Synthesis and Properties of the Valence Tautomer of *cis*-Iodosocyclopropanecarboxylic Acid: 4,5-Methano-1-hydroxyiodoxol-3(1*H*)-one

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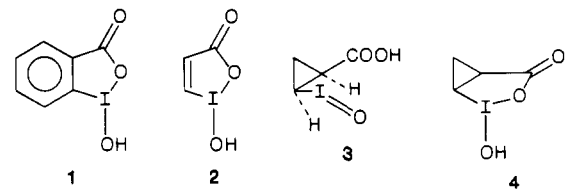
Abstract: 4,5-Methano-1-hydroxyiodoxol-3(1*H*)-one (**4**) was synthesized from propionic acid in six steps. Key reactions included Simmons–Smith cyclopropanation of *cis*-3-iodopropen-2-ol, followed by pyridinium dichromate oxidation to *cis*-iodocyclopropanecarboxylic acid. The final iodo to iodoso oxidation used either chlorination/hydrolysis or peracetic acid procedures. Compound **4** exists in the 1-hydroxyiodoxolone form, not in the "open" *cis*-cyclopropanecarboxylic acid form (**3**), as shown by its "high" pK_a (7.55) and by its ability to cleave *p*-(nitrophenyl)diphenyl phosphate (k = 0.0044 s^{-1}) in pH 8 aqueous micellar solution. Compound **4** disproportionates to iodo (**5**) and iodoxy (**7**) compounds in pH 8 aqueous buffer with k = 0.027 L/(M·s). Ab initio molecular orbital calculations are described which help rationalize the observed properties of **4**. The reactivity of **4** (and related species) is intimately connected to the structure and bonding around the formally hypervalent iodine atom.

Alkyliodoso compounds (RI=O) and the related iodo dichlorides are notoriously unstable.[1,2] Iodosoalkanes (R_HI=O) appear not to have been isolated, and open-chain alkyliodo dichlorides are generally unstable above ~−10 °C,[2b] often affording products via R—I bond cleavage.[1a,b] Attempts to obtain *stable* examples of $RICl_2$, where R is either a cyclopropyl or the 7,7-dimethyl-1-norbornyl (bridgehead) residue, have not succeeded; the desired materials were apparently formed at low temperature but were unstable at 0 °C. Moreover, their basic hydrolysis did not afford the corresponding alkyliodoso compounds.[1c] Analogous failures attended attempts to convert the *bis*(*m*-chlorobenzoate) trivalent iodine ester of 4-iodotricyclene to 4-iodosyltricyclene by basic cleavage.[1g]

Aromatic iodoso compounds (ArI=O) appear to exist as polymers,[3a] indicative of the inherent instability of the iodosyl group, but examples of $ArICl_2$ are well-known,[2] possibly reflecting the greater stability of the C—I bond in $ArICl_2$ versus $RICl_2$. Perhaps in a related vein are the isolable *perfluoro*alkyliodoso compounds[3b] and iodomethyl sulfone dichlorides,[4] where at least heterolytic C–I cleavages (that would impose additional positive charge on the α-carbon atom) are disfavored.[2b]

Although aromatic iodoso compounds (e.g., iodosobenzene) seem to stabilize the iodosyl group intermolecularly (by polymerization),[3a] the presence of a vicinal carboxyl moiety (as in *o*-iodosobenzoic acid) furnishes an *intramolecular* option: heterocyclization. Thus, *o*-iodosobenzoic acid[5] and *cis*-β-iodosoacrylic acid[6] preferentially exist in their hydroxyiodoxolone valence tautomeric forms **1** and **2**, respectively.



