reagents (whether assisted by Li[5] or not[20]) from that hemisphere about the dimer which does not enclose the bulkier groups.[22] Even the poorer enantioselectivity of the Z-(CαCβ) imine anions[5] may be explained without[20] recourse to dechelation,[5] because Cβ substituents in cis relation to the nitrogen alkyl substituents would force the face-differentiating groups further away from the reacting Cβ atom.

Acknowledgment. We thank the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft, and the Stiftung Volkswagenwerk for their support.

Supplementary Material Available: Tables of refined atomic coordinates and temperature factors for $[(CH_2{=}C(t\text{-Bu})NPh)\text{-}Li(OEt_2)]_2$ (2 pages). Ordering information is given on any current masthead page.

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Mechanism of Induction of Parkinson's Disease by 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Chemical and Electrochemical Characterization of a Geminal-Dimethyl-Blocked Analogue of a Postulated Toxic Metabolite

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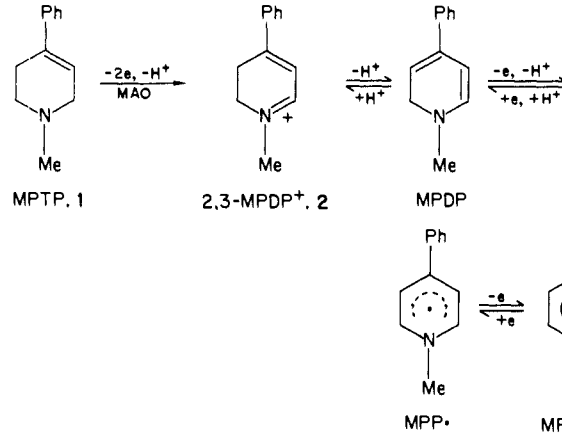
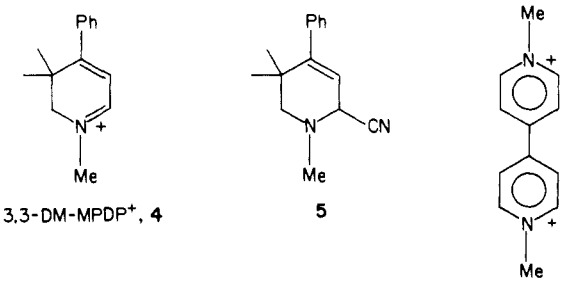
The discovery that 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, **1**), present as an impurity in an illicit narcotic preparation, produced an irreversible Parkinson's Disease (PD) syndrome in man[1] has led to vigorous research aimed at elucidating the molecular mechanisms responsible for this effect.[2-6] As in PD, MPTP neurotoxicity is associated with the selective destruction of the substantia nigra, a pigmented (neuromelanin) dopaminergic cell group at the base of the brain. The finding that monoamine oxidase B (MAO-B) inhibitors protect against this effect[7] suggests that oxidized metabolites of MPTP are responsible for neurotoxicity. MPTP is oxidized by MAO-B in the brain to 1-methyl-4-phenyl-2,3-dihydropyridinium (2,3-MPDP$^+$, **2**),[8] which is ultimately converted to 1-methyl-4-phenylpyridinium (MPP$^+$, **3**), the major metabolite detected in brain tissue (eq 1).[9] Although



(1)

MPP$^+$ has recently been shown to be a potent cytotoxin in its own right,[10] it is not definitively known if it is entirely responsible for MPTP neurotoxicity. It is also conceivable that 2,3-MPDP$^+$ is neurotoxic, perhaps via a catalytic redox cycle in which it oxidizes dopamine to cytotoxic dopamine quinone and then is regenerated by MAO,[8] or through its action as an alkylating[11] and/or oxidizing agent toward biological nucleophiles (e.g., thiol enzymes). A direct assessment of the neurotoxicity of 2,3-MPDP$^+$ is complicated by its rapid oxidation in biological tissue to MPP$^+$,[12] and an evaluation of its potential physiologically relevant chemistry is hampered by its redox disproportionation at pH 7 to equal amounts of MPTP and MPP$^+$.[8,13] For these reasons we synthesized the geminal 3,3-dimethyl analogue of 2,3-MPDP$^+$ (3,3-DM-MPDP$^+$, **4**),[14]



