3H, N-10-CH_3), 3.45-3.65 (m, 4H, C4a-CH_2, indoline-CH_2), 3.70 (s, 3H, N-3-CH_3), 6.63 (d, *J* = 8.3 Hz, 1H, Ph), 6.75 (br s, 1H, Ph), 6.94 (br s, 1H, H-6), 7.10-7.20 (m, 3H, H-9, Ph), 7.20 (br s, 1H, Ph); ^{13}C NMR: 13.3 (N-5-CH_3), 19.4 (C-7-CH_3), 19.7 (C-8-CH_3), 28.3 (N-10-CH_3), 29.4 (indoline-CH_2), 32.5 (N-3-CH_3), 44.7 (indoline-CH_2), 47.2 (N-5-CH_2, C4a-CH_2), 65.2 (C4a), 106.6, 109.0, 123.0 (minor), 123.1 (major), 125.9, 127.4 (major), 127.6 (minor), 129.9, 132.0, 138.2 (indoline Ph), 117.1 (C-6), 125.4 (C-9), 132.7 (C-7), 133.6 (C-8), 133.8 (C9a), 153.4 (C-10a), 157.0 (indoline), 164.5 (C-2), 168.1 (C-4); IR: ($CHCl_3$) 3333 (br), 2954 (w), 1713 (w), 1667 (s), 1610 (m), 1554 (s), 1497 (m), 1462

(m), 1416 (m), 1366 (w), 1280 (m), 1102 (s) cm^{-1}; EIMS: *m/z* (relative intensity) 417 (M^+, 39), 360 (75), 271 (28), 197 (69), 181 (41), 166 (76), 118 (45); HRMS: *m/z* 417.2160 ($C_{24}H_{27}O_2N_5$ requires 417.2165).

20: ^1H NMR: (mixture of isomers) 0.90 (t, J = 7.10 Hz, 3H, N-5-CH_3), 2.20 (major) (s, 3H, C-7-CH_3), 2.22 (major) (s, 3H, C-8-CH_3), 2.26 (minor) (s, 3H, C-7-CH_3), 2.28 (minor) (s, 3H, C-8-CH_3), 3.15-3.23 (m, 2H, N-5-CH_2), 3.37 (s, 3H, N-10-CH_3), 3.38-3.62 (m, 6H, C4a-CH_2, ring-CH_2), 3.67 (s, 3H, N-3-CH_3), 3.73 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.82 (s, 1H, ring-CH-N), 3.83 (s, 1H, ring-CH-N), 6.36 (major) (s, 1H, C4a-Ph), 6.39 (major) (s, 1H, C4a-Ph), 6.49 (minor) (s, 1H, C4a-Ph), 6.57 (minor) (s, 1H, C4a-Ph), 6.85 (s, 1H, H-6), 6.96 (s, 1H, H-9); ^{13}C NMR: 13.2 (N-5-CH_3), 19.5 (C-7-CH_3), 19.7 (C-8-CH_3), 27.4 (N-10-CH_3), 29.2 (C4a-CH_2), 33.0 (N-3-CH_3), 41.6 (C4a-CH_2), 46.3 (N-5-CH_2), 47.7 (C4a-CH_2), 55.8 (OCH_3), 71.0 (C4a-CH), 72.0 (C4a), 109.2 (C4a-Ph), 111.2 (C4a-Ph), 117.2 (C-6), 124.5 (C4a-Ph), 125.4 (C-9), 126.7 (C4a-Ph), 130.8 (C5a), 132.0 (C-7), 133.5 (C-8 and C9a), 135.9 (C4a-Ph), 147.3 (C10a), 162.1 (C-2), 163.8 (C-4); IR: ($CHCl_3$) 2937 (w), 1713 (w), 1663 (s), 1614 (w), 1557 (s), 1519 (s), 1464 (m), 1418 (m), 1365 (w), 1318 (w), 1257 (m), 1226 (m), 1121 (s), 1015 (m), 913 (m) cm^{-1}; EIMS: *m/z* (relative intensity) 491 (M^+, 0.1), 460 (0.4), 412 (3), 300 (37), 271 (100), 213 (48), 171 (18); HRMS: *m/z* 491.2555 ($C_{27}H_{33}N_5O_4$ requires 491.2533).

