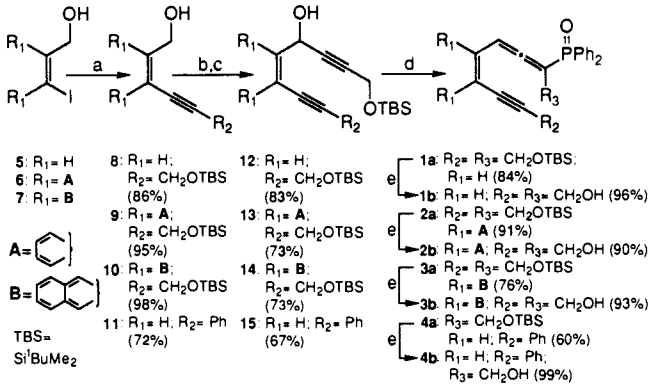
Scheme III[a]

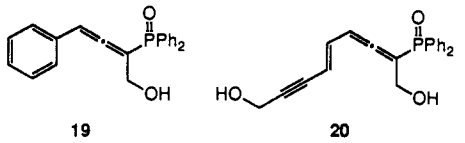


[a] Synthesis of compounds **1b**, **2b**, **3b**, and **4b**. Reagents and conditions: (a) 1.1 equiv of $R_2C{\equiv}CH$, 0.04 equiv of $Pd(PPh_3)_2Cl_2$, 0.16 equiv of CuI, 1.5 equiv of Et_2NH, benzene, 0 °C, 1 h; (b) excess MnO_2, benzene, 25 °C, 24 h; (c) 1.2 equiv of $Me_2{}^tBuSiOCH_2C{\equiv}CH$, 1.1 cquiv of *n*-BuLi, THF, -10 °C, 0.5 h, then 1.0 equiv of aldehyde, THF, -20 °C, 1 h; (d) 1.0 equiv of Ph_2PCl, 1.0 equiv of Et_3N, CH_2Cl_2, -78 °C, 1 h; (e) 48% HF, MeCN, 25 °C, 15 min.

type III were found to be rather labile and not suitable for practical DNA or antitumor activity studies. The phosphorus series, however, proved to be easily prepared and handled and exhibited the expected properties of DNA cleavage and antitumor activity in the temperature range 37-47 °C.

Compounds **1a,b**-**4a,b** (Scheme II) were designed and synthesized as summarized in Scheme III.[5] The key operations involved (a) vinyl iodide-acetylene couplings via Pd(0)-Cu(I) catalysis (step a, Scheme III); (b) acetylide addition to aldehydes (step c, Scheme III); and (c) 2,3-sigmatropic rearrangements (step d, Scheme III).

Compounds **1a**, **2a**, and **3a** were sufficiently stable for isolation, but smoothly cyclized to aromatic systems [**16a** (60%), **17a** (75%), and **18a** (80%), respectively], presumably via diradicals, upon warming in the presence of cyclohexadiene (Scheme II).[6] The half-lives ($t_{1/2}$), of these systems at 37 °C (**1a**, $t_{1/2}$ = 8 h; **2a**, $t_{1/2}$ = 23 h; **3a**, $t_{1/2}$ = 117 h) indicated that they or their derivatives[7] may be good DNA and tumor cell damaging agents with prolonged periods of action. This expectation was reinforced when it was realized that **1a**-**4a** served as excellent acceptors of nucleophiles (e.g., *n*-$BuNH_2$, Et_2NH, $HSCH_2COOMe$)[8] at ambient temperatures, pointing to a possible nucleophilic scenario for reaction with DNA. Indeed, compounds **1b**-**4b** exhibited DNA-cleaving properties at 37, 42, and 47 °C in the absence of any additives. Thus incubation of compounds **1b**-**4b** with supercoiled DNA (form I) aerobically (or anaerobically)[9] at pH 8.5 and at various temperatures caused DNA rupture, leading initially to form II and finally to form III DNA as shown in Figure 1. Compounds **19** and **20**, which are incapable of undergoing the



19 **20**

cyclization reaction, showed considerably weaker DNA-cleaving properties than **1b** and **2b**, respectively,[9] supporting the notion of a dual mechanism of action for these compounds. On the other hand, compounds **1b**-**4b** exhibited lower potencies as DNA-cleaving agents at pH 6 than at pH 8.5 (suppression of nucleophilic mode of action), an observation also indicating a dual mode of action. As expected, the cyclized products **16b**-**18b** did not show any DNA-cleaving properties in control experiments.[9]

Compounds **1b**-**4b** exhibited potent, concentration-dependent cytotoxicity against human carcinoma cells, thus fulfilling the initial expectations that led to the design of these systems.[10] The reported results suggest new possibilities for the development of useful biotechnology tools[11] and novel therapeutic agents.

