where an asterisk and cross signify electronically and vibrationally excited species respectively.

$$A \xrightarrow{h\nu} A^* \rightarrow B^{\ddagger} \rightarrow B \quad \begin{matrix}\text{(conventional}\\ \text{environment)}\end{matrix} \qquad (3)$$

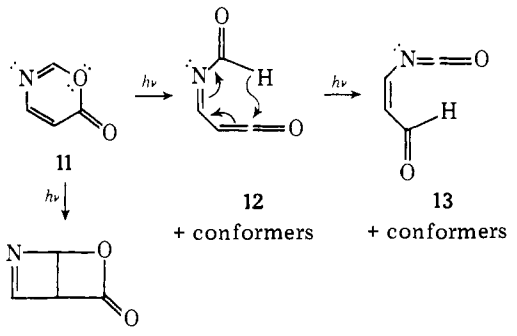
$$A \xrightarrow{h\nu} A^* \rightarrow B^{\ddagger} \rightarrow C^{\ddagger} \rightarrow C \quad \begin{matrix}\text{(cryogenic } T,\\ \textit{rare gas matrix)}\end{matrix} \qquad (4)$$

Stabilizing B requires efficient energy transfer from $B^{\ddagger}$ to the matrix, a requirement which is not met in this hypothetical scheme (eq 4).

Thus, depending upon the situation the matrix environment could have a stabilizing or "destabilizing" effect on photochemically generated species.

In the present case, it is clear that at least two discrete photochemical steps are responsible for producing **6** from **4** (or **7** from **5**). Specifically labeled aldoketene **7**, a primary photochemical product of **4**, is in turn converted to **6**, if the conformational requirements are met, as a result of a further photochemical event.

During the irradiation of the 1,3-oxazin-6-one **11**[14] we have observed a band at 2250 cm^{-1} due to a species which appears to be interconvertible with the ketenes **12**. A 1,5-hydrogen shift from **12** would give rise to an aldoisocyanate **13**, which would be expected to absorb near ν 2250 cm^{-1}.[15] Thus the photoreactions of the oxazinone **11** appear to be analogous to the α-pyrone system.[14]



11 12 13 16

Studies designed to uncover further degenerate processes such as sigmatropic shifts of oxygen across the cyclobutene framework of **9** and hypothetical condensation of carbon dioxide **14** with [^{13}C]cyclobutadiene **15** are in progress.

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Studies of Mitochondrial Monoamine Oxidase. Inactivation of the Enzyme by Isomeric Acetylenic and Allenic Amines Yielding Mutually Exclusive Products

Sir:

Monoamine oxidases (MAO), [EC 1.4.3.4], the mitochondrial membrane-bound flavin-linked class of enzymes whose members metabolize putative neurotransmitters and play a role in controlling levels of diverse exogenous and endogenous amines,[1] have been the object of recent intense interest.[2-8] Studies of the chemical inactivation of MAO by active-site directed reagents are potentially useful in defining the modes of reactivity of the enzyme. The inhibitory action of β,γ-acetylenic amines, substances which have been exploited clinically to control depression and hypertension,[9] has been a point of focus.[2]

