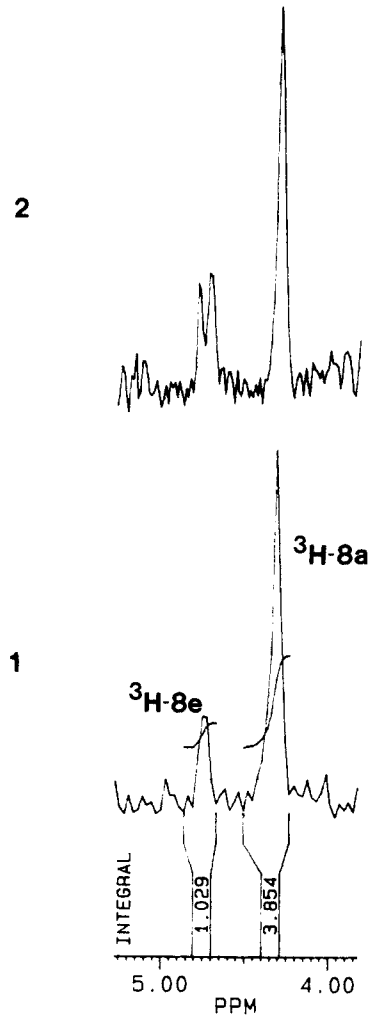

Figure 2. Tritium NMR spectra of **4** generated from (methyl-*S*)[methyl-$^2H_1$,^3H]-**3** with BBE. Sample contains 153 μCi ^3H, solvent CD_3OD, repetition time 1.0 s; spectrum 1, composite pulse broadband ^1H decoupled, 76 472 acquisitions; spectrum 2, ^1H gated decoupled, WALTZ-16 ^2H broadband decoupled, 47 347 acquisitions.

and coupling constants are consistent with the B/C *trans*-tetrahydroprotoberberine configuration. Upon removal of the broadband proton decoupling the ^3H NMR signal at 4.76 ppm split into a doublet (J = 15.3 Hz), whereas the signal at 4.29 ppm remained unchanged. Hence, 80% of the tritium is present in the *pro*-8*R* position flanked by deuterium (0.05 ppm isotope shift), and 20% is present in the *pro*-8*S* position coupled to ^1H.

It follows from the data that BBE operates highly or completely stereospecifically, replacing an *N*-methyl hydrogen by the phenyl group in an inversion mode. Consistent with earlier findings[5] the hydrogen abstraction involves a primary kinetic isotope effect ($k_H/k_D \sim 4$). It is proposed that the enzyme abstracts an electron from the nitrogen and a hydrogen atom from the methyl group in an anti fashion to generate, from (methyl-*S*)[methyl-$^2H_1$,^3H]-**3**, the (*Z*)-methyleneiminium ion which is then attacked by C-2 of the phenyl ring on the *si* face (Scheme III). The observation of nonstereospecific hydrogen removal from C-8 in the aromatization of ring C supports existing notions about the mechanism of this process. On the basis of the observed stoichiometry, 1.5 mol of O_2 consumed and 1 mol of H_2O_2 produced per mol of substrate, it has been suggested[7,8] that the enzyme STOX only catalyzes the dehydrogenation of the substrate to the 7,14-iminium ion. The latter than undergoes spontaneous air oxidation to **6** or **7**, respectively. This proposal is supported by the finding by Battersby and co-workers[19] that scoulerine tritiated stereoselectively at C-13 is converted in *Chelidonium majus* plants into berberine and coptisine with "extensive and nonstereospecific loss of hydrogen from C-13".[20]

In addition to unraveling the steric course of berberine bridge formation, the above data attest to the remarkable sensitivity of tritium NMR. In the present work, even on a medium field instrument 30 μCi of tritium in a single position were readily detected in an overnight run, suggesting that on a high field instrument under optimal conditions the detection limit can probably be pushed below 10 μCi per position.