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(14) 1,3,3-Trimethyl-4-piperidone[15] was reacted with phenyllithium, and HCl-mediated dehydration of the resulting tertiary carbinol gave 4-phenyl-1,3,3-trimethyl-1,2,3,6-tetrahydropyridine. The latter was converted to the *N*-oxide (30% H_2O_2), which upon treatment with $(CF_3CO)_2O$ in CH_2Cl_2, addition of 1 equiv of HBr, and evaporation gave 4-phenyl-1,3,3-trimethyl-2,3-dihydropyridinium bromide (200-MHz NMR, UV, TLC).
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which should exhibit similar chemistry to that of 2,3-MPDP$^+$, except for its inability to deprotonate to an enamine or be oxidized to a pyridinium species. The studies discussed below suggest that 2,3-MPDP$^+$ is unlikely to play a major neurotoxic role.[16]

Although it was previously reported[13] that dopamine does not react with 2,3-MPDP$^+$ at pH 5.0–7.6, a slow reaction could have been masked by the inevitable redox disproportionation of 2,3-MPDP$^+$ in this pH range.[17] Nonetheless, we found that 3,3-DM-MPDP$^+$, which is stable at pH 7,[18] also gave no reaction with dopamine or even with the more easily oxidized 3,5-di-*tert*-butylcatechol[20] or pyrogallol.[21]

The cyclic voltammograms[22] of 2,3-MPDP$^+$ and 3,3-DM-MPDP$^+$ show only a single, one-electron reduction wave with values of E_p equal to −0.605 and −0.649 (pH 4) and −0.605 and −0.613 (pH 7) V vs. NHE, respectively.[26] The absence of a corresponding anodic wave on the reverse scan is attributed[22] to the known EC process for reductive coupling (radical dimerization) of iminium compounds.[25] The close similarity of the redox behavior of 2,3-MPDP$^+$ and 3,3-DM-MPDP$^+$ makes it evident that the 3,3-dimethyl substitution in the latter does not perturb the electronic properties of the dihydropyridinium ring. Although E_p and $E^{\circ\prime}$ values are not directly comparable,[27] the fact that the above E_p values are more negative than the $E^{\circ\prime}$ value reported for dopamine (+0.35 V vs. NHE, pH 7)[28] by nearly 1 V, provides thermodynamic confirmation of the observed lack of redox reactivity between dopamine and 2,3-MPDP$^+$.

With regard to the reactivity of 2,3-MPDP$^+$ as an electrophile, 3,3-DM-MPDP$^+$ was found to add cyanide readily to form **5**. In contrast, although the addition of $PhCH_2SH$, $PhCH_2NH_2$, and imidazole could be demonstrated by NMR in $CDCl_3$ solution (containing 1 equiv of Cs_2CO_3), no stable adducts could be isolated (TLC showed only the starting components), and no reaction of 3,3-DM-MPDP$^+$ with cysteine, lysine, or histidine was evident in aqueous solution. These results are not completely unexpepected, since nucleophilic adducts of dihydropyridinium species have been reported to be labile even in the absence of 4-phenyl stabilization of the eniminium conjugation.[29] Thus it appears that 2,3-MPDP$^+$ would function as an electrophilic alkylating agent of biological nucleophiles only if the intrinsically unstable adducts were stabilized by the particular biological microenvironment.[30]