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Supplementary Material Available: Listing of selected R_f, IR, ^1H and ^{13}C NMR, UV, and mass spectral data for compounds **1a,b**-**4a,b**, **4c,d**, **12**-**15**, **16a**-**18a**, **19**, and **20** as well as photographs of electrophoresis gels for control experiments (14 pages). Ordering information is given on any current masthead page.

(5) New compounds exhibited satisfactory spectral and/or analytical data.
(6) Under similar conditions, cyclization of compound **4a** to the corresponding aromatic system proceeded at a slower rate and lower yield.
(7) For a similar system, see: Nagata, R.; Yamanaka, H.; Okazaki, E.; Saito, I. *Tetrahedron Lett.* **1989**, *29*, 4995.
(8) As expected, attack by N or S occurred at the central allene carbon, leading to the expected 1,4-adducts. Selected data for one adduct of $HSCH_2COOMe$ (**4c**) and one adduct of *n*-$BuNH_2$ (**4d**) with compound **4a** are given in the supplementary material. Details of these and related reactions will be reported in due course.
(9) Photographs of electrophoresis gels supporting this statement are included in the supplementary material.
(10) Although it is tempting to link DNA cleavage with cytotoxicity, proof of this connection will have to await further experimentation.
(11) It is noteworthy that compound **3a** upon cyclization leads to a fluorescent product (**18a**), a property that should enhance the potential of these systems as biological probes.

Reaction of Cyclohexene with Iodosylbenzene Catalyzed by Non-Porphyrin Complexes of Iron(III) and Aluminum(III). Newly Discovered Products and a New Mechanistic Proposal

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Iodosylbenzene has been widely used as a source of oxygen atoms in metal-catalyzed oxygenation reactions.[1] Until recently, it has been widely assumed that such reactions proceed exclusively via high-valent metal oxo intermediates. However, the recent discovery that olefin epoxidations by iodosylbenzene may be catalyzed by certain nonredox metal complexes incapable of forming high-valent metal oxo complexes[2] indicates that additional pathways for these oxygen-transfer reactions must exist. Iodine(III) compounds are known to react with olefins in the absence of metal catalysts, although epoxides have never been reported as products.[3] Nevertheless, the possibility, originally proposed

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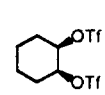
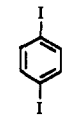
Table I. Products Observed in Reactions of Cyclohexene with OIPh Catalyzed by Metal Complexes in CH_3CN[a]

ML_n	product concentration, mM						
							
$Fe(OTf)_3$	28	1	3	11	0.4	116	0.6
$Fe(OTf)_3$ + Li(OTf)	34	3	5	9	1.3	122	0.6
$Al(OTf)_3$	28	3	3	13	0.2	120	0.6
$Al(OTf)_3$ + Li(OTf)	14	3	3	3	0.3	77	0.3
$(Et_3HN)Fe(bpb)(OTf)_2$	15	3	2	4	trace	60	0.4
$(Et_3HN)Fe(bpb)(OTf)_2$ + Li(OTf)	20	5	5	10	0.1	88	0.6

[a] OIPh (0.8 mmol) was added to a 5-mL acetonitrile solution of 5 mM ML_n (and 80 mM Li(OTf) when indicated) and 2 M cyclohexene. The mixture was stirred for 2 h at room temperature under an inert atmosphere. The reaction mixture was filtered and analyzed by GC/MS. The numbers in this table represent the concentrations (mM) of products detected. No epoxide nor 3-acetamidocyclohexene was detected in control reactions of iodosylbenzene with cyclohexene in the absence of metal catalysts. Neither *cis*-1,2-cyclohexanediol ditriflate nor 3-acetamidocyclohexene was detected in control reactions of ML_n with cyclohexene in the absence of iodosylbenzene. None of these three products was obtained in the reaction of Li(OTf) with cyclohexene and iodosylbenzene.

