Hypervalent Iodine Oxidants: Structure and Kinetics of the Reactive Intermediates in the Oxidation of Alcohols and 1,2-Diols by *o*-Iodoxybenzoic Acid (IBX) and Dess−Martin Periodinane. A Comparative ^{1}H-NMR Study

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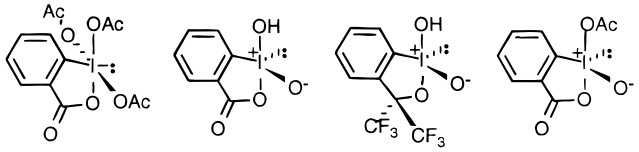
Alcohols and 1,2-diols oxidation by *o*-iodoxybenzoic acid (IBX) has been examined by ^{1}H-NMR spectroscopy. Reversible formation of reactive intermediates, iodic esters **5,** has been observed, and their structures in DMSO-d_6 solution have been defined as 10-I-4 axial alkoxyiodinane oxides by comparison of the chemical shift difference data with those obtained for Dess−Martin periodinane (DMP)−alcoholate and −diolate adducts. The dichotomous behavior exhibited by IBX and DMP with 1,2-diols can be explained in terms of the different architecture of the reactive intermediates involved in the oxidation. With aliphatic alcohols, kinetic evidences support a two-step reaction mechanism involving a fast pre-equilibrium step leading to **5**, followed by a rate-determining disproportionation step. With electronically activated benzyl alcohol, the attainment of pre-equilibrium is largely dependent on initial water concentration as a consequence of a particularly high k_2 value. The influence of the alcohol structure on measured equilibrium (K_{eq}) and rate constants (k_2) and the effect of water on the overall reaction rate are discussed.

Introduction

The oxidizing properties of hypervalent iodine(V) compounds are becoming increasingly appreciated by organic chemists.[1] The widespread utilization of 12-I-5 Dess−Martin periodinane (DMP, **1**,[2] namely 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one), for the efficient oxidation of alcohols to carbonyl compounds testifies for this trend. Its direct precursor, the polymeric, highly insoluble 10-I-4 iodinane oxide **2** (1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide, *o*-iodoxybenzoic acid, IBX[3]) was first synthesized in 1893,[4] but until recently little was known about its chemical properties.



1 DMP **2** IBX **3** **4**

In 1994, we reported that IBX can be readily dissolved in DMSO and pointed out that IBX itself functions as a valuable oxidant toward a variety of alcohols.[5] Although with simple primary and secondary alcohols, IBX in DMSO closely parallels the reactivity pattern of DMP in chlorinated solvents, some differences are observed in the oxidation of polyfunctional alcohols. We have shown that IBX cleanly oxidizes alcohols in the presence of amino and sulfide functional groups,[6] which are not usually tolerated by DMP. While DMP displays no selectivity in competitive oxidations of saturated alkanols,[2b] site selectivity has been reported in IBX oxidation of polyalcohols.[6−8] A major difference is observed in the oxidation of 1,2-diols. Thus, while DMP generally cleaves the glycol C−C bond,[2b,9] IBX oxidizes them to α-ketols or α-diketones.[5,10] Significantly, another 10-I-4 species, 1-hydroxy-1,3-dihydro-3,3-bis(trifluoromethyl)-1,2-benziodoxole 1-oxide (**3**), performs the clean conversion of α-hydroxylactols to α-hydroxylactones.[9a,b]

In this paper, we present kinetic and spectroscopic data which may shed some light on the mechanistic aspects that control the observed selectivity of IBX and clarify the origin of the dichotomous behavior exhibited by 10-I-4 and 12-I-5 species in the oxidation of 1,2-diols.

[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1996.

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(3) The acronyms IBX and IBA, for 2-iodoxybenzoic acid and 2-iodosobenzoic acid, respectively, were coined by Katritzky. See: Katritzky, A. R.; Duell, B. L.; Gallos, J. K. *Org. Magn. Reson.* **1989**, *27*, 1007.

(4) (a) Hartman, C.; Meyer, V. *Chem. Ber.* **1893**, *26*, 1727. Other syntheses of IBX have been reported in the literature: (b) Greenbaum, F. R. *Am. J. Pharm.* **1936**, *108*, 17. (c) Banerjee, A.; Banerjee, G. C.; Dutt, S.; Banerjee, S.; Samaddar, H. *J. Indian Chem. Soc.* **1980**, *57*, 640. (d) Banerjee, A.; Banerjee, G. C.; Ghattacharya, S.; Banerjee, S.; Samaddar, H. *J. Indian Chem. Soc.* **1981**, *58*, 605. For a more convenient preparation of IBX, see ref 2b.

(5) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.

(6) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272.

(7) Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, *36*, 3485.

(8) During the preparation of this article, kinetic evidences have been provided which explain the observed selectivity of IBX in the oxidation of 1,4-diols to γ-lactols: Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, *36*, 7945.

(9) Isolated examples of the variable cleaving ability of DMP on 1,2-dihydroxy compounds have appeared in the literature: (a) Grieco, P. A.; Collins, J. L.; Moher, E. D.; Fleck, T. J.; Gross, R. S. *J. Am. Chem. Soc.* **1993**, *115*, 6078. (b) VanderRoest, J. M.; Grieco, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 5841. (c) Pancrazi, A.; Anies, C.; Collemand, J. *Tetrahedron Lett.* **1995**, *36*, 7771.

(10) Over 15 diols were tested with IBX in our laboratories, and only (+)-pinanediol gave some percentage of oxidative cleavage product (27% in DMSO at room temperature, 1.1 equiv of IBX, 0.4 M). This mode of action is probably a manifestation of the ring strain in this diol.