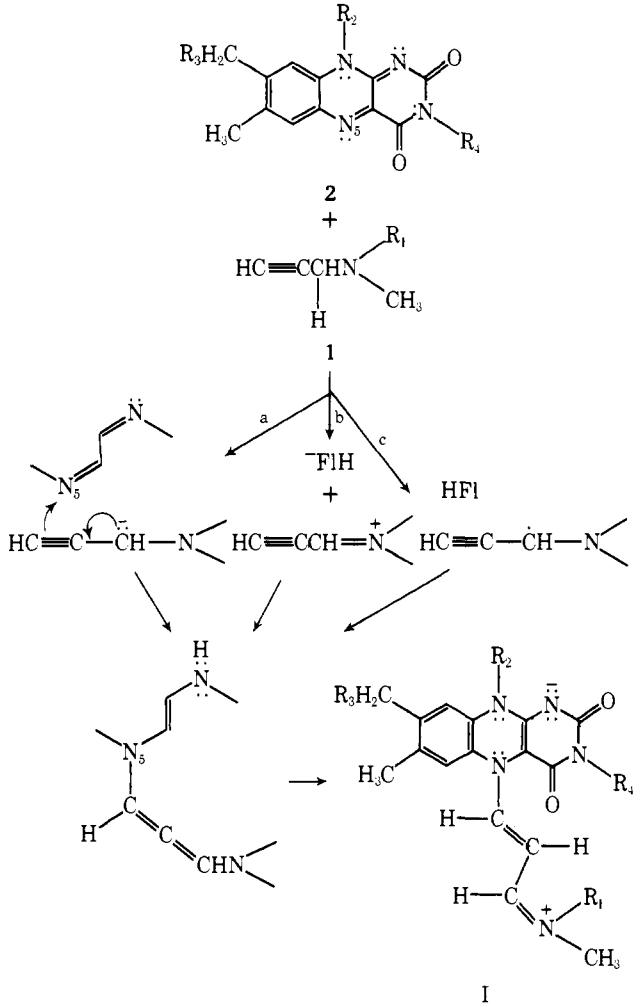
Abeles, Singer, and coworkers have studied the inactivation of bovine liver MAO **2a** with 3-dimethylaminopropyne (**1**, $R_1 = CH_3$) and have assigned the flavocyanine Ia as the most probable structure of the irreversibly formed adduct between **1** and the enzyme.[2] Their conclusion exploits the finding that the electronic spectrum of the inactivated enzyme is very similar to that of the flavocyanine Ib, a photoproduct of **1** with 3-methyllumiflavin **2b** which possesses an unusually intense absorption band at 391 nm (ϵ 25 500, pH 7.0).[10-12]

Three mechanisms (Scheme I) have been advanced to explain the formation of Ia upon inactivation of the enzyme.[2] Path a features attack on the oxidized form of the flavin of a resonance stabilized, formally, carbanionic species. Another, path b, views the adduct as a consequence of the union of flavin and oxidized substrate. A third, path c, involves generation of a radical-pair complex between flavin and substrate, which collapses to form a new, stable covalent bond. From a different mechanistic standpoint, Rando[7] has emphasized the possible role of allenes in the inhibition of MAO by β,γ-acetylenic amines, and has categorized the latter substances as enzyme-suicide inhibitors, after the example provided by Bloch.[8]

In this context we wish to report our findings with a pair of inhibitors of monoamine oxidase. *N*-But-2-ynyl-*N*-benzylmethylamine[13] (**3a**) and *N*-2,3-butadienyl-*N*-benzylmethylamine[14] (**4**) are related as tautomers, and it might be expected that, if their respective reactions with the enzyme followed any of the paths outlined in Scheme I, the identical flavocyanine, **5a**, would be produced in both cases (Scheme II). This point is illustrated for path a and is based on the assumption that intermediate enamines would be rapidly converted by proton transfer to a common flavocyanine.

When a sample of the bovine liver MAO (15.6 mg of protein/mL, specific activity 2.56 μmol/min mg of protein),[15,16] purified according to Salach's procedure,[2,17] is made 10^{-4} M in **3a**, loss of enzymatic activity is accompanied by dramatic

Scheme I



a, R_2 = adenine dinucleotide
R_4 = H; R_3 = apoenzyme
b, R_3 = H; R_2 = R_4 = CH_3

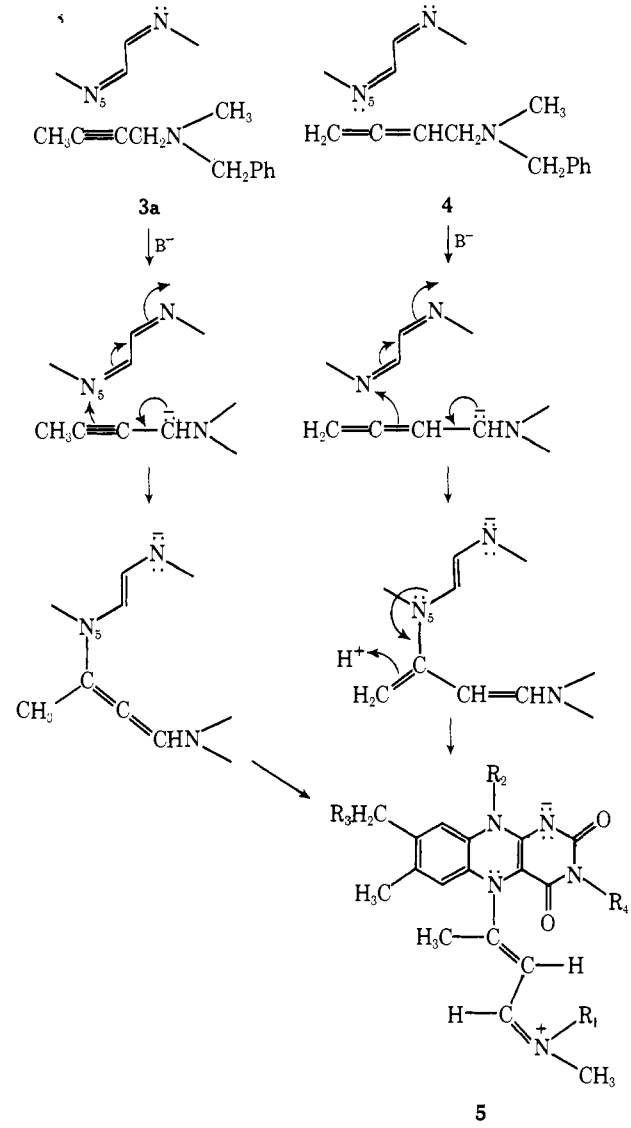
changes in the UV-visible region of the spectrum. The observation of strong absorption centered at 391 nm (ϵ 2–3 × 10^4) with concomitant loss of the 455-nm band of the native flavoenzyme, signals the formation of an adduct between the flavin prosthetic group and the acetylenic amine **3a.**