Our discovery[5c] that the conjugate (IO^-) base of **1** is a powerful O-nucleophile for the cleavage of phosphates and esters has quickened interest in iodosocarboxylates.[6,7] It occurred to us that the placement of a carboxylic acid residue cis and vicinal to the iodine atom of an iodocyclopropane might make it possible to intramolecularly "trap" the unknown *cis*-iodosocyclopropanecarboxylic acid (**3**) as its valence tautomer, 4,5-methano-1-hydroxyiodoxol-3(1*H*)-one (**4**), an aliphatic analogue of valence tautomerized "*o*-iodosobenzoic acid" (**1**). Moreover, a successful preparation of **4** from a precursor iodo dichloride would stand in contrast to Dence and Roberts' inability to obtain characterizable iodoso derivatives from the parent compound, iodocyclopropane dichloride.[1c]

Here, we describe the synthesis and chemical properties of **4**, which, to our knowledge, is the first well-described valence tautomer of a saturated, aliphatic iodoso compound. In accord with its structural formulation, the conjugate base of **4** cleaves reactive phosphates as an O-nucleophile. Finally, ab initio calculations support and rationalize conclusions drawn from the experimental results.

Results and Discussion

Synthesis. Target compound **3**/**4** was prepared as outlined in Chart I. Addition of 57% aqueous HI to propiolic acid, catalyzed by CuI,[8,9] gave (*Z*)-3-iodopropenoic acid.[9] The configuration was secured by the cis vicinal olefinic proton coupling constant, $J_{2,3}$

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(8) Kurtz, A. N.; Billups, W. E.; Greenlee, R. B.; Hamil, H. F.; Pace, W. T. *J. Org. Chem.* **1965**, *30*, 3141. The method described for HCl addition is applicable to HI addition.[9]

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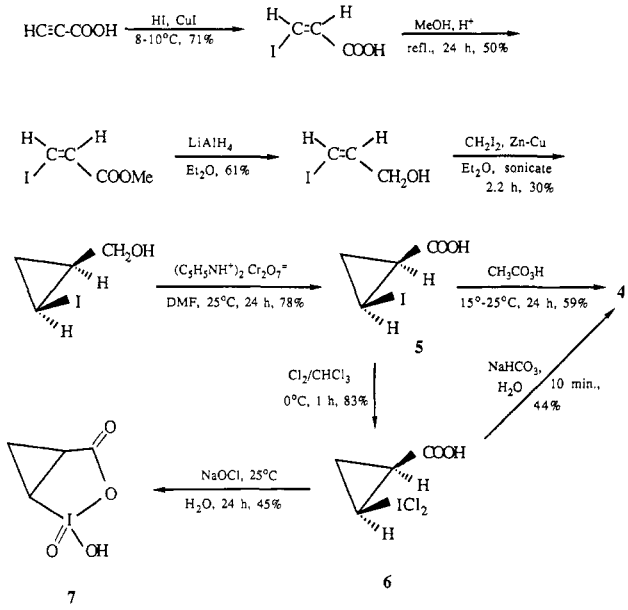
Chart I[a]



[a] Yields refer to isolated, purified materials.

= 8.1 Hz.[8] Esterification[9] gave methyl (*Z*)-3-iodopropenoate (contaminated by ~10% of *E* isomer), which was purified by distillation (bp 61–62 °C/12 mmHg;[9] $J_{2,3}$ = 8.1 Hz).

Direct methylenation of the methyliodopropenoate (Simmons–Smith reaction or $CH_2N_2/CuCl$) failed, so we first reduced the ester ($LiAlH_4$) to an allylic alcohol to utilize the activating effect of the hydroxyl group in a subsequent Simmons–Smith reaction.[10] We thus obtained (*Z*)-3-iodopropenol,[11] purified by chromatography on silica gel. Its NMR spectrum ($J_{2,3}$ = 7.7 Hz) was consistent with previous reports. Cyclopropanation with $CH_2I_2/Zn(Cu)$[10,12] was achieved in refluxing dry ether under continuous sonic irradiation.[13] The reaction was monitored by a gas chromatograph and then stopped when formation of the formal[14] [$(ICyCH_2O)_2CH_2$] became significant. Chromatography afforded pure *cis*-1-(hydroxymethyl)-2-iodocyclopropane, which was characterized by an appropriate exact mass molecular weight and 400-MHz ^1H NMR spectrum.