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Results and Discussion

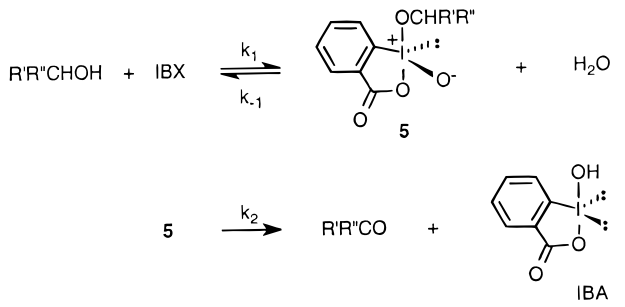
Detection of Intermediates in IBX Oxidations. Activated alkoxyperiodinane intermediates have been observed in the reaction of alcohols with DMP[2a,b,11a] (*vide infra*) and a number of other 12-I-5 species.[2a,11b−e] Conversely, there is no report of detection of analogous complexes with 10-I-4 hypervalent species.[12] We have examined the reaction of IBX with a few alcohols by ^{1}H-NMR spectroscopy and have observed formation and decay of reactive intermediates.[6] The obvious importance of understanding the role and the structure of these transient species has prompted us to carry out a systematic NMR analysis on a variety of simple alcohols and diols. To begin our studies, we first examined the reaction of IBX with nonoxidizable substrates. After combination of **2** and *t*-BuOH in a 1:1 molar ratio at 23 °C in DMSO-d_6, a small singlet, whose intensity did not change in time, appeared at 1.50 ppm in the ^{1}H-NMR spectrum. The signal was assigned to a *tert*-butoxy group tethering an iodinane oxide moiety as in 1-*tert*-butoxy-1,2-benziodoxol-3(1*H*)-one 1-oxide. This conclusion was bolstered by the observation that the mixed acetic anhydride of IBX, 1-acetoxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (Ac-IBX, **4**),[2b,d,13] reacts with *t*-BuOH to provide the same compound in high yield.[14] Treatment of IBX with pinacol under the aforementioned conditions resulted in a solution which exhibited, besides the known resonances for the oxidant[5] and the diol, a series of four peaks in the high-field region of the ^{1}H-NMR spectrum, symptomatic of a pinacolate species with a lower symmetry than that of pinacol itself. Again, upon mixing Ac-IBX and pinacol, we observed one adduct, which showed the same ^{1}H- and ^{13}C-NMR signals.[15] In both experiments with IBX, the intensity of the signals of the alkoxyiodinane oxides turned out to be directly proportional to the alcohol and IBX concentrations, while it was largely diminished by added water. The results discussed so far account for an equilibrium leading to alkoxyiodinane oxide **5** with concomitant release of a water molecule through a process of ligand exchange at iodine, as already suggested by Dess and Martin (Scheme 1).[2b] The calculated values for the equilibrium constants are 0.002 for *t*-BuOH and 0.059 for pinacol (Table 1). The greater affinity of pinacol for IBX is probably due to the presence of the 1,2-diol functionality. Resonably, the second, unbound alcohol moiety of the diol is set in close proximity to the iodine atom, and ligation is therefore entropically favored.[16] This process may eventually result in an intramolecular transesterification. This seems to be a general characteristic of 1,2-diols.[17] We next turned our attention to the case of oxidizable alcohols. As expected, reaction of IBX and ethanol (1 equiv) proceeds through the intermediacy of an ethoxyiodinane oxide whose intensity decreases rapidly in time as the oxidation goes on. This underlines the prime role of alkoxyiodinane oxides **5** in the oxidation process either as products of the equilibrium between the alcohol and the oxidant or as the reactive species which disproportionate to IBA[3] and carbonyl derivative through a reductive elimination of the iodosoarene moiety (Scheme 1). This behavior holds true for all the alcohols discussed herein. The results of these NMR studies are summarized in Table 2 (columns 2−4, alcohols) and Table 3 (diols) as a collection of relative shifts data for the observed intermediates **5**. A few points are noteworthy. (1) IBX does not undergo complete ligand exchange with alcohols. The equilibrium constants for formation of adducts **5** are reported in Table 1 and were calculated using the formula $K_{eq} = ([\mathbf{5}][H_2O])/([IBX][ROH])$ (see the Experimental Section). (2) Even employing excess of ligand, only *one* adduct type is observed during the oxidation of symmetric alcohols and diols. (3) The coexistence of unbound alcohol, oxidation products, and alkoxyiodinane oxide introduces a significant complexity in pursuing the complete assignment of the ^{1}H-NMR spectra. Moreover, due to the dissymmetrical nature of IBX,[18] chiral alcohols and diols give rise to diastereoisomers and complexes derived from alcohols which contain enantiotopic groups originate proton NMR spectra which

Table 1. Equilibrium Constants K_{eq} for Formation of the IBX−Alcoholate Complex in DMSO-d_6 Solutions and Rate Constant k_2 for Disproportionation Reaction

entry	alcohol	K_{eq}[a]	k_2[a] (s^{-1})
1	methanol	0.040	0.006
2	ethanol	0.050	0.007
3	isopropyl alcohol	0.037	0.005
4	isobutyl alcohol	0.047	0.009
5	neopentyl alcohol	0.035	0.011
6	2,4-dimethyl-3-pentanol	0.017	0.022
7	benzyl alcohol	0.027	0.234
8	*tert*-butyl alcohol	0.002	
9	*tert*-pentyl alcohol	0.002	
10	pinacol	0.059	

[a] Due to the low relative intensity of the adduct signals, the precision of the ^{1}H-NMR integrals of **5** is very low. Consequently, also K_{eq} and k_2 values are imprecise (ca. ±20%).

Scheme 1



(11) (a) Linderman, R. J.; Graves, D. M. *J. Org. Chem.* **1989**, *54*, 661. (b) Kokunov, Y. V.; Sharkov, S. A.; Buslaev Y. A. *Koord. Khim.* **1982**, *8*, 55. (c) Oates, G.; Winfeld, J. M. *J. Chem. Soc., Dalton Trans.* **1974**, 119. (d) Frohn, H. J.; Pahlmann, W. *J. Fluorine Chem.* **1984**, *24*, 219. (e) Frohn, H. J.; Pahlmann, W. *J. Fluorine Chem.* **1985**, *28*, 191.

(12) In the oxidation of alcohols by **3**, no evidence for intermediates was obtained when the reaction was monitored by ^{1}H-NMR. See ref 2b.

(13) DMSO-d_6 solutions of AcOIBX **4** were obtained by partial hydrolysis of DMP with wet DMSO-d_6. ^{1}H-NMR (DMSO-d_6): δ_H 2.20 (s, 3H, C*H*$_3$COO), 7.93 (br t, 1H, J = 7.2 Hz, H-6), 8.09 (m, 2H, H-4 and H-5), 8.49 (br d, 1H, J = 7.2 Hz, H-7).

(14) Selected ^{1}H- and ^{13}C-NMR resonances in DMSO-d_6 for the IBX−*tert*-butyl alcohol addduct. The values for the corresponding signal of the free alcohol are reported in parentheses: δ_H 1.50, (1.12, Me); δ_C 31.7 (31.3, Me), 78.5 (67.0, *C*O).

(15) Selected ^{1}H- and ^{13}C-NMR resonances in DMSO-d_6 for the IBX−pinacol adduct. The values for the corresponding signals of the free alcohol are reported in parentheses: δ_H 1.22, 1.27, 1.37, 1.39 (1.07, Me); δ_C 24.8, 25.6, 25.8, 26.0 (24.9, Me), 76.0 (73.6, *C*OH), 85.2 (IO*C*).

(16) We consider probable the cyclization of the open-chain adduct **9** to the unstable 12-I-5 spirobicyclic dialkoxyhydroxyperiodinane **10** and a fast reversion to the 10-I-4 adduct.