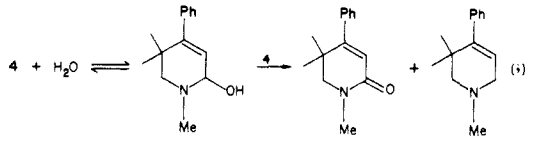
The above findings provide evidence that 2,3-MPDP$^+$, the initial MPTP metabolite preceding MPP$^+$, is unlikely to exert potent neurotoxic effects via oxidation (of catecholamines or thiols) or electrophilic mechanisms, though possible redox interactions with other neuronal constituents cannot be excluded. In a related study, we found that 3,3-DM-MPDP$^+$ is about 2 orders of magnitude less toxic than MPP$^+$ when these agents are administered directly into the substantia nigra of rats.[31] These results, coupled with the finding that MPP$^+$ is selectively taken up into[32] and accumulated within dopamine neurons,[33,9b] are consistent with MPP$^+$ as the agent responsible for MPTP neurotoxicity.

Although the mechanistic basis of MPP$^+$ cytotoxicity is not known, MPP$^+$ has been observed to inhibit site 1 mitochondrial respiration,[34] and this effect has been shown to be capable of reproducing MPP$^+$ neurotoxicity in vivo.[35] Another possibility is suggested by the structural similarity of MPP$^+$ to the herbicide paraquat (methylviologen, MV^{2+}, **6**),[36] which is toxic to lung cells by virtue of "redox cycling" catalysis, a process whereby the MV^{2+}/MV^+ couple short-circuits oxidative metabolism by shuttling electrons from cellular reductants (e.g., NADPH) directly to O_2, leading to toxic O_2-reduction products.[38] A comparison of the reduction potential of 2,3-MPDP$^+$ to those of MPP$^+$

(16) Presented in part at the 17th Central Regional ACS Meeting, Akron, OH, June 6, 1985, paper 98, and the 190th National ACS Meeting, Chicago, Sept 8–13, 1985, Abstr ORGN 130.

(17) In fact, the rate of disproportionation of 2,3-MPDP$^+$, as followed by UV spectrophotometry, was found to increase with increasing dopamine concentration.

(18) At higher pH values (10–11), 3,3-DM-MPTP$^+$ undergoes a "pseudobase redox disproportionation" (eq i), observed previously for isoquinolinium cations.[19]



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(27) Observed E_p values for the cathodic process in 2,3-MPDP$^+$ and 3,3-DM-MPDP$^+$ are shifted positive of the reversible E_p values by the subsequent chemical reaction[24] and therefore represent only an approximate upper limit to the values of $E^{\circ\prime}$ for the 1e reduction of these species.

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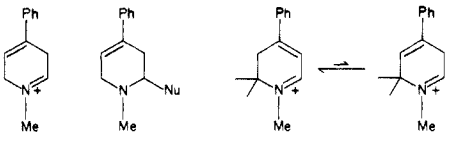

stability than those that would form from 3,3-DM-MPDP$^+$.[8c] However, using the geminal 2,2-dimethyl isomer **9**, we have been unable to observe the addition of nucleophiles other than cyanide.

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($E^{\circ\prime}$ -1.18 V vs. NHE in acetonitrile[39]) and paraquat (-0.44 V)[37] suggests that 2,3-MPDP$^+$ could theoretically function as a more efficient redox cycling catalyst than MPP$^+$, though the significance of such is uncertain in view of the apparent short lifetime of 2,3-MPDP$^+$ in biological tissue.

Acknowledgment. This work was supported by the National Institutes of Health (NS 18714 and NS 22688 to L.M.S.).

(39) MPP$^+$ undergoes a quasi-reversible 1e reduction at a Pt electrode, and the value of $E^{\circ\prime}$ given was determined by comparison to an internal ferrocenium/ferrocene couple.[40] Similar values of $E^{\circ\prime}$ were obtained by CV at a glassy carbon (GC) electrode (-1.17 V) and by OSWV (-1.20 V (Pt), -1.19 V (GC)). Reference 37 reports only that the reduction of MPP$^+$ occurs below -1.0 V in water.