The position and intensity of the new band are similar to values observed for the corresponding inhibitions with **1** (R_1 = CH_3)[2] and pargyline (**1**, R_1 = CH_2Ph),[3] and are typical values for flavocyanines. In fact, Hemmerich[12] has recently prepared a model for the flavocyanine **5a,** which has spectral properties (λ 391 nm (ϵ 22 800)) similar to **3a**-inhibited MAO.

At concentrations of 10^{-5}–10^{-6} M, *N*-2,3-butadienyl-*N*-benzylamine[13] (**4**) is a potent inhibitor of MAO. The mere presence of allenic functionality is not a sufficient condition for inactivation of MAO, since 2,3-butadienol[18] (**6**), at concentrations of 10^{-3} M does not inactivate the enzyme. Incubation of purified bovine liver MAO in solutions (0.066 M phosphate buffer, pH 7.2, 25 °C) which are 10^{-5} M in **4,** results in bleaching of the 455-nm band of the native enzyme, but, in contrast to the action of **3a,** the electronic spectrum of the product shows no absorption characteristic of a flavocyanine, nor does it show any new absorption in the region above 360 nm.

Normal substrates of MAO protect against the inhibition. Dialysis of the inhibited enzyme for 17 h against several changes of phosphate buffer does not lead to restoration of the enzyme activity or to any significant spectral changes, nor does

Scheme II



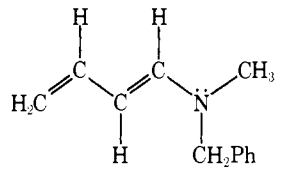
a, R_2 = adenine dinucleotide
R_4 = H; R_3 = apoenzyme

exposure of the system to molecular oxygen regenerate the spectrum of oxidized flavin as would be expected if the flavin had simply been reduced to a dihydro form.

Even after denaturation of the allene-inhibited enzyme with trichloroacetic acid followed by enzymatic digestion, no evidence for flavocyanine absorption can be found. Hence a tautomer of the flavocyanine **5a** seems an unlikely product of the association of **4** with MAO. An upper limit of 15% for "unreactive" flavin, could be estimated from treatment of the inactivated enzyme with trichloroacetic acid, enzymatically digesting the resulting precipitate with chymotrypsin, trypsin, and then pronase, and then titrating flavin with dithionite.[19-21] The balance (~85%) of flavin is neither titratable nor spectrally detectable in the oxidized form, owing to adduct formation. It seems evident that the adduct which is of sufficient strength to survive the acid and protease treatment is most probably covalent.

Under conditions in which **4** rapidly inactivates MAO, the isomeric butadienylamine[22,23] **7** (prepared from crotonaldehyde and *N*-benzylmethylamine) is not an effective inhibitor of the enzyme. If **7** (or its cis isomer) is involved in the inactivation of MAO, then it must act before release from the surface of the enzyme.

It is clear that the isomeric inhibitors **3a** and **4** do not give rise to the same adduct, as might have been expected if they



7

both followed paths advanced for the action of acetylenic inhibitors outlined above. Hence, neither inhibitor is being converted into the other nor are they being converted to a common intermediate.