(17) High percentages of iodic esters derivatives have been observed in qualitative preliminary experiments. K_{eq} values not calculated.

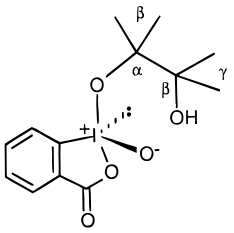
(18) IBX has C_1-symmetry, each crystal containing only one enantiomer. For a proposed convention for the designation of absolute configuration in optically active pentacoordinated species, see: Martin, J. C.; Balthazor T. M. *J. Am. Chem. Soc.* **1977**, *99*, 152.

Table 2. ^{1}H-NMR Chemical Shift Difference ($\Delta\delta$)[a] Data for the IBX−Alcoholate 5ax in DMSO-d_6 and for the Axial and Equatorial DMP−Alcoholate Isomers 6ax, 6eq in $CDCl_3$ Solutions

	5ax			6ax			6eq			
R	α[b]	β	γ	α	β	γ	α	β	γ	ax/eq[c]
methyl	0.66			0.96			0.65			5.7
ethyl	0.72	0.24		1.01	0.17		0.74	−0.04		6.3
propyl	0.71	0.27	0.12	0.96	0.27	0.08	0.66, 0.67[d]	−0.06	−0.13	7.4
isopropyl	0.91	0.28, 0.30[e]		1.12	0.19		0.88	0.04, −0.06[e]		8.1
sec-butyl	0.95, 0.97[f]	0.29[g]	0.10	1.21	0.26[g]	0.07	0.94	0.00[g]	−0.12, −0.13[f]	4.5
		h,*i*			0.20[h]			0.05, 0.06[f,h]		
neopentyl	0.71		0.18	1.06		0.12	0.63		−0.06	11.6
isobutyl	0.73	0.33	0.15, 0.13[e]	0.97	0.24	0.09	0.63, 0.70[e]	*i*	−0.14, −0.15[e]	4.6
tert-butyl		0.38			0.36			0.14		4.4
tert-pentyl		0.34[g]	*i*		0.31[g]	0.11		0.07[g]	−0.15	3.5
		0.43, 0.44[e]			0.38[h]			0.22, 0.19[e,h]		

[a] $\Delta\delta = \delta$(complex) − δ(alcohol). [b] Column headings refer to the position of the probe protons relative to the oxygen atom. [c] Ratio between axial and equatorial isomers. [d] Diastereotopic methylene hydrogens. [e] Diastereotopic methyl groups. [f] Two diastereomeric complexes are forme3d. [g] Methylene hydrogens. [h] Methyl group. [i] Overlapping signal.

Table 3. ^{1}H-NMR Chemical Shift Difference Data for the IBX−Diolate Complex Series in DMSO-d_6 Solutions



	Δδ[a]			
parent diol	α[b]	IOC-C*H*-OH	β	γ
ethylene glycol	0.85	0.29		
pinacol			0.30, 0.32[c]	0.28, 0.15[c]
(*R*,*R*)-2,3-butanediol	0.81	0.21	0.32, 0.32[d]	0.13, 0.18[d]
1,2-propanediol				
(2-iodoxy)	0.95	*e*	0.27, 0.29[d]	
(1-iodoxy)	0.88	0.33		0.13, 0.15[d]
cis-1,2-cyclohexanediol	1.02	0.28	*e*	*e*
trans-1,2-cyclohexanediol	0.85	0.25	*e*	*e*

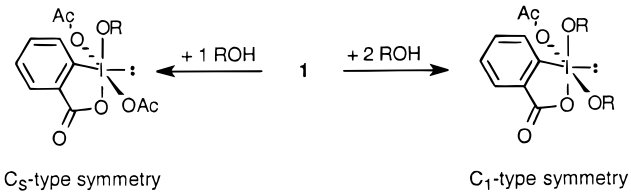
[a] $\Delta\delta = \delta$(complex) − δ(alcohol). [b] Column headings refer to the position of the probe protons relative to the aryliodoxy group. [c] Diastereotopic methyl groups. [d] Two diastereoisomers are formed. [e] Overlapping signals.

are often complicated also by diastereotopy. (4) Asymmetrically substituted 1,2-diols produce statistical mixtures of constitutional isomers, evidencing the low sensitivity of the complexation step to steric hindrance. In order to unveil the stereochemistry at the iodine atom of IBX−alcoholate intermediates, comparative analysis with the intermediates involved in DMP oxidations proved to be a fundamental step.

Detection of Intermediates in DMP Oxidations. As mentioned above, it has been shown by ^{1}H-NMR analysis that DMP reacts very rapidly with 1 equiv of alcohol to give 12-I-5 diacetoxyalkoxyperiodinanes. When more than 1 equiv of alcohol (or a diol) is employed, double displacement takes place, producing acetoxydialkoxyperiodinanes (Scheme 2).[2b]

We have widened the survey already present in the literature for DMP to comprise the alcohols and diols tested with IBX in order to obtain two series of data (Table 2, columns 5−10, and Table 4 for alcohols and diols, respectively), to be compared with those reported for the corresponding IBX adducts (Table 2, columns 2−4, and Table 3). Before we describe the results of the comparative study, a few aspects relative to DMP adducts deserve some comments. (1) Regardless of the structure

Scheme 2



of the alcohol, the ligand exchange reaction is quantitative. In accord with the existing literature, the major adduct type observed, **6ax,** appeared to bind the alkoxy group axially.[19] (2) In all cases, evidence was found for a second monoaddition adduct type with asymmetric structure, **6eq**, in which the alkoxy group binds at the equatorial[11a] position. This arrangement was confirmed by the observation of a uniform upfield shift (−0.25 ppm) for the alkoxy α-protons of **6eq** relatively to the corresponding signals for the axial isomer **6ax** (Table 2, colums 8 and 5, respectively).[20] (3) With diols, complete double ligand exchange is observed to produce chiral spirobicyclic intermediates.[21] In these adducts, the iodine atom is asymmetric. Thus, only symmetrically substituted diols, devoid of stereogenic centers, give one adduct (and its enantiomer). In all the other cases, mixtures of diastereoisomers and constitutional isomers are formed (see Table 4).

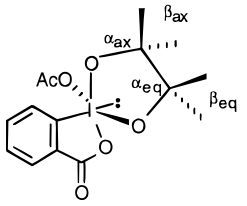
Structure of Monodentate Ligand Adducts. Two adduct types with C_1-symmetry can reasonably be expected when monodentate ligands, such as simple alcohols, react with IBX with formation of water: (1) complex **5ax**, and its enantiomer, with a significantly electropositive equatorial oxide ligand and an electronegative alkoxy group occupying the apical ligand site, and (2) complex **5eq**, and its enantiomer, with an opposite and energetically unfavored ligand arrangement.[22] Structures **7** and **8**, with the lone pair electrons in a position

(19) Displacement of the axial acetate, which lies in the plane of symmetry of DMP, does not confer stereogenicity on the iodine atom, while substitution of one of the enantiotopic equatorial acetates by a different group originates a chiral adduct molecule. For a discussion about chirality in octahedral complexes, see: Cahn, R. S.; Ingold, C. K.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385.