General Procedure for Stopped-Flow Kinetic Measurements. Stopped-flow experiments were carried out by using a Bio-Sequential DX-17MV Sequential Stopped-Flow ASVD Spectrometer (Applied Photophysics) with a total injection volume of 200 μL. A stopped-flow workstation equipped with a RISC-processor unit (32-bit) linked to a Acorn 5000 computer and Taxan 775 monitor was used. The light source for absorption spectroscopic measurments was a 150 W xenon Arc lamp. Glint software was used to analyze time-dependent spectra generated from the stopped-flow reaction analyzer. The software performed global optimization of reaction parameters using the Marquardt-Levenberg algorithim.[23] The dead-time (t_d) was determined by use of the reduction of 2,6-dichlorophenolindophenol by L-ascorbic acid,[24] and calculated from $t_d/t_{1/2} = \ln(x_{total}/x_{obs})/\ln 2$ (also $\ln(\Delta A_{obs}) = \ln(\Delta A_{total})-k_{app}t_d$), plotted as ln(Δabsorbance) *vs.* rate constant (slope=t_d), and was found to be 2.0 ms (2 mm pathlength). Unless otherwise noted, all solutions were purged with O_2-free argon prior to there use in the kinetic experiments.

Concentrated stock solutions of the flavinium salt and amine in anhydrous acetonitrile in calibrated 10 or 20 mL volumetric flasks at 25°C were diluted to give the concentrations recorded below. In all reactions, the flavinium salt concentration was kept constant (0.05 mM or 0.1 mM), and the amine concentration varied starting from minimum values of 0.5 mM or 1.0 mM. The rates for reduction of the flavinium salt were monitored at 550 and 420 nm and the rates of formation of the C4a-adducts were monitored at 338 nm unless otherwise specified. An average of at least 5 k_{obs} values were measured for each amine concentration at each wavelength. The rates of reduction of the flavinium salt followed a first order exponential decay curve, and the rates of formation of the C4a-adducts followed first order exponential growth curves. A single exponential, floating end point function was assigned to these curves by using the Marquardt algorithim to provide the value for k_{obs}. Plots of k_{obs} *vs.* [amine] gave slopes which were used to calculate the rate constants for flavinium salt disappearance and C4a-adduct formation listed in Table 1.

C4a-Adduct Elimination Reactions. Solutions of the C4a-adducts (9 mM) in CD_3CN containing benzylamine (90 mM) were allowed to stand at 30°C for 42 min. ^1H NMR spectra were recorded at a temperature of 25°C. The concentrations of the starting materials and products were calculated based on

comparisons of the intensities of representative ^1H NMR resonances relative to those of triphenylmethane as an internal standard.

Rates of C4a-Adduct Elimination Reactions. Solutions of freshly prepared C4a-adducts **2**, **11** and **14** (0.032 mM final concentration) in CD_3CN were mixed with benzylamine (0.32 mM final concentration) and monitored periodically over a 15 h time period at 40°C by ^1H NMR spectroscopy to determine (by intergration relative to triphenylmethane as an internal standard) the concentrations of the starting C4a-adducts and aldimine products. Plots of ln([C4a-adduct]-[aldimine]) vs. time gave the k_{obs} values which were then used to calculate the absolute rate constants for elimination recorded in Table 2.

Flavinium Perchlorate Catalyzed Amine Oxidations. All reactions were carried out in CD_3CN in non-sealed NMR tubes protected from light under an air atmosphere. ^1H NMR spectroscopy was used to monitor C4a-adduct and aldimine formation. The general procedure is exemplified by that used for the catalytic oxidation of benzylamine. To a solution of 3.0 mmol flavinium salt **1** was added 40 mmol benzylamine. The resulting solution after standing at 22°C for 4 d was analyzed and shown to contain 2.5 mmol (83%) of benzylamine C4a-adduct **2**, 5.4 mmol (180%) of benzaldimine **3**, and 0.8 mmol (27%) of rearrangement product **21**. Further standing for 12 days at 22°C resulted in formation of 28 mmol (933%) of benzaldimine **3** and 2.7 mmol (90%) of rearrangement product **21**.