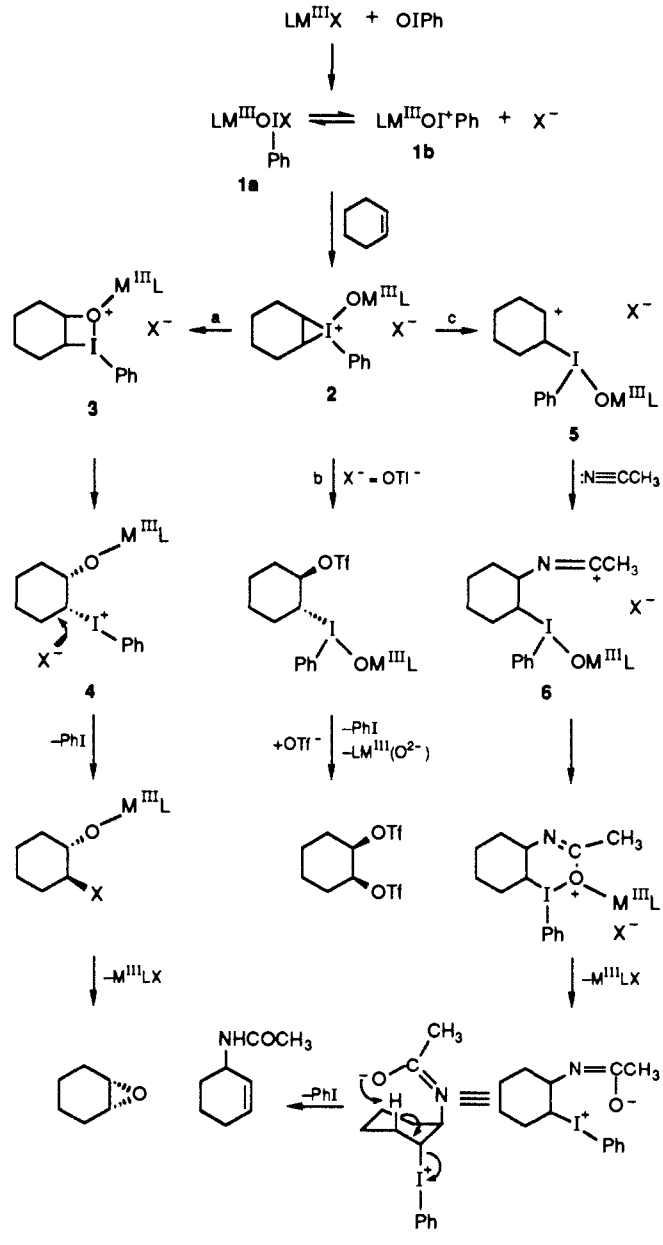
by Moriarty et al.,[4] that metal-catalyzed reactions of iodosylbenzene with olefins may involve I^{III}-containing intermediates wherein I^{III}, rather than oxygen or the metal, is the electrophilic center must be considered. We report here studies of reactions of iodosylbenzene with olefins in the presence of complexes or salts of Fe^{III} and Al^{III}. We find products, in addition to epoxides, whose presence suggests strongly that the mechanisms of these reactions are related to those occurring between olefins and soluble I^{III}-containing compounds in the absence of any metal catalyst.[3]

Table I lists the results of reactions of cyclohexene with iodosylbenzene in the presence of $Fe(OTf)_3$ (OTf = SO_3CF_3),[5] $(Et_3HN)Fe(bpb)(OTf)_2$,[6] or $Al(OTf)_3$.[7] In all of the reactions, epoxide is the predominant product and only small amounts of allylic oxidation products are found. The fact that the reactivity of $Al(OTf)_3$ and other nonredox metal complexes[2] is very similar to that of $Fe(OTf)_3$ suggests similar reaction mechanisms, and we therefore conclude that high-valent metal oxo species are not involved.

Difunctionalization of cyclohexene by triflate to form *cis*-1,2-cyclohexanediol ditriflate was also observed in these reactions[8] (see Table I); the yield was enhanced when an extra source of triflate, i.e., Li(OTf), was added. The same product has been found in the reaction of cyclohexene with (μ-oxo)bis[(triflato)-(phenyl)iodine].[3c] Stereospecific formation of *cis*-1,2-cyclohexanediol ditriflate in our reaction is analogous to cis-1,2-difunctionalization of olefins by a variety of I^{III} compounds,[3] suggesting that this product is the result of electrophilic attack of I^{III} on olefins.

Substantial amounts of 3-acetamidocyclohexene were also produced in these reactions[9] (see Table I). The formation of this

Scheme I



amide is reminiscent of products formed in the Ritter reaction[11] and implies that a carbonium ion intermediate is involved.[12] In

(4) Moriarty, R. M.; Penmasta, R.; Prakash, I. *Tetrahedron Lett.* **1985**, *26*, 4699.