(20) The ratio of axial to equatorial substitution isomers (Table 2, last column) did not vary notably throughout the oxidation process, indicating equal oxidation rates or fast interconversion.

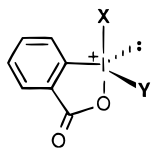
(21) DMSO-d_6 does not hinder the double displacement process. DMP reacts with pinacol in this solvent to give quantitatively one compound which shows an NMR pattern analogous to that observed in $CDCl_3$. Selected ^{1}H-NMR resonances in DMSO-d_6 for the DMP−pinacol adduct and relative shifts from pinacol signal are δ_H 0.72 ($\Delta\delta$ −0.36), 1.08 (0.00), 1.22 (0.14), 1.35 (0.27).

Table 4. ^{1}H-NMR Chemical Shift Difference Data for the DMP−Diolate Complex Series in $CDCl_3$ Solutions

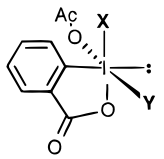


	Δδ[a]			
parent diol	α_{ax}[b]	α_{eq}	β_{ax}	β_{eq}
ethylene glycol	0.84, 0.78[c]	0.67, 0.54[c]		
pinacol			0.18, 0.04[d]	−0.10, −0.47[d]
(*R*,*R*)-2,3-butanediol[e]	0.35	0.09	−0.10	0.22
	0.38	−0.21	0.22	0.02
1,2-propanediol				
(2-iodoxy)[e]	0.22	1.22, 0.53[c]	0.14	
	0.48	1.07, 0.50[c]	−0.01	
(1-iodoxy)[e]	1.34, 0.03[c]	0.50		0.29
	1.34, −0.21[c]	0.50		0.30
cis-1,2-cyclohexanediol	0.85	0.59	*f*	*f*
trans-1,2-cyclohexanediol[e]	0.32	−0.08	*f*	*f*
	0.28	−0.33	*f*	*f*

[a] $\Delta\delta = \delta$(complex) − δ(alcohol). [b] Column headings refer to the position of the probe protons relative to the aryliodoxy group. [c] Diastereotopic methylene protons. [d] Diastereotopic methyl groups. [e] Two diastereoisomers are formed. [f] Overlapping signals.

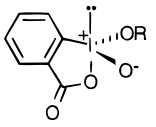


	X	Y
5ax	OR	O⁻
5eq	O⁻	OR



	X	Y
6ax	OR	OAc
6eq	OAc	OR

different from the equatorial or the electronegative iodoxolone ring linking two equatorial positions, were not



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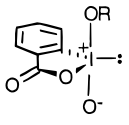

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considered on the basis of electronegativity rules for hypervalent compounds[23] and a number of X-ray crystallographic studies on related species.[2b,24] Two important factors are expected to influence the chemical shift of the probe protons upon complex formation: (1) the magnetic anisotropy of the benzene ring and (2) the *iodoxylation shift*, analogous to the well-known acylation shift of alcohols.[25] If the alkoxy ligand resides in the aryl deshielding region, as in **5ax** adducts as well as in axial 12-I-5 alkoxydiacetoxyperiodianes **6ax**, cooperation of the above-mentioned contributions invariably leads to strongly positive Δδ values. Comparison of the Δδ data reported in Table 2 for IBX and DMP complexes does enable us to decide between the two more probable situations. Δδ values for the same alkoxy ligand are significantly similar, even if the solvent is different, and diminish regularly with increasing distance from the iodine atom, always remaining positive. An average Δδ of +0.77 is associated with protons α to the oxygen atom, +0.32 with the *β* position, and +0.14 with the *γ* position in IBX complexes (Table 2, columns 2−4). In the axial DMP alcoholate series, averaged Δδ values of +1.02, +0.27, and +0.09, respectively, are observed (Table 2, columns 5−7). The enhanced deshielding effect at the α position, uniformly associated with protons in DMP axial complexes, possibly reflects the higher electronegativity of the iodine atom in 12-I-5 complexes **6ax**. Substantially different is the pattern of shielding and deshielding effects (averaged Δδ, +0.73 for α, +0.06 for *β*, and −0.13 for *γ* protons) observed for equatorial DMP−alcoholate series (Table 2, columns 8−10), substantiating the diverse ligand arrangement around the iodine atom in complexes **6eq**. Finally, downfield signals for aromatic protons *ortho* to iodine, *peri* to apical I−O⁻ charge dipole, as would be expected[26] for H-7 in **5eq**-type adducts, are not observed. These results strongly indicate that *axial ligation*, predominantly obtained upon coordination of monodentate ligands with DMP, does, indeed, *exclusively* take place with IBX to produce **5ax**-type complexes.

Structure of Bidentate Ligand Adducts. Having obtained cogent evidences indicating axial ligation in IBX adducts of monodentate alcohol ligands, we set up to investigate the behavior of IBX with potentially chelating ligands. With 1,2-diols, the initial displacement of the apical hydroxy ligand of IBX is expected to produce a 1-(*β*-hydroxyalkoxy)-1,2-benziodoxol-3(1*H*)-one 1-oxide (**9**).

(22) Although a 10-I-4 hypervalent species with an apical oxide ligand has been isolated and fully characterized,[2b] this structural feature is expected to introduce significant destabilization. Calculations on trigonal bipyramidal 10-P-5 phosphorane oxide anions showed the isomer with an apical oxide ligand to be 15.5 kcal/mol less stable than the isomer with an equatorial oxide ligand. See: Deakyne, C. A.; Allen, L. C. *J. Am. Chem. Soc.* **1976**, *98*, 4076 and references therein.

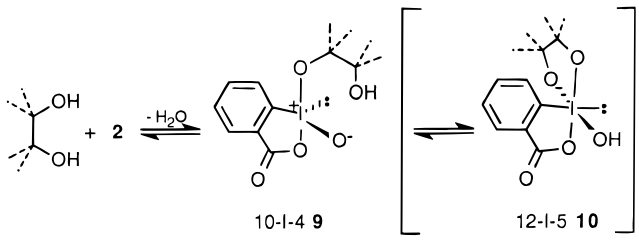
(23) (a) Gorenstein, D.; Westheimer, F. M. *J. Am. Chem. Soc.* **1970**, *92*, 634. (b) Gorenstein D. *J. Am. Chem. Soc.* **1970**, *92*, 644. (c) Musher J. I. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 54.