Acknowledgment. We are indebted to Drs. Jonathan Lee and Thomas Zydowsky for carrying out some of the early steps in the synthesis of chirally labeled AdoMet, to Kyungok Lee for the chirality analyses of acetic acid, and to the National Institutes of Health (GM 32333) and Deutsche Forschungsgemeinschaft (SFB 145) for financial support. We also thank Prof. E. Leete for a valuable suggestion for improvement of the manuscript.

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The Reaction of 2,3-Diazabicyclo[2.2.2]oct-2-ene with Stable Cation Radical Salts

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Whereas the free-radical chemistry of azoalkanes, initiated by photochemical and thermal decompositions, is richly documented,[1] their oxidative chemistry has begun to emerge only in the last few years.[2-11] For example, 1,1′-azoadamantane is oxidized by thianthrene cation radical ($Th^{\bullet+}$) perchlorate in acetonitrile solution, affording primarily nitrogen and cation-derived products.[2] We report here a novel reaction in the oxidative chemistry of azoalkanes.

Reaction of 2,3-diazabicyclo[2.2.2]oct-2-ene (DBO) with tris(*p*-bromophenyl)aminium ($TBPA^{\bullet+}$) hexachloroantimonate in degassed acetonitrile at 25 °C took place rapidly, but no N_2 was produced. The solution deposited a red solid, λ_{max} 523 nm, ϵ 24 300 in CH_2Cl_2, whose structure was determined by X-ray crystallography as the diazenium salt **1**.[12] As seen from the

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(12) Crystal data are as follows: monoclinic, space group $P21/n$, a = 11.974 (2) Å, b = 20.208 (2) Å, c = 12.507 (2) Å, β = 96.77 (1)°, Z = 4, D_{calcd} = 1.87 g cm^{-3}. Intensity data were collected on a Rigaku AFC-5S diffractometer with graphite-monochromated Mo Kα radiation in the $2\theta \leq 50°$ range. The structure was solved with the direct methods program MITHRIL in the TEXSAN (v 2.0) Structure Analysis Package (Molecular Structure Corporation). Refinement converged with R = 0.033, R_w = 0.043 for 3073 (4806 collected) independent reflections with $I > 3\sigma(I)$.

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Table I. Products of Reaction of DBO with $TBPA^{\bullet+}SbF_6^-$

reactants, μmol			products,[a] μmol				
DBO	$TBPA^{\bullet+}SbF_6^-$	DTBP[b]	DBO	TBPA	BrTBPA[c]	Br_2TBPA[d]	**1**
113	113[e]	111	56.4 (50.1)[f]	25.2 (21.5)[g]	33.7 (28.8)	2.7 (2.3)	47.2 (41.9)

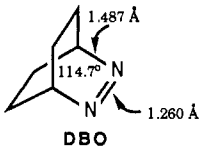
[a] Numbers in parentheses are percent yields. [b] 2,6-Di-*tert*-butylpyridine. [c] Bis-(4-bromophenyl)-2,4-dibromophenylamine. [d] Bis-(2,4-dibromophenyl)-4-bromophenylamine. [e] 117 μmol of 97% pure material by iodometric titration. [f] DBO balance = 50.1% + 41.9% = 92.0%. [g] TBPA balance = 21.5% + 28.8% + 2.3% + 41.9% = 94.5%.

Table II. Products of Reaction of DBO with $Th^{\bullet+}ClO_4^-$

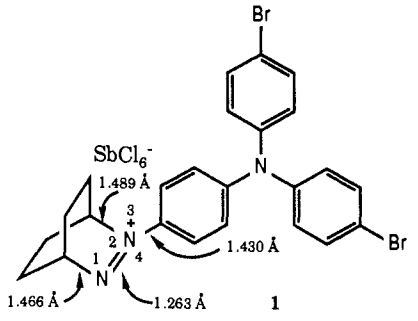
reactants, μmol			products,[a] μmol				
DBO	$Th^{\bullet+}ClO_4^-$	DTBMP[b]	DBO	Th	DTBMP[b]	ThO	**2**
500	500	0	208 (41.6)[c,d]	240 (48.0)[e,f]		11.5 (2.3)	228.5 (45.7)[c]
500	1000	1200	0 (0)	472 (47.2)[e,g]	1130 (94.2)	19 (1.9)	448 (89.6)[c]