Oxidation of the alcohol with excess pyridinium dichromate,[15] followed by acidic aqueous/ethereal extraction, afforded the key relay compound, *cis*-2-iodocyclopropanecarboxylic acid, **5**, mp 64.5–66 °C (after three recrystallizations from hexane). The structure of **5** rests on a satisfactory elemental analysis (C, H, I), an appropriate IR spectrum (C=O, 1712 cm^{-1}, KBr), and the 400-MHz ^1H NMR spectrum ($CDCl_3$) which displayed four multiplets at δ 1.38–1.33, 1.56–1.50 (CH_2), 1.88–1.82 (C*H*CO-OH), 2.85–2.79 (CHI), and 8.1 (br s, OH).[16]

Iodo acid **5** could be converted into the iodosocarboxylate ether by chlorination–hydrolysis[7a,17] or by peracetic acid oxidation.[18] Chlorination (1 equiv of Cl_2 in $CHCl_3$) gave yellow iodo dichloride **6**, which was isolated and characterized by C, H, I analysis and 400-MHz ^1H NMR. The relative stability of **6** contrasts with the reported[1c] lability of iodocyclopropane dichloride above 0 °C. Obviously, the carboxylic acid substituent of **6** retards some (possibly heterolytic) decomposition pathway that is prevalent with iodocyclopropane dichloride.

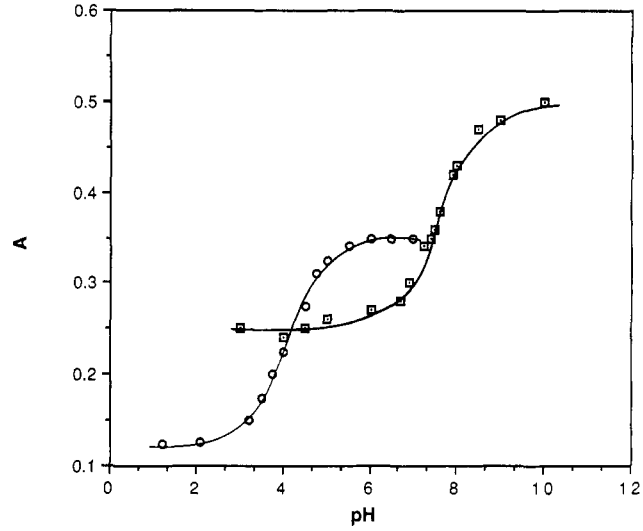


Figure 1. Spectrophotometric titrations of iodo acid **5** (○) and 1-hydroxyiodoxolone **4** (□); absorbance versus pH. The pK_a's were 4.10 and 7.55, respectively, as determined from the linear plots of log $(A - A_{min})/(A_{max} - A)$ versus pH; thus pK_a = pH when the logarithmic quantity = 0.

Mild basic hydrolysis of **6** then afforded the desired heterocycle, **4**, mp 84–86 °C (dec), in 44% yield after CH_2Cl_2 extraction of the HCl-acidified, pH 6 aqueous solution, drying, removal of CH_2Cl_2, and 5-fold trituration with ether. We note here the anticipated contrast between the basic hydrolysis of *o*-carboxylic acid substituted **6**, which affords **4**, and that of iodocyclopropane dichloride itself, which gave "considerable amounts of elemental iodine, but no iodoso derivative...".[1c]

Compound **4** could also be obtained directly from **5** by oxidation with 35% peracetic acid,[18] followed by hydrolysis, lyophilization, and ethereal trituration. Iodo dichloride **6** could also be converted to 2-*iodoxy*cyclopropanecarboxylic acid, **7**, by oxidation–hydrolysis with excess 5% aqueous NaOCl.[19] Yellow **7**, mp 80–82 °C (dec), was characterized by analysis, NMR and IR spectroscopies, and $KI/Na_2S_2O_3$ iodometric titrimetry[17] (95% of theory for iodoxyl).[20] We represent **7** in its heterocyclic form in analogy to the behavior of *o*-iodoxybenzoic acid[2b,21] and because of its "high" titrimetric pK_a (7.90).