(24) For 10-I-4 species, see: (a) Viess, W. J.; Baird, H. W. *Chem. Commun.* **1967**, 1903. (b) Gilbert, D. D. *Nucl. Sci. Abstr.* **1973**, *28*, 26892. (c) Dess, D. B.; Wilson, S. R.; Martin, J. C. *J. Am. Chem. Soc.* **1993**, *115*, 2488. For isostructural 10-S-4, 10-Se-4 and 10-Te-4 species, see: (d) Perozzi, E.F.; Martin, J. C.; Paul, I. C. *J. Am. Chem. Soc.* **1974**, *96*, 6735. (e) Paul, I. C.; Martin, J. C.; Perozzi, E. F. *J. Am. Chem. Soc.* **1972**, *94*, 5010 and references cited therein.

(25) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: Oxford, 1969; p 176.

(26) Aromatic hydrogens held in proximity to an I−O⁻ charge dipole are strongly deshielded. Dess, D. B.; Wilson, S. R.; Martin, J. C. *J. Am. Chem. Soc.* **1993**, *115*, 2488 and references therein quoted.

Scheme 3



Double coordination may occur by intramolecular reaction of the β-hydroxy group with the electrophilic iodine atom (Scheme 3). In this event, a 12-I-5 spirobicyclic periodinane (**10**) is produced, whose structure closely resembles the double displacement products observed upon reaction of DMP with bidentate ligands. The second step of the complexation pathway was expected to be facile on the basis of the recognized proclivity of 10-I-4 hypervalent species to obtain a pentacoordinated state around the iodine atom.[27] Comparative analysis of NMR values presented in Tables 3 and 4 again proved to be adequate for unraveling the actual situation which takes place during the oxidation of diols. In spirobicyclic intermediates of DMP, the relative rigidity of the framework emphasizes chemical shift differences between diastereotopic atoms or groups (Table 4). Strong diamagnetic shielding contributions are expected to play a particularly significant role for groups, bonded to either axial or equatorial substituent, above the face of the aromatic ring, often overwhelming even the strong contact deshielding contributions for α protons. Conversely, groups far away from the aromatic ring should experience less important diamagnetic contributions. Reasonably, the apical substituent, which is roughly coplanar with the aromatic ring, should be the most downfield-shifted. Moreover, changes in conformation due primarily to steric interactions with the iodine lone pair electrons can contribute in altering this qualitative prediction, as in the case of 1,2-propandiol (Table 4).

If the intermediates observed in IBX oxidation possessed the 12-I-5 pseudooctahedral structure **10**, we should observe the same pattern of shielding and deshielding effects such as data in Table 4 provide. Indeed, downfield-shifted values are uniformly observed in Table 3, suggesting that, in the preferred conformation, all the alkoxy protons are held in the deshielding region of the benzene ring. This is possible only for monoesterified, axially bonded diols. In fact, the NMR data reported in Table 3 compare extremely favorably with the data in Table 2 (columns 2−4), confirming beyond any doubt the intermediacy of the 10-I-4 species in IBX oxidation of diols. In the light of these results, a rationale which explains the dichotomy observed with 10-I-4 and 12-I-5 species in the oxidation of 1,2-diols is offered, based on the different architecture of the reactive intermediates (Scheme 4). With 12-I-5 DMP, reaction with chelating ligands produces a cyclic iododioxolane (**11**) with a double fate. It breaks down to cleavage products, reasonably via a favored two-electron process, or decomposes with cleavage of the C_α−H bond to oxidation products. This second reaction pathway is less probable but frequently observed.[28] With 10-I-4 IBX, the oxidation of diols always proceeds through an open-chain intermediate (**9**), whose disproportionation occurs without C−C bond cleavage and is likely to involve intramolecular abstraction of the α-hydrogen by the strongly nucleophilic oxide ligand.[29] A second, minor reaction pathway is available and originates cleavage products. Anyway, this is very rarely active[10] and is dominant only in the special case of *tert*,-*tert*-1,2-diols. Reasons why the open-chain 10-I-4 intermediate does not cyclize to a 12-I-5 species are not yet clear. Possibly, thermodynamic instability of spirobicyclic 1,1-dialkoxy-1-hydroxyperiodinanes can account for the observed behavior.[30] In fact, the contemporaneous presence of two relatively electron-rich ligands (alkoxy and hydroxy groups) at the terminal sites of the hypervalent bond developed in the cyclization is expected to render the spirobicyclic dialkoxyhydroxyperiodinane **10** much more unstable than **11**, where the acetoxy ligand stabilizes the equatorial hypervalent bond.[31]

Kinetics of Alcohol Oxidations by IBX. As is clearly evidenced by the reaction mechanism depicted in Scheme 1, water plays a fundamental role. In fact, the detectability of intermediate **5ax** is strongly dependent on water concentration, and the inverse dependence of the observed oxidation rate from $[H_2O]$ suggests that the rate-determining step is the disproportionation of the IBX−alcoholate adduct.[8] Moreover, in the case of oxidizable alcohols, the K_{eq} value was fairly constant (±10% RSD) during the reaction course, indicating an effectively fast pre-equilibrium step. This hypothesis is fully supported by kinetic studies. Using the steady state approximation (d[**5**]/dt = 0),[32] alcohol consumption is described by

$$-\mathrm{d[ROH]}/\mathrm{d}t = k_2k_1[\mathrm{IBX}][\mathrm{ROH}]/(k_{-1}[\mathrm{H_2O}] + k_2) \quad (1)$$

At low and equimolar concentrations of reactants (*e.g.*, $[\mathrm{IBX}]^0 \approx [\mathrm{ROH}]^0 \approx 0.04$ M), in the early stage of the reaction, we may approximate $[\mathrm{H_2O}] \approx [\mathrm{H_2O}]^0$. Moreover, in the pre-equilibrium hypothesis, we may neglect k_2 in comparison with $k_{-1}[\mathrm{H_2O}]$, and consequently eq 1 can be further rearranged and integrated as follows:

$$-\mathrm{d[ROH]}/[\mathrm{ROH}]^2 = k_2(K_{eq}/[\mathrm{H_2O}]^0)\,\mathrm{d}t \quad (2)$$

$$1/[\mathrm{ROH}] - 1/[\mathrm{ROH}]^0 = k_2(K_{eq}/[\mathrm{H_2O}]^0)t \quad (3)$$

In the presence of a large excess of water (>10 equiv), the reaction rate is pseudo-second-order, with high percentages of conversion. This is demonstrated by the

(27) In IBX and related species, intermolecular contacts (secondary bonds) have been shown to be strongly operative either in the solid state or in solution, leading to dimeric or polymeric structures. IBX is essentially pentacoordinated in the solid state, see: (a) Gougoutas, J. Z. *Cryst. Struct. Commun.* **1981**, *10*, 489. Dimer formation in acetonitrile solutions has been observed for **3**.[2b] Aggregation phenomena have been suggested for **4** in $CDCl_3$ solutions.[2d]

(28) For examples of reactions in which oxidation without cleavage is the only observed pathway, see: (a) Wary, G.; Faser, R. *Can. J. Chem.* **1994**, *72*, 69. (b) Broka, C. A.; Ruhland, B. *J. Org. Chem.* **1992**, *57*, 4888.