[a] Numbers in parentheses are percent yields. [b] 2,6-Di-*tert*-butyl-4-methylpyridine. [c] Based on starting DBO. [d] DBO balance = 41.6% + 45.7% = 87.3%. [e] Based on starting $Th^{\bullet+}ClO_4^-$. [f] $Th^{\bullet+}ClO_4^-$ balance = 48.0% + 2.3% + 45.7% = 96.0%. [g] $Th^{\bullet+}ClO_4^-$ balance = 47.2% + 1.9% + (89.6%)/2 = 93.9%.

selected bond distances and angles given below, the positively charged nitrogen of **1** is planar, and the geometry about the azo linkage is similar for DBO[13] and **1**. Detailed 300 MHz ^1H and ^{13}C NMR analysis of **1** allowed us to assign all protons and carbons in the structure.[14]



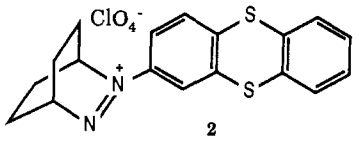
DBO



1

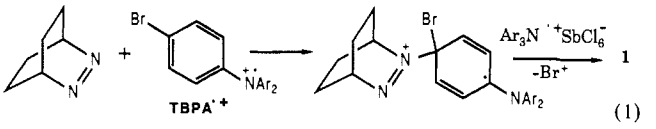
bond angles
1: CNN 110.7°
2: NNC 117.8°
3: CNC 123.6°
4: NNC 118.5°

Similarly, reaction of DBO with $Th^{\bullet+}ClO_4^-$ in acetonitrile gave another red solid, mp 214–215 °C, λ_{max} 408 nm, ϵ 5550; λ_{sh} 480 nm, ϵ 3800 in CH_2Cl_2. Detailed ^1H and ^{13}C NMR[16] as well as elemental analysis[17] were consistent with the analogous structure **2**.

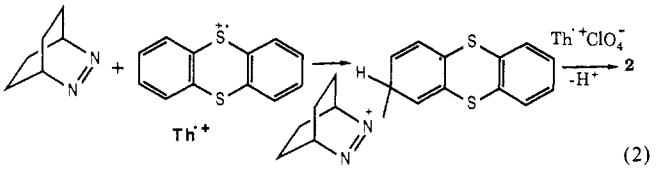


2

The stoichiometry (Tables I and II) for formation of **1** and **2** was found to be 2 mol of cation radical per mol of DBO.[18] These reactions, therefore, follow those that have been observed frequently between $Th^{\bullet+}$ and nucleophiles[19,20] and recently between $TBPA^{\bullet+}$ and acetate ion.[21] Thus, DBO is apparently resistant to oxidative decomposition and behaves as a nucleophile in these CE-type reactions (eq 1 and 2). The initial step in eq 1 and 2



(1)



(2)

is analogous to the known nucleophilic attack of DBO on 2,4-dinitrobromobenzene.[22] All these reactions may involve prior complexation, by analogy with the mechanism proposed for the cation radical oxidation of anisole.[20]

The Br^+ liberated in reaction with $TBPA^{\bullet+}$ (eq 1) served to brominate TBPA, as shown by the presence of higher brominated triarylamines among the products (GC/MS analysis, Table I). The proton liberated in reaction with $Th^{\bullet+}$ (eq 2) served to protonate DBO and thereby removed half of the starting DBO from reaction. Reaction in the presence of added base diverted this protonation, and allowed all of the DBO to participate in formation of **2** (cf. Table II). The protonation of DBO has been illustrated with the isolation of the stable salts $DBOH^+ClO_4^-$[22] and $DBOH^+BF_4^-$.[23]

The question immediately arises why some azoalkanes liberate N_2 on one-electron oxidation while DBO produces the diazenium salts **1** and **2**. Since the ionization potentials of virtually all azoalkanes[24,25] lie above the 7.90 eV of Th,[2] one would expect oxidation of azoalkanes by both $Th^{\bullet+}$ and $TBPA^{\bullet+}$ (a less powerful