Hygroscopic, moderately stable[22] **4** displayed a protonated molecular ion at *m/e* 229 (ethanolamine CI mass spectrum) and 98% of theoretical iodosyl oxidative capacity upon iodometric titration.[17] The NMR spectrum (200 MHz, δ, D_2O) revealed four one-proton multiplets at 3.52–3.43 (C*H*IO), 1.92–1.81 (C*H*CO), and 1.43–1.31 and 1.18–1.09 (CH_2). The IR spectrum (KBr) displayed the C=O absorbance at 1680 cm^{-1}; the shift to lower wavelength from the 1712-cm^{-1} location of C=O *iodo*carboxylate **5** is characteristic[5b] of the iodoxolone structure (i.e., **4** not **3**).

Chemistry. Also characteristic of a 1-hydroxyiodoxolone structure is weaker acidity, relative to that of its precursor iodocarboxylic acid.[23] Indeed, the pK_a of **4**, determined by absorption spectroscopy (212 nm, 0.02 M phosphate buffer), is 7.55, compared to pK_a = 4.10 for iodocarboxylate **5**, similarly measured at 206 nm;[24] see Figure 1. The latter value is typical of 2-

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(12) Shank, R. S.; Shechter, H. *J. Org. Chem.* **1959**, *24*, 1825.
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(15) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.
(16) Double-resonance experiments gave *J* = 8 Hz for C*H*IC*H*COOH.
(17) Lucas, H. J.; Kennedy, E. R. In *Organic Syntheses*; Horning, E. C., Ed.; Wiley: New York, 1955; Collect. Vol. 3, pp 482–484.
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(19) Formo, M. W.; Johnson, J. R. In *Organic Syntheses*; Horning, E. C., Ed.; Wiley: New York, 1955; Collect. Vol. 3, pp 486–7.
(20) Iodoso compound **4** disproportionates in MeOH (24 h) to iodo compound **5** and iodoxy compound **7**; see below. Compound **7** was identical from either disproportionation or synthetic origins: TLC (silica gel, MeOH) R_f (**4**), 0.70, R_f (**7**), 0.44.
(21) Gougoutas, J. *Cryst. Struct. Commun.* **1981**, *10*, 489.
(22) Iodoxolone **4** decomposed slowly (~40 h) on standing at 25 °C. Its disproportionation in aqueous solution is described below.
(23) Willgerodt, C. Reference 5b, pp 3721–2 and ref 6 cited there.
(24) The pK_a of **4** was also determined as 7.65 by titration with 0.5 N NaOH in water at 25 °C and as 7.52 from a pH–rate profile[7a] (not shown) for the cleavage of *p*-(nitrophenyl)diphenyl phosphate by **4** in 1 × 10^{-3} M aqueous cetyltrimethylammonium chloride and 0.02 M phosphate buffers (pH 6.8–8.0), at 25 °C.

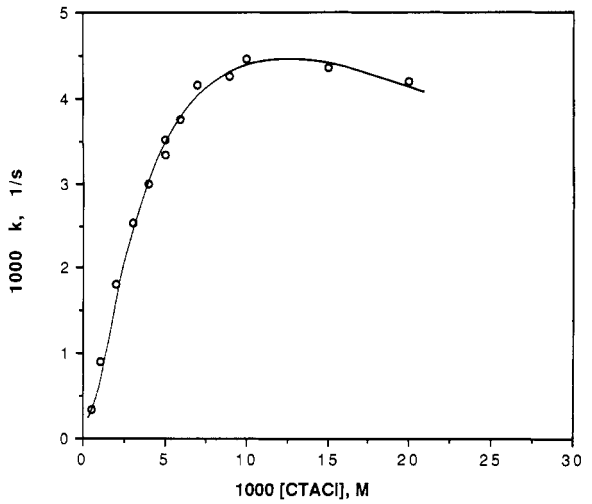

Figure 2. Pseudo-first-order rate constants (k_ψ, s^{-1}) for the cleavage of 1×10^{-5} M PNPDPP by 1×10^{-4} M **4** as a function of [CTACl] at pH 8; see text for other conditions. Each reaction was followed spectrophotometrically, monitoring the release of *p*-nitrophenoxide ion at 400 nm.