(29) The nucleophilic characteristics of oxide ligand are manifested in the high catalytic activity displayed by hypervalent iodoso and iodoxy compound in phosphoric and carboxylic esters hydrolysis. (a) Moss, R. A.; Alwis, K. W.; Shin J. *J. Am. Chem. Soc.* **1984**, *106*, 2651. (b) Moss, R. A.; Alwis, K. W.; Bizzigotti, G. O. *J. Am. Chem. Soc.* **1983**, *105*, 681. (c) Katritzky, A. R.; Duell, B. L.; Durst, H. D.; Knier, B. L. *J. Org. Chem.* **1988**, *53*, 3972.

(30) A series of exploratory experiments indicates also the possibility of interaction of DMSO molecules with the hypervalent iodine. This can contribute in stabilizing the open-chain adduct. Nucleophilic stabilization of hypervalent compounds by solvent molecules has been frequently observed: (a) Yamamoto, Y.; Chen, X.; Akiba, K. *J. Am. Chem. Soc.* **1995**, *117*, 7906. (b) Yamamoto, Y.; Chen, X.; Kojima, S.; Ohdoi, K.; Kitano, M.; Akiba, K. *J. Am. Chem. Soc.* **1995**, *117*, 3922. (c) Kawakami, T.; Sugimoto, T.; Shibata, I.; Baba, A.; Matsuda, M.; Sonoda, N. *J. Org. Chem.* **1995**, *60*, 2677 and references therein.

linearity of the plot 1/[ROH] *vs* time, as exemplified in Figures 1 and 2 for *i*-PrOH and $PhCH_2OH$, respectively. K_{eq} and k_2 values reported in Table 1 were obtained from kinetic runs carried out under experimental conditions where the initial concentration of the intermediate is in the order of 1% of reactants and monitoring the oxidation reaction within 3% conversion (see the Experimental Section). Good linear relationships were obtained upon plotting the reciprocal of alcohol concentration as a function of the variable $(K_{eq}/[H_2O]^0)t$. Fitting the data to eq 3 gave directly the rate constant values k_2. The observed influence of steric hindrance in determining the acceleration of the intermediate decomposition can be interpreted, as already suggested in the literature for the chromic acid oxidation of secondary alcohols,[33] either as the result of steric strain relief in the transition state or in terms of a preferred conformation about the I−OR bond that favors the intramolecular abstraction of the α-protons by the equatorial oxide ligand. This effect is evident in the case of 2,4-dimethyl-3-pentanol (Table 1, entry 6), which is oxidized faster than ethanol in a competitive experiment, in spite of its lower K_{eq} value (relative observed oxidation rate, *ca*. 1.6).

Kinetics of Benzyl Alcohol Oxidation by IBX. In the case of benzyl alcohol, the assumption $k_2 \ll k_{-1}[H_2O]$ is no more valid in the reaction conditions described above, as demonstrated by the nonlinear dependence of the k_{obs} on $[H_2O]$ (Figure 3). The observed oxidation rate for $PhCH_2OH$ is much larger than that for simple aliphatic alcohols, and the pre-equilibrium is not attained at low relative concentration of water. In fact, very low percentages (*ca*. 0.5%, $\Delta\delta$ +0.65) of the intermediate species were observed by ^{1}H-NMR spectroscopy only in concentrated solutions ([IBX] ≈ [ROH] ≈ 0.5 M). Therefore, different tentative experiments had to be carried out in order to determine the values for the equilibrium constant K_{eq} and the rate constant k_2. K_{eq} was estimated from a series of single-scan spectra taken at 10 s intervals from a 0.35 M solution of the reactants in DMSO-d_6 containing 2M H_2O.[34] A value of K_{eq} = 0.027 was obtained (0.4% of iodic ester intermediate).

At constant $[H_2O]$ and equimolar concentrations of reactants, eq 1 can be solved to give the following

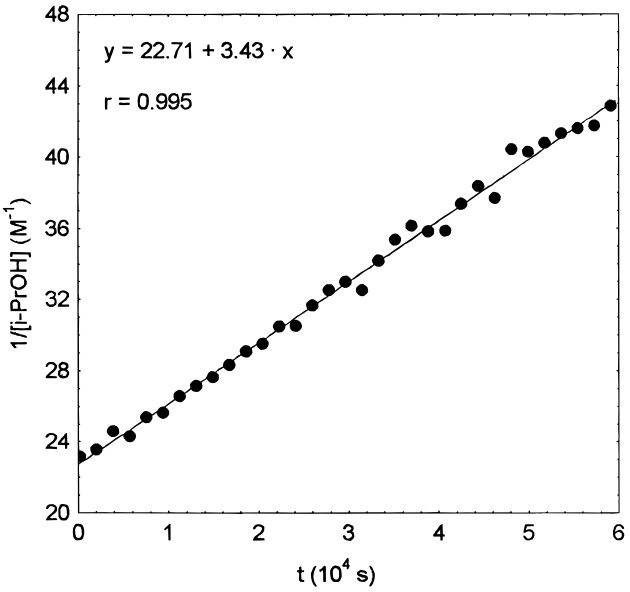


Figure 1. Pseudo-second-order plot for the oxidation of isopropyl alcohol with IBX ([*i*-PrOH] = [**2**] = 0.045 M in DMSO-d_6; $[H_2O]$ 0.51 M). The reaction was monitored during 16 h (48% conversion). Solid line is from linear regression analysis (see text).