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(14) ^1H NMR (CD_2Cl_2) δ 1.86 (m, 4 H, endo), 2.31 (m, 4 H, exo), 5.72 (s, 1 H), 5.86 (s, 1 H), 7.06 (d, J = 9.3, 2 H), 7.13 (d, J = 8.7, 4 H), 7.57 (d, J = 8.7, 2 H), 7.91 (d, J = 9.3, 4 H); ^{13}C NMR δ 24.2, 25.8, 64.9, 119.8, 120.7, 124.6, 128.7, 133.8, 135.5, 143.5, 154.9. The bridgehead C and H near the positive N are at 64.9 and 5.86 ppm, respectively. This proton assignment is opposite that of alkyldiazenium salts.[15] We thank Dr. Alan M. Kook for assistance with the NMR work.

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(16) ^1H NMR (CD_2Cl_2) δ 1.92 (m, 4 H, endo), 2.40 (m, 4 H, exo), 6.01 (br s, 1 H), 6.22 (br s, 1 H), 7.35 (m, 2 H), 7.52 (m, 2 H), 7.8 (d, J = 8.6, 1 H), 8.1 (dd, J = 2.6, 8.6, 1 H), 8.16 (d, J = 2.5, 1 H); ^{13}C NMR δ 24.4, 26.0, 68.4, 69.1, 121.8, 122.0, 129.1, 129.2, 129.25, 129.3, 130.4, 133.0, 139.3, 142.9, 147.8. We thank David W. Purkiss for assistance with the NMR work.

(17) Calcd for $C_{18}H_{17}N_2ClO_4S_2$: C, 50.94; H, 4.04; N, 6.60; Cl, 8.25; S, 15.08. Found: C, 50.79; H, 3.92; N, 6.60; Cl, 8.05; S, 14.76.

(18) Because the reaction of DBO with $TBPA^{\bullet+}$ was cleaner with SbF_6^- than with $SbCl_6^-$ as the anion, the stoichiometry was determined by using $TBPA^{\bullet+}SbF_6^-$. The details are given in the Supplementary Material.

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oxidizer[20]) to be endothermic.[26] It is likely that the endothermic oxidations of many azoalkanes are driven to nitrogen evolution by the instability of R—N=N—R$^{\bullet+}$.[7] These cation radicals become less stable when the hydrocarbon cation radicals formed by deazatation are more heavily substituted. In the bridgehead dimethyl derivative of DBO, for example, we find that reaction with 2 equiv of TBPA$^{\bullet+}$ causes quantitative nitrogen evolution and no formation of red material.

The pattern of behavior of azoalkanes which begins to emerge from this and other studies may, perhaps, be fitted to the general concept of nucleophile/cation radical reactions popularized by Parker.[20] If an initial encounter between an azoalkane and a cation radical leads to a complex, one can imagine that this complex either breaks up to produce the azoalkane cation radical or undergoes further oxidation by the reactant cation radical. In the case of DBO, further oxidation would end in covalent bonding as shown in products **1** and **2**.

In summary, we find that DBO oxidatively forms an adduct with stable cation radical salts, in contrast to previously studied azoalkanes that undergo oxidative deazatation.

Acknowledgment. We thank the National Science Foundation (Grants No. CHE 86-12031 and CHE 86-04364) and the Robert A. Welch Foundation (Grants No. D-028 and C-499) for financial support.

Supplementary Material Available: ORTEP diagram and stick diagram of **1**, listing of positional and thermal parameters, bond distances, bond and torsion angles, and method for determining stoichiometry shown in Tables I and II (14 pages). Ordering information is given on any current masthead page.

(26) We use ionization potentials because unpublished work from our laboratory and that of Prof. S. F. Nelsen has shown that electrochemical oxidation of azoalkanes is irreversible.