Preparation of the Aldimine Products. The general procedure used is exemplified by the preparation of N-benzyl-3,4,5-trimethoxybenzaldimine (**29**). A solution of 3,4,5-trimethoxybenzaldehyde (0.12 g, 0.60 mmol) in anhydrous diethyl ether (1 mL) containing benzylamine (0.064 g, 0.598 mmol) was stirred for 15 min at 22°C and concentrated *in vacuo* to give aldimine **29** (0.11 g, 80%). ^1H NMR 3.99 (s, 3H, p-OCH_3), 4.01 (s, 6H, m-OCH3), 4.93 (s, 2H, CH_2Ph), 7.15 (s, 2H, $(CH_3O)_3Ph$-H), 7.45 (s, 5H, Ph-H), 8.40 (s, 1H, =C-H); ^{13}C NMR: 56.1 (OCH_3), 56.2 (OCH_3), 60.8 (OCH_3), 64.7 (CH_2), 105.2, 106.6, 127.0 (Ph), 128.4 (=CCH_2), 131.6(m-C(OCH_3)), 139.0 (p-C(OCH_3)-), 153.3 (C-CH=N-), 161.6 (-HC=N-); IR: ($CHCl_3$) 3060 (w), 2998 (w), 2938 (m), 2838 (m), 1642 (s), 1585 (s), 1504 (s), 1454 (s), 1417 (s), 1378 (s), 1329 (s), 1233 (s), 1184 (m), 1151 (m), 1127 (s), 1007 (s) cm^{-1}; EIMS: *m/z* (relative intensity) 285 (M^+, 100), 270 (14), 254 (13), 238 (16), 210 (11), 91 (71); HRMS m/z 285.1365 ($C_{17}H_{19}NO_3$ requires 285.1365).

A similar procedure was used to prepare the following aldimines:

25: ^1H NMR: 4.76 (s, 2H, CH_2), 7.20-7.27 (m, 5H, Ph), 7.56 (d, J = 8.2 Hz, 2H, Ph), 7.78 (d, J = 8.2 Hz, 2H, Ph), 8.33 (s, 1H, =CH); ^{13}C NMR: 65.1 (CH_2), 121.2 (Ph), 125.5 (CH), 125.6 (Ph), 126.6 (Ph), 127.2 (CH), 128.0 (CH), 128.4 (Ph), 128.6 (CH), 132.0, 132.7, 138.8, 139.3 (Ph), 160.4 (=CH); IR: ($CHCl_3$) 3000 (s), 2950 (s), 1640 (w), 1590 (s), 1550 (s), 1502 (s), 1220 (s) cm^{-1}; EIMS: *m/z* (relative intensity) 263 (M^+, 17), 244 (3), 185 (6), 91 (100); HRMS: *m/z* 263.0915 ($C_{15}H_{12}NF_3$ requires 263.0922).

26: ^1H NMR: 4.89 (s, 2H, CH_2), 7.30 (m, 5H, Ph), 7.48 (m, 1H, NO_2-Ph), 8.14 (m, 1H, NO_2-Ph), 8.48 (s, 1H, N=CH); ^{13}C NMR: 46.4 (CH_2), 123.8, 126.7, 127.0, 127.7, 127.8, 128.5, 128.9, 129.7 (Ph), 138.2, 142.0, 144.0 (quaternary Ph), 162.0 (N=CH); IR: ($CHCl_3$) 3124 (s), 2960 (s), 1640 (w), 1594 (s), 1551 (s), 1500 (s), 1400 (s), 1360 (s), 1280 (s), 1220 (s), 1130 (s), 1020 (s) cm^{-1}; CIMS: *m/z* (relative intensity) 241 (M^+ + 1, 24), 195 (23), 106 (25), 91 (100), 77 (19); HRMS: *m/z* 241.0979 ($C_{14}H_{13}O_2N_2$ requires 241.0977).