(5) (a) VanAtta, R. B.; Franklin, C. C.; Valentine, J. S. *Inorg. Chem.* **1984**, *23*, 4121. (b) Valentine, J. S.; VanAtta, R. B.; Margerum, L. D.; Yang, Y. In *The Role of Oxygen in Chemistry and Biochemistry*; Ando, W., Ed.; Elsevier: New York, 1988; pp 175–184.

(6) (a) H_2bpb, 1,2-bis(2-pyridinecarboxamido)benzene, was made according to Barnes et al.: Barnes, D. J.; Chapman, R. L.; Vagg, R. S.; Watton, E. C. *J. Chem. Eng. Data* **1978**, *23*, 349. (b) $(Et_3HN)Fe(bpb)(OTf)_2$ solutions were made by adding 2 equiv of Ag(OTf) to solutions of $(Et_3HN)Fe(bpb)Cl_2$ in acetonitrile followed by removal of AgCl by filtration. For details of the synthesis and structure of $(Et_3HN)Fe(bpb)Cl_2$, see: Yang, Y.; Diederich, F.; Valentine, J. S., manuscript in preparation.

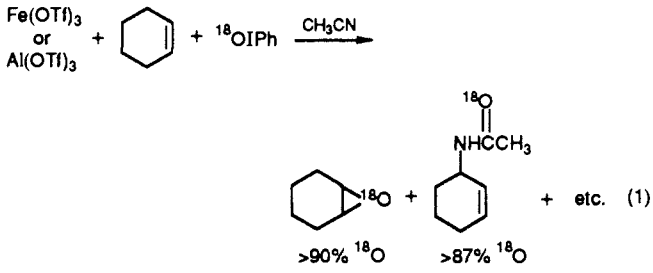
(7) Solutions of $Al(OTf)_3$ were made by addition of 3 equiv of Ag(OTf) to $AlCl_3$ in acetonitrile followed by removal of AgCl by filtration. A satisfactory elemental analysis was obtained for $Al(OTf)_3 \cdot 3CH_3CN$, which was obtained by removal of the acetonitrile solvent under vacuum.

(8) *cis*-1,2-Cyclohexanediol ditriflate was identified by ^1H NMR by comparison with published data[3g] and quantitatively analyzed by GC/MS. Only trace amounts of the trans isomer were detected in all of the reactions.

(9) 3-Acetamidocyclohexene was identified by ^1H and ^{13}C NMR, IR, and mass spectrum and quantitatively analyzed by GC/MS. Reaction of ^{18}OIPh (made from 97.5 atom % $H_2{}^{18}O$)[10] with cyclohexene and $Fe(OTf)_3$ or $Al(OTf)_3$ resulted in incorporation of ^{18}O into the amide group in more than 87% yield as shown by GC/MS.

(10) Schardt, B. C.; Hill, C. L. *Inorg. Chem.* **1983**, *22*, 1563.

the Ritter reaction, the amide oxygen is derived from H_2O.[11] Our reactions were carried out in dry acetonitrile, however, with insufficient water to account for the product. We therefore carried out an isotopic labeling study using ^{18}OIPh to ascertain the source of oxygen. We find that the amide oxygen is derived from iodosylbenzene (reaction 1).



One additional product, 1,4-diiodobenzene, was observed in these reactions[13] (see Table I). This interesting product was found whether or not cyclohexene was present. Similar products have been found in reactions of iodonium ions.[14]

In Scheme I, we propose mechanisms that account for all of the observed products. We believe that **1a** is the first species formed when the metal complex reacts with the insoluble OIPh polymer. Related complexes have been isolated by Hill and co-workers from reactions of manganese porphyrins with iodosylbenzene.[15] Based on the work of Koser[3a] and Zefirov,[3d,f] we expect that I^{III} in **1a** will be electrophilic. We therefore propose that **1a** or **1b** reacts with the double bond of cyclohexene, forming **2**, which resembles the intermediate proposed by Koser and co-workers in their reactions.[3a] This intermediate can then react by several pathways. In pathway a, **2** rearranges to give **3**, which then forms **4** by O–I bond cleavage. Nucleophilic addition of the anion X^- and loss of PhI followed by oxygen–carbon bond formation yield epoxide. In pathway b, **2** is attacked by a nucleophile, triflate, and *cis*-1,2-cyclohexanediol ditriflate is formed by two steps of nucleophilic addition of triflate. This mechanism is further supported by the fact that the amount of *cis*-1,2-cyclohexanediol ditriflate increased when an extra source of triflate, i.e., Li(OTf), was added. In pathway c, a carbonium ion **5** is formed and then attacked by the acetonitrile solvent. This step of the reaction is analogous to the Ritter reaction. However, under the conditions of our reaction, i.e., in dry acetonitrile solvent, the oxygen originating from iodosylbenzene attacks the carbonium ion of **6** to form a six-membered-ring intermediate. Abstraction of a proton from the cyclohexane ring gives the final product, 3-acetamidocyclohexene.