Allylamines are also inhibitors of MAO,[13] bleaching its spectrum[26] and forming covalent adducts,[27] but they require considerably higher concentrations than their acetylenic analogues to effect the same change in MAO activity. One distinction that can be drawn between the allylic and propargylic inhibitors that may account for the greater reactivity of the latter is the acidity of their α protons.[28] The ease of removal of such propargyl and allylic protons was evaluated by measuring the rates of deuterium exchange of the quaternary ammonium salts **10** and **11**,[29] which we assume crudely represent the form of the amine at the enzyme's active site. Whereas **10** (0.48 M) undergoes exchange of its propargylic protons[30] in 1 M NaOD-D_2O with a half-life of 5 min at 25 °C, allyl trimethylammonium ion **11** under the same conditions shows little evidence of exchange even after 6 months.[31-36] At 70 °C, **11** (0.48 M) has a half-life of ~60 h in 1 M $NaOCD_3$-CD_3OD. Attempts to measure the rate of exchange of protons from *N*,2,3-butadienyltrimethylammonium ion **12** at 25 °C were undermined by a facile base-induced decomposition producing trimethylamine **13** and vinylacetylene **14.**

$HC{\equiv}CCH_2N^+(CH_3)_3Br^-$ $H_2C{=}CHCH_2N^+(CH_3)_3Br^-$

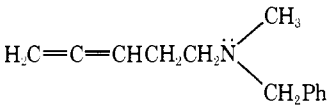
10 **11**

$H_2C{=}C{=}CHCH_2N^+(CH_3)_3OMes^-$

12

A most intriguing feature of inactivation by unsaturated amines concerns the mechanism and mode of attachment of MAO to the allenic amine inhibitor, because it may reveal a hitherto unrecognized mode of reactivity, of general applicability for the design of allenic inhibitors of flavoenzymes. Is **4** an enzyme suicide reagent[7b,37] dependent for its reactivity upon a catalytic act of the enzyme, or is **4** functioning as an allenic affinity label? Could it be that the allene by binding to the enzyme is activated for cycloaddition to the flavin prosthetic group?[38]

Suffice it to say that *N*-3,4-pentadienyl-*N*-benzylmethylamine[23b] (**15**) acts not as an inactivator, but merely as a weak inhibitor of MAO with benzylamine as substrate.



15

Substitution for the allenic hydrogens of **4** severely alters its inhibitory power. The rate of MAO inhibition is reduced by approximately two orders of magnitude by a single methyl substituent at the terminal allenic position. For the latter inactivation at 0.927×10^{-4} M the loss of enzymatic activity has a $t_{1/2}$ of 3 min. The compound with two methyl groups at the terminus is an ineffective inhibitor at this concentration.[39] At the internal allenic position, a methyl group also destroys the inhibitory ability of the allenic amine.[40] On the basis of the foregoing data, the essential structural unit for allenic amine inactivation of MAO appears to be $>C{=}C{=}CHCH_2\ddot{N}<$.

The characterization of enzymatic and photoadducts between flavin and allenic amine is being pursued, along with kinetic studies of the enzymatic reaction.

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(26) The UV-visible spectrum of allylamine-inactivated MAO is similar to that resulting from inactivation of MAO with **4**: A. Krantz, unpublished results.
(27) Independent observations, privately communicated by R. H. Abeles, Department of Biochemistry, Brandeis University, Waltham, Mass., and R.

R. Rando, Department of Pharmacology, Harvard Medical School, Boston, Mass.
(28) Hydrogen removal has been shown to be at least partially rate determining in the reaction of MAO with substrates: B. Belleau and J. Moran, *Ann. N.Y. Acad. Sci.*, **107**, 822 (1963).
(29) The quaternary salts **10**, **11**, and **12** were prepared from the reaction of the corresponding unsaturated bromides or mesylate with trimethylamine.
(30) Solubilization of **10** in neutral deuterium oxide (25 °C) leads instantaneously (on the NMR time scale) to exchange of the terminal, acetylenic proton.
(31) The overwhelming preference for removal of propargyl vs. allylic protons is in accord with the much greater electron-withdrawing power of the ethynyl group than the vinyl group.[32-34]
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(40) Private communication from Dr. R. P. Hallday, Norwich Pharmacal Co., Norwich, N.Y.