Hyperconjugation as a Factor in Face Selectivity during Cycloaddition

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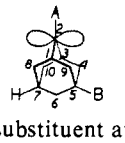
Several instances have been published in which 2,5-disubstituted adamantane derivatives were used as probes in research aimed at stereoselection in additions to trigonal carbon; these have included the capture of nucleophiles by carbocations,[1] carbenes,[2] and ketones[3] and of electrophiles by olefins.[4] The principal merit of these probes is that they are essentially free from steric bias, yet they direct facial stereoselection by virtue of electronic induction by substituent B. The results to date demonstrate that



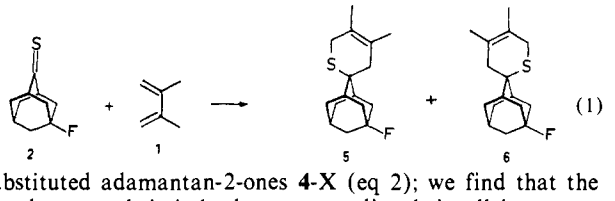
an electron-withdrawing substituent at C_5 causes syn approach by *both* nucleophiles and electrophiles. We have interpreted these results in terms of a model proposed by Cieplak[5] to explain the well-known axial approach observed in the reduction of cyclohexanones; this model holds that hyperconjugation of antiperiplanar σ bonds with the incipient σ^* orbital is responsible for the selectivity. Extending the model to adamantanones and to electrophiles, we correctly predicted that syn approach is favored with an electron-withdrawing substituent B, because the C_1–C_8 and C_3–C_{10} bonds are the better donors for hyperconjugative σ assistance. Recent X-ray[6] and NMR[7] results are consistent with an influence of hyperconjugation even on the ground-state structures of such electronically perturbed cations and adamantanone complexes. The corollary of this work has been the general rule that the approach during addition to trigonal carbon is always anti to the electron richest bond,[4] sometimes even when steric effects oppose such selectivity.[8] We report here that both thermal and photocycloadditions are accommodated by this prediction.

Table I. Stereochemical Course of Photocycloaddition of 5-Substituted Adamantan-2-ones with Fumaronitrile[a] in Acetonitrile at Room Temperature

5-substituent X	%[b] 7-X	%[b] 8-X	analysis
F	57	43	VPC, NMR, X-ray
Cl	58	42	VPC, NMR
Br	59	41	VPC, NMR
OH	53	47	VPC, NMR

[a] Comparable results were obtained in those cases in which measurable amounts of adducts were obtainable from the maleonitrile formed by photoisomerization (*cis*-oxetanes *E*:*Z* = 60:40 for X = Cl and Br). [b] Errors ca. ±2%.

We have tested the rule in the Diels–Alder reaction of 2,3-dimethylbuta-1,3-diene (**1**) with 5-fluoroadamantane-2-thione (**2**) (eq 1) and in the photocycloadditions of fumaronitrile (**3**) to several



(1)

5-substituted adamantan-2-ones **4**-X (eq 2); we find that the favored approach is indeed syn as predicted, in all instances.

Treatment of 2 mmol of **2**[9] with 0.1 mmol of hydroquinone and 20 mmol of **1** in 15 mL of toluene at reflux for 3 days[10] gives 80% of a mixture consisting of **5** and **6** in a 2:1 ratio (GC). The isomers were separated and converted into sulfones by means of K_2SO_5 oxidation. The sulfone of the major product was indeed (*E*)-**5**-O_2 as shown by the effect of the shift reagent Eu(fod)$_3$; carbons 8 and 10 were affected more than twice as strongly as carbons 4 and 9 (identified by their ^{19}F coupling), and even C_5 is shifted downfield one third more than C_7. Application of the ^{13}C NMR additivity scheme[11] with the sulfides furthermore leads to carbon resonances correctly predicted to within ±0.3 ppm if the major product is assumed to have the *E*-configuration, whereas the deviations are several ppm if the opposite assumption is used. When **5** and **6** are separately subjected to the exact reaction conditions that gave rise to them, each can be recovered unchanged with no trace of the other: both products are formed in kinetically controlled processes.

This result is noteworthy not only because it agrees with what we anticipate but also because it is opposite to the prediction made on the basis of another model recently proposed to account for Diels–Alder face selectivity.[12]

[†] Columbia University.
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