27: ^{1}H NMR: 3.78 (s, 3H, OCH_3), 4.82 (s, 2H, CH_2), 6.96 (d, J = 8.6 Hz, 2H, m-H of MeO-Ph), 7.39 (m, 5H, Ph), 7.79 (d, J = 8.6 Hz, o-H of MeO-Ph). 8.32 (s, 1H, N=CH); ^{13}C NMR: 54.9 (OCH_3), 64.6 (CH_2), 113.6, 113.9, 126.6, 127.6, 128.1, 129.5 (Ph), 131.6, 139.4 (quaternary Ph), 160.9 (N=CH); EIMS: *m/z* (relative intensity) 225 (M^+, 68), 210 (4), 194 (4), 134 (18), 117 (14), 91 (100); HRMS: m/z 225.1159 ($C_{15}H_{15}NO$ requires 223.1154).

28: ^{1}H NMR: 3.86 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.77 (s, 2H), 6.83 (d, J = 8.2 Hz, 1H, Ph), 7.16 (d, J = 1.7 Hz, 1H, Ph), 7.18 (d, J = 1.7 Hz, 1H, Ph), 7.25 (m, 1H, Ph), 7.33 (m, 4H, Ph), 7.48 (d, J = 1.6 Hz, 1H, Ph), 8.26 (s, 1H, N=CH); ^{13}C NMR: 55.8 (OCH_3), 64.7 (CH_2), 108.6, 110.2, 123.2, 126.8, 127.8, 128.3 (C-H of Ph), 129.2, 139.3, 149.2, 151.3 (quaternary, Ph), 161.4 (N=CH); EIMS: *m/z* (relative intensity) 255 (M^+, 100), 240 (13), 224 (11), 164 (7), 91 (71); HRMS: *m/z* 255.1254 ($C_{16}H_{17}O_2N$ requires 255.1259).

30: ^{1}H NMR: 4.88 (s, 2H, CH_2), 7.45 (d, J = 7.0 Hz, 2H, Ph), 7.59 (d, J = 8.1 Hz, 2H, Ph), 7.67 (d, J = 8.2 Hz, 2H, Ph), 7..88 (d, J = 8.1 Hz, 2H, Ph), 8.45 (s, 1H, N=CH); ^{13}C NMR: 64.4 (CH_2), 125.5, 125.6, 125.7, 128.1, 128.5 (C-H of Ph), 129.3, 130.0, 139.0, 143.0 (quaternary Ph), 161.1 (N=CH); IR: ($CHCl_3$) 2950 (w), 1640 (m), 1620 (m), 1440 (s), 1400 (s), 1350 (s), 1160 (s), 1120 (s), 1070 (s) cm^{-1}; EIMS: *m/z* (relative intensity) 331 (M^+, 55), 312 (13), 262 (10), 185 (22), 172 (18), 159 (100), 109 (20); HRMS: *m/z* 331.0806 ($C_{16}H_{11}NF_6$ requires 331.0796).

31: ^{1}H NMR: 3.78 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.71 (s, 2H, CH_2), 6.88 (br t, J = 8.6 Hz, 4H, Ph), 7.23 (d, J = 8.7 Hz, 2H, Ph), 7.7 (d, J = 8.7 Hz, 1H, Ph), 8.28 (s, 1H, N=CH); ^{13}C NMR: 55.3 (OCH_3), 64.4 (CH_2), 113.8, 113.9, 129.1, 129.8 (C-H of Ph), 129.8, 131.6, 158.6 (quaternary Ph), 161.0 (N=CH); EIMS: *m/z* (relative intensity) 255 (M^+, 24), 196 (2), 121 (100), 91 (4), 77 (7); HRMS: *m/z* 255.1260 ($C_{16}H_{17}O_2N$ requires 255.1259).

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