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Highly Reactive Transition Metal Powders. Oxidative Insertion of Nickel, Palladium, and Platinum Metal Powders into Aryl-Halide Bonds

Sir:

We have reported a new procedure for producing highly reactive metal powders.[1,2] This procedure consists of reduction of a metal salt from an ethereal or hydrocarbon solvent with an alkali metal. The primary consideration is that the metal salt in question be partially soluble in the solvent used. In most cases, the alkali metal used had a melting point lower than the boiling point of the solvent;[2] however, this is not necessary in all cases. In this paper we wish to report that, using a modification of this approach, highly reactive transition metal slurries can be prepared. Nickel, palladium, and platinum produced by this method are found to undergo oxidative insertion into C-X bonds and in some cases at relatively low temperatures.

Oxidative addition of RX to transition metals has been observed using the metal atom or metal vaporization approach of Skell.[3,4] Klabunde has reported that nickel and palladium, when cocondensed with aryl halides, readily undergo oxidative insertion into the carbon-halogen bond.[5-8] Cocondensation of nickel or palladium with pentafluorobromobenzene and triethylphosphine gave good yields of the bromopentafluorobis(triethylphosphine)metal complex. The corresponding solution reaction of common commercial nickel powders or palladium powders with aryl halides has not been observed due to the poor reactivity of these and most other transition metals toward oxidative addition.

Initially we tried the standard approach of reduction of NiI_2, $NiBr_2$, or $NiCl_2$ with potassium in refluxing THF. Finely divided black nickel powders were obtained; however, they showed rather limited reactivity toward oxidative insertion into carbon-halogen bonds. Similar results were found with palladium.

We have demonstrated with several of the main group elements that the reactivity of the resulting metal is highly dependent on such factors as the solvent, reducing agent, anion, or in the case of some metals the presence of additional alkali salts.[2,9,10] In the case of the transition metals to be discussed in this paper, the presence of a triaryl- or trialkylphosphine during the reduction yields a highly reactive metal slurry. When triethylphosphine is added to NiI_2 in THF, the well known and highly soluble diiodobis(triethylphosphine)nickel(II) complex is formed. Addition of 2 mol of potassium to this mixture, and then heating at reflux, yields a very fine black metal slurry of nickel. The reduction time is very dependent upon the type of phosphine used. For example, when triethylphosphine or triphenylphosphine were used the reduction times were approximately 20 and 2 h, respectively.

The particle size of the black powder is much smaller than that resulting from the standard procedure without the presence of the triethylphosphine. Elemental imaging of the black nickel powder using energy dispersive analysis at a magnification of 5000 indicated that the distribution of nickel, potassium, and iodide is essentially random. When the reduction is completed, the precipitated KI is obtained in almost quantitative yields. These facts, coupled with the fact that the black metal slurry does not flash when added to water, strongly indicates that no potassium remains after the reduction and that the black slurry contains considerable nickel (0).

Not only is the particle size smaller when the reduction is carried out in the presence of the triethylphosphine but the reactivity of the metal toward oxidative additions is greatly enhanced. Upon the addition of pentafluorobromobenzene to the black nickel slurry produced[11] in the presence of triethylphosphine, a rapid reaction occurred yielding bromopentafluorophenylbis(triethylphosphine)nickel(II) in 60% yield.

$$\mathrm{Ni} + 2\mathrm{Et_3P} + \mathrm{C_6F_5Br} \longrightarrow \mathrm{C_6F_5NiBr}\begin{matrix}\mathrm{PEt_3}\\ \\ \mathrm{PEt_3}\end{matrix}$$

Triphenylphosphine seems to have a similar effect. In fact, nickel slurries produced by reducing NiI_2 in the presence of triphenylphosphine are more reactive than those generated with the triethylphosphine procedure. Addition of pentafluorobromobenzene to the black nickel slurry at −78 °C resulted in an almost immediate reaction. Workup of the reaction yielded 46% of the bromopentafluorophenylbis(triphenylphosphine)nickel(II). Thus, the nickel generated by this method appears to be more reactive but the yield of the oxidative addition product was slightly less. These two sets of experiments suggest that the reaction was not occurring via oxidative addition of the tetrakis(triethylphosphine)nickel(0) or the tetrakis(triphenylphosphine)nickel(0) complexes. Parshall[12] and others[13] have shown that the tetrakis(triphenylphosphine)nickel(0) complex is less reactive than the tetrakis(triethylphosphine)nickel(0) complex in oxidative additions into aryl-halogen bonds. In several cases, reaction of the tetrakis(triphenylphosphine)nickel(0) complex with aryl halides often requires several hours of refluxing. Thus, it would