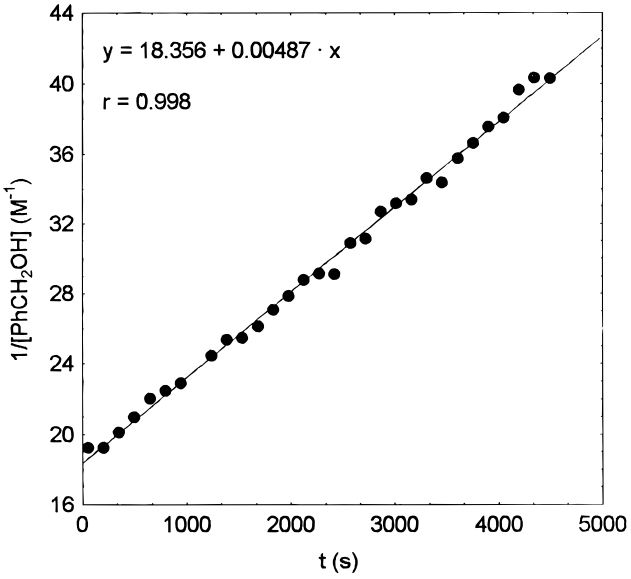
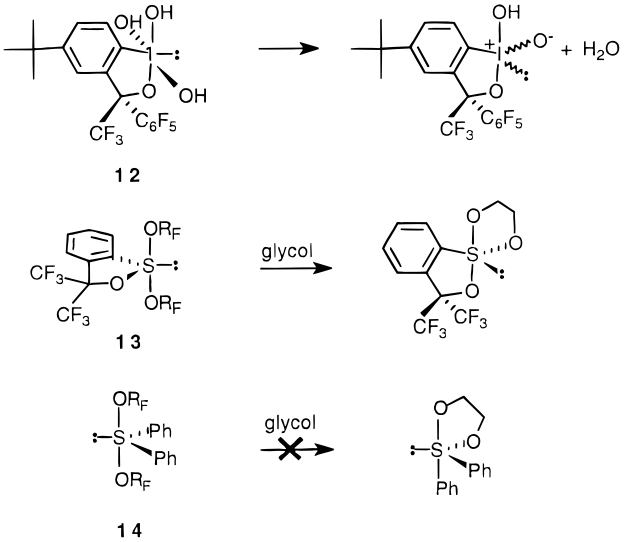


Figure 2. Typical pseudo-second-order plot for the oxidation of benzyl alcohol with IBX ([$PhCH_2OH$] = [**2**] = 0.052 M in DMSO-d_6; $[H_2O]$ 1.45 M). The reaction was monitored during 1.25 h (53% conversion). Solid line is from linear regression analysis (see text).

(31) Significantly, the decomposition of the pinacolate complex of DMP is catalyzed by the addition of 1 equiv of alcohol. This is believed to form unstable trialkoxyperiodinanes, which decompose by a dissociative mechanism to periodonium ions and then to oxidation products.[2b] A very recent paper discloses the tendency of the 12-I-5 trihydroxyperiodinane **12**, pseudooctahedral in the solid state, to lose one molecule of water when dissolved in $CDCl_3$. This process restores the 10-I-4 structure and hence the observed stereogenicity of the iodine atom. See: Stickley, S. H.; Martin, J. C. *Tetrahedron Lett.* **1995**, *36*, 9117.



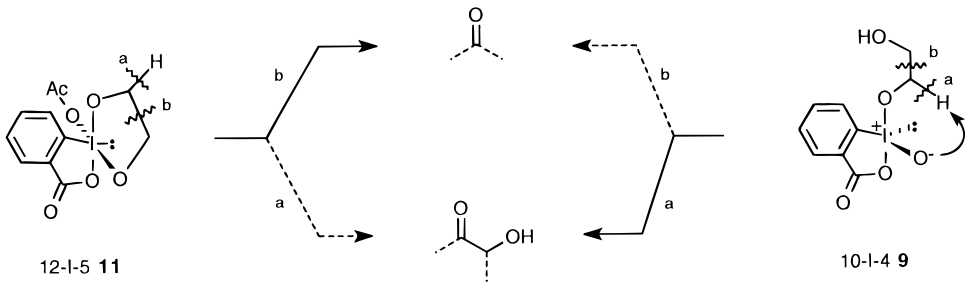
12 **13** **14**

On a similar basis, the contrasting reactivity of aryltrialkoxysulfurane **13** and diaryldilakoxysulfurane **14** is primarily a reflection of ligands' electronic characteristics. Thus, while spirobicyclic 10-S-4 sulfuranes, possessing an apical, strongly electron-withdrawing bis(trifluoromethyl)alkoxyl ligand, obey polarity rules and are easily synthesized from **13** by double ligand exchange (Astrologes, G. W.; Martin, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 4390), **14** does not form a cyclic product with diols, to avoid the destabilizing influence of an aryl group at the apical ligand site (Martin, J. C.; Franz, J. A.; Arhart, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 4604).

(32) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, 1992; p 221.

(33) Kwart, H.; Francis, P. S. *J. Am. Chem. Soc.* **1959**, *81*, 2116.

Scheme 4



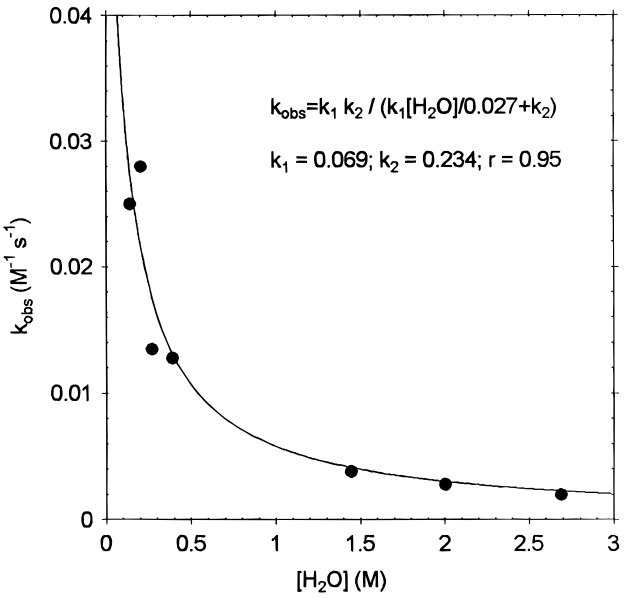


Figure 3. Dependence of k_{obs} (M^{-1} s^{-1}) on [H_2O] (M^{-1}) for the oxidation of benzyl alcohol with IBX (ca. 0.04 M). Solid line is from nonlinear regression analysis (see text).

equations:

$$1/[\mathrm{ROH}] - 1/[\mathrm{ROH}]^0 = k_{obs}t \qquad (4)$$

$$k_{obs} = k_2k_1/(k_{-1}[\mathrm{H_2O}] + k_2) \qquad (5)$$

To calculate values of the rate constants, a series of kinetic runs were carried out, varying the concentration of water in the range 0.2−2.7 M (for an example, see Figure 2). The concentration of reactants used was *ca.* 0.04 M. Nonlinear least-squares fitting of the experimental data to eq 12, using the value $K_{eq} = k_1/k_{-1} = 0.027$, gave the following result: $k_1 = 0.069$, $k_2 = 0.234$ (Figure 3). Therefore, the disproportionation of the iodic ester **5** derived from IBX and benzyl alcohol is about 40 times faster than in the case of simple aliphatic alcohols and 10 times faster than the decomposition of the adduct obtained from 2,4-dimethyl-3-pentanol.