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Stereospecific 1,2-Migrations in Carbohydrates. Stereocontrolled Synthesis of α- and β-2-Deoxyglycosides

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Despite the many advances made in the chemistry of carbohydrates, several problems[1] still remain in this important area of natural products. Two of the most common, but often difficult to reach, goals in carbohydrate chemistry are (a) the selective functionalization of the ring system and (b) the stereocontrolled construction of glycoside bonds, particularly in the 2-deoxy series. In this paper we report a new series of stereospecific 1,2-migrations, within the pyranoside carbohydrate framework, of a variety of groups that provide solutions to several objectives, including the two mentioned above. Specifically, we have discovered new and practical synthetic technology for (a) introduction of fluorine at C-1,[2] (b) introduction of O-, S-, and N-containing substituents at C-2, (c) inversion of configuration at C-2, (d) deoxygenation at C-2, and (e) stereocontrolled synthesis of α- and β-glycoside bonds including the hitherto difficult to construct 2-deoxy-β-glycosides.[3]

Scheme I, eq 1, outlines the mechanistic considerations that led to the design of these stereospecific migrations. Thus, it was anticipated that a migratory group at C-1 might be induced to shift to the neighboring position (C-2) by a "pull" from the "host" carbon initiated by the departure of a leaving group and (b) a "push" from the ring oxygen lone pair of electrons, providing the groups involved were stereoelectronically oriented in the proper fashion. In consideration of practical means to realize this scenario from simple and readily available starting materials, and in order to maximize the synthetic potential of the resulting products, (diethylamino)sulfur trifluoride (Et_2NSF_3, DAST) was chosen to operate on hydroxysubstrates I (Scheme I).[4] Indeed, when compounds I (X = OMe, OAc, SPh, N_3; Scheme I, eq 2) were treated with excess DAST in CH_2Cl_2 at 0-45 °C the glycosyl fluorides II were obtained in high yields (see Table I).[6] Fur-

Table I. 1,2-Migrations in Carbohydrates[a]

Entry	Substrate	Product[b]	Temperature (°C)	Yield (%)
1	X=OMe, R=Si^{t}BuMe$_2$		45	77
2	X=OMe, R=CH_2Ph		45	81
3	X=OAc, R=Si^{t}BuMe$_2$		0	91
4	X=SPh, R=Si^{t}BuMe$_2$		0	88
5	X=N_3, R=Si^{t}BuMe$_2$		45	78
6	X=OMe, R=Si^{t}BuMe$_2$		45	70
7	X=SPh, R=Si^{t}BuMe$_2$		0	93
8			0	88
9	R_1=Si^{t}BuPh$_2$, R_2=CH_2Ph		25	68
10	X=SPh, R=Me		0	86
11	X=N_3, R=Me		45	75
12	X=OCH_2Ph, R=H		25	66
13			0	88
14	R_1=CH_2Ph, R_2=Si^{t}BuMe$_2$		0	85
15	R_1=Si^{t}BuMe$_2$, R_2=Me		0	86
16	R=CH_2Ph		25	56

[a] Conditions: 3.0 equiv of Et_2NSF_3 (DAST), CH_2Cl_2. [b] In entries 3, 4, 7, 8, 10, 13, and 14 the indicated anomer was exclusively formed, whereas in the remaining entries the indicated anomer predominated in an anomeric mixture (α:β ratio): 1 (40:60), 2 (40:60), 5 (50:50), 6 (25:75), 9 (40:60), 11 (50:50), 12 (60:40), 15 (70:30), 16 (62:38).[5,9]

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(3) For some previous entries into 2-deoxy-β-glycosides, see: Bock, K.; Lundt, I.; Pedersen, C. *Carbohydr. Res.* **1984**, *130*, 125 and references cited therein.

(4) For the use of DAST to prepare α-fluoro-β-amino acids from β-hydroxy-α-amino acids via nitrogen 1,2-shift, see: Somekh, L.; Shanzer, A. *J. Am. Chem. Soc.* **1982**, *104*, 5836.

(5) The starting materials utilized in this work (Schemes I and II and Table I) were prepared by standard methods from commercially available carbohydrates and are optically active.

0002-7863/86/1508-2466$01.50/0