halocyclopropanecarboxylic acids,[25] whereas the "high" pK_a of **4** is similar to those of iodoxolones **1** (7.25) and **2** (7.78).[6]

The strong O-nucleophilic reactivity toward phosphates characteristic of cationic micellar solutions of the 1-oxidoiodoxolone conjugate bases of **1** and **2**[6,7a] is also displayed by **4-O⁻**. The kinetic properties of **4-O⁻** were examined by determining a full rate constant–[surfactant] profile (Figure 2) for the cleavage of 1×10^{-5} M *p*-nitrophenyl diphenyl phosphate (PNPDPP) by 1×10^{-4} M **4-O⁻** in varying concentrations of cetyltrimethylammonium chloride (CTACl) at 25 ± 0.5 °C. Other conditions included 0.02 M phosphate buffer, μ = 0.08 (NaCl). From Figure 2 we see that, at the maximum, 1×10^{-4} M **4-O⁻** in 1.0×10^{-2} M aqueous micellar CTACl solution cleaved PNPDPP with $k_\psi = 0.0044$ s^{-1}. Comparable rate constants are **1-O⁻**, 0.064 s^{-1} (at 1×10^{-3} M CTACl); **2-O⁻**, 0.010 s^{-1} (at 3×10^{-3} M CTACl); and 1×10^{-2} M CTACl alone, 0.00009 s^{-1}.[26] The anion of **4** is clearly a potent O-nucleophile toward PNPDPP in pH 8 micellar solution, with $k_4/k_0 \sim 50$, although it is somewhat less reactive than the anions of **1** and **2**.

Aqueous solutions of **4-O⁻** are also *less stable* than those of **1-O⁻** and **2-O⁻** with respect to *disproportionation*. In pH 8 aqueous solution, disproportionation of 0.01 M **4** to iodocarboxylate **5** and iodoxycarboxylate **7** could be followed by NMR or HPLC.[27] Quantitative HPLC analysis as a function of time gave concentration data from which the **4** → **5** + **7** reaction was shown to be second order, with $k = 0.027$ L/(M·s) and $\tau_{1/2} \sim 62$ min. Comparable half-times for the disproportionations of **1** and **2**, similarly determined by HPLC, were ~6.2 and 1.7 *days*, respectively.[28]

Calculations. We carried out ab initio molecular orbital calculations on **1/1-O⁻** and **4/4-O⁻** using a locally modified version of the GAMESS electronic structure program package.[29] High-level calculations on molecules of this size are facilitated by the use of effective core potentials, which eliminate explicit representation of the "chemically unimportant" core electrons. The inner core electrons for I (K,L,M,4s²4p⁶4d¹⁰), C (1s²), and O (1s²) were replaced by the ab initio effective core potentials of Wadt and Hay (I)[30a] and Stevens et al. (C, O),[30b] respectively. The valence electrons of these atoms were described with basis sets of split valence (C, O) or split valence plus polarization (I) quality; the H atoms were described with the minimal MINI-3 basis set developed by Huzinaga.[30c] The I (3s,3p) valence basis set was augmented with a d-type function (exponent = 0.25) and contracted (3s,3p,1d) → [2,$^1/_2$,$^1/_1$]. The C and O basis sets were (4s,4p) → [3,$^1/_3$,1]. These choices resulted in 99 basis functions covering 29 electron pairs in **1**; for **4**, the corresponding values were 75 and 23.

The electronic ground states were calculated within the standard single-determinant restricted Hartree–Fock method described by Roothaan.[31a] We used the natural bond orbital (NBO) localization procedures proposed by Weinhold and co-workers[31b] to generate electronic population indexes and bonding analyses. The geometries were optimized (C_s symmetry for **1/1-O⁻**, no symmetry