In summary, all of our observations are consistent with a mechanism that does not require changes in oxidation state of the metal ion and that involves electrophilic attack of I^{III} on the olefin. We believe that this or a similar mechanism prevails in most of the non-porphyrin metal catalyzed reactions and that it should be considered as a possibility in the metalloporphyrin-catalyzed reactions as well.

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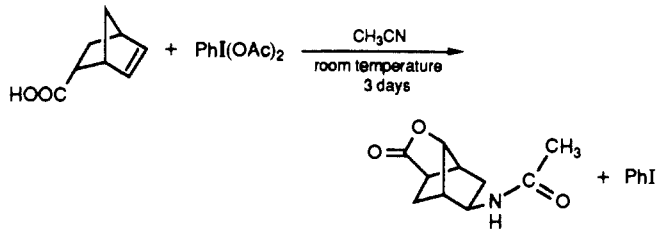
(11) The Ritter reaction is the formation of an amide by the addition of a nitrile to a wide variety of compounds capable of forming carbonium ions, e.g.,

$$(CH_3)_3C^+ + :N{\equiv}CCH_3 \xrightarrow{H_2O} (CH_3)_3CNHCOCH_3$$

See: Krimen, L. I.; Cota, D. J. In *Organic Reactions*; Wiley Inc.: New York, 1969; Vol. 17, pp 213.

(12) We have found similar amide products in reactions of iodobenzene diacetate with olefins, e.g.,



See ref 6b.

(13) Trace amounts of 1,2-diiodobenzene were also detected. The same reaction in the absence of cyclohexene gave the same amount of 1,4-diiodobenzene. The control reaction of iodosylbenzene in acetonitrile in the presence of iodobenzene gave approximately 0.05 mM 1,4-diiodobenzene.

(14) For example,

$$2C_6H_5I{=}O \xrightarrow{H_2SO_4} (IC_6H_4I^+C_6H_5)HSO_4^- + H_2O$$

$$IC_6H_4I^+C_6H_5 + Cl^- \rightarrow C_6H_5I + IC_6H_4I + C_6H_5Cl + IC_6H_4Cl$$

Koser, G. F. In *The Chemistry of Functional Groups, Supplement D*; Patai, S., Rappoport, Z., Eds., John Wiley & Sons Ltd.: Chichester, 1983; Chapter 25, pp 1265-1351.

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Effect of a Polarizable Medium on the Charge-Transfer States of the Photosynthetic Reaction Center from *Rhodopseudomonas viridis*

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Photosynthetic electron transfer is arguably the most important series of chemical transformations for life on this planet.[1-3] In recent years the structure of the reaction centers (RC) from the photosynthetic bacteria *Rhodopseudomonas viridis* and *Rhodobacter sphaeroides* have been presented.[4-7] On the basis of these structures, several mechanisms have been proposed to explain the primary electron-transfer event[8-10] with as yet no consensus.

We report here INDO/S[11-13] calculations of the excited states of a model of the RC of *Rps. viridis* in both the absence and presence of a polarizable medium.[14] For our calculations we model the RC as the bacteriochlorophyll b (BChlb) dimer (P) and the auxiliary BChlb (B_L, B_M), and bacteriopheophytin b (H_L, H_M) chromophores (L and M branches, respectively). Also included are the four histidine amino acid side chains that coordinate with the fifth position of the Mg atoms of the BChl's. The phytol tails of the chromophores are truncated.

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(11) Ridley, J. E.; Zerner, M. C. *Theor. Chim. Acta* **1973**, *32*, 111.
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(13) Zerner, M. C.; Löew, G. H.; Kirchner, R. F.; Mueller-Westerhoff, U. T. *J. Am. Chem. Soc.* **1980**, *102*, 589.
(14) For previous INDO calculations on the excited states of the reaction center, see: Scherer, P. O.; Fischer, S. F. *Chem. Phys.* **1989**, *131*, 115.

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