Conclusions

We have shown that the oxidation reaction of alcohols by IBX is well described by a two-step mechanism, the first of which is a fast pre-equilibrium, at least in the case of electronically unactivated alcohols, and produces transient axial 10-I-4 iodic esters **5ax**, whose structure has been determined by ^{1}H-NMR spectroscopy. The initial presence of water is critical for the detectability of the intermediate species and influences the overall reaction rate. The opposite outcome in the oxidation of diols with IBX and DMP is the result of the different structure of the reactive intermediates (Scheme 4). In fact, while DMP gives spirobicyclic periodinane adducts **11**, IBX binds reversibly with 1,2-diols, originating open-chain iodic monoesters **9**, probably reflecting the different electronic characteristics of the ligands in the oxidants. Apart from diols, which strongly stabilize the intermediate complex, the K_{eq} values calculated for a series of monodentate aliphatic alcohols demonstrate the low proclivity of tertiary alcohols toward the esterification ($K_{eq} \approx 0.002$), while steric factors are less clear-cut for primary and secondary alcohols. Only in the case of the highly hindered 2,4-dimethyl-3-pentanol was the equilibrium constant ($K_{eq} = 0.017$) significantly lower than the values obtained for less hindered alcohols (*ca.* 0.04). Apart from benzyl alcohol, in which the electronic influence of the aromatic group is largely predominant ($k_2 = 0.234$ s^{-1}), the opposite trend is observed for the disproportionation constants k_2 (*e.g.*, 0.022 *vs* 0.005 s^{-1} for 2,4-dimethyl-3-pentanol and isopropyl alcohol, respectively). The overall observed oxidation rate is thus a balance of these effects. Therefore, attention must be used in foreseeing and interpreting the relative oxidation rates in polyalcohols.

Experimental Section

Caution! IBX has been reported to detonate upon heavy impact or heating over 200 °C.[35] Dess and Martin reported[2b] that heating and striking IBX with a hammer did not cause any detonation, and in our hands,[6] using IBX at temperatures between 20 and 70 °C, no hazard has been experienced.

General. IBX was prepared according to the reported method.[2b] Its purity was 93%, the remaining part being IBA[36] (^{1}H-NMR). DMP was prepared as described in ref 2d. DMSO-d_6 (CIL, Cambridge Isotope Laboratories) was distilled under reduced pressure prior to use and stored over activated molecular sieves (residual water, 0.134 M, Karl Fisher determination). $CDCl_3$ (CIL) was distilled from anhydrous K_2CO_3 and stored over activated molecular sieves (ca. 3 mM residual water). Mesitylene was present in both cases at 0.05 M concentration as an internal standard. ^{1}H- (^{13}C-)NMR spectra were recorded at 300.13 (75.39) MHz in DMSO-d_6 solutions, using DMSO-d_5 (-d_6) as internal referencing for chemical shifts (δ 3.49 for ^{1}H, δ_C 39.5 for ^{13}C). Elemental analyses and water (Karl Fisher) determination were carried out by Redox, Cologno Monzese (Milano, Italy).

(34) Water concentration was increased until the intermediate signal became constant. These experimental conditions were the result of a compromise between sensitivity and pre-equilibrium condition.

(35) Plumb, J.; Harper, D. J. *Chem. Eng. News* **1990**, Jul 16, 3.

(36) Alcohols react reversibly also with IBA to form an alkoxyiodinane. This second equilibrium is characterized by a very slow onset rate (≫12 h for 0.04 M solutions in DMSO-d_6) and can be neglected in the experimental conditions adopted for the kinetic experiments herein described.

Intermediates Detection. In a typical experiment, 1 equiv of alcohol was added via microsyringe to a 0.2 M solution of IBX in DMSO-d_6 (or 0.8 equiv of alcohol to a 0.1 M solution of DMP in $CDCl_3$). ^{1}H-NMR spectroscopy was used to monitor formation of intermediates and oxidation products within the first minute of the reaction. However, DMP−diolate adducts are much more stable and long-lasting species (for example, DMP−*trans*-1,2-cyclohexanediol adduct is still present in more than 50% yield after 18 h at room temperature).

Kinetic Measurements. All of the oxidation reactions were followed by monitoring the signal intensities by ^{1}H-NMR spectroscopy, *i.e.*, the aldehyde proton in the case of primary alcohols and a suitable methyl group for the secondary ones. The oxidation products were unambiguously identified at the end of the reactions by comparison with the spectra obtained from authentic materials. In a typical kinetic experiment, 7 mg of IBX (93%, 0.023 mmol) was dissolved in 0.5 mL of DMSO-d_6 containing 0.025 of mmol mesitylene and 0.067 mmol of H_2O; 1 equiv of alcohol (neat or DMSO-d_6 solution) was then added in the NMR tube via microsyringe. After the usual lock and field homogeneity optimization procedures (usually 30−40 s), a series of 21 spectra was automatically registered every 28 s with the following parameters: 10 scans were collected for each spectrum (number of points, SI = 16K; acquisition time, AQ = 2.015 s; spectral width, SW = 4065 Hz; relaxation delay, RD = 0 s). NMR data were transferred via NMRLINK to a 486 PC and analyzed with the WIN-NMR Bruker software. The FIDs were weighed for higher signal-to-noise ratio (LB = 0.5) and Fourier transformed, and the resulting spectra were manually integrated with the tangential baseline option after suitable phase correction. The concentration of the various species [i] was obtained as follows: $[i] = f_i A_i[std]/A_{std}$, where [i] = [**5**], [OX], [IBX]; [std] = 0.05 M mesitylene; [OX] is the oxidation product; A_i is the NMR integral value for 1H of the corresponding molecule; f_i is the relative correction factor for the area value A_i, obtained from a separate experiment with a long relaxation delay (60 s) and used to take into account the difference in relaxation times between the peak of interest and the signal of the internal standard (mesitylene aromatic hydrogens). The equilibrium constants for oxidizable alcohols were calculated at each point of the kinetic experiment from the following formula: $K_{eq} = ([\mathbf{5}][H_2O])/([IBX][ROH])$, where $[ROH] = [ROH]^0 - [\mathbf{5}] - [OX]$. The actual concentration of water was calculated taking into account the initial water content of DMSO-d_6 and that formed during the oxidation reaction, *i.e.*, $[H_2O] = [H_2O]^0 + [\mathbf{5}] + [OX]$; $[H_2O]^0 = 0.134$ M. Statistical calculations and curve fitting were carried out with the Statistica program, Statsoft.

Acknowledgment. Appreciation is expressed to Mrs. Simona Sputore for preparing batches of Dess-Martin periodinane and to Dr. Piero Melloni for supporting this work.

Supporting Information Available: Copies of ^{1}H-NMR spectra (300 MHz) of IBX and DMP complexes discussed in Tables 2−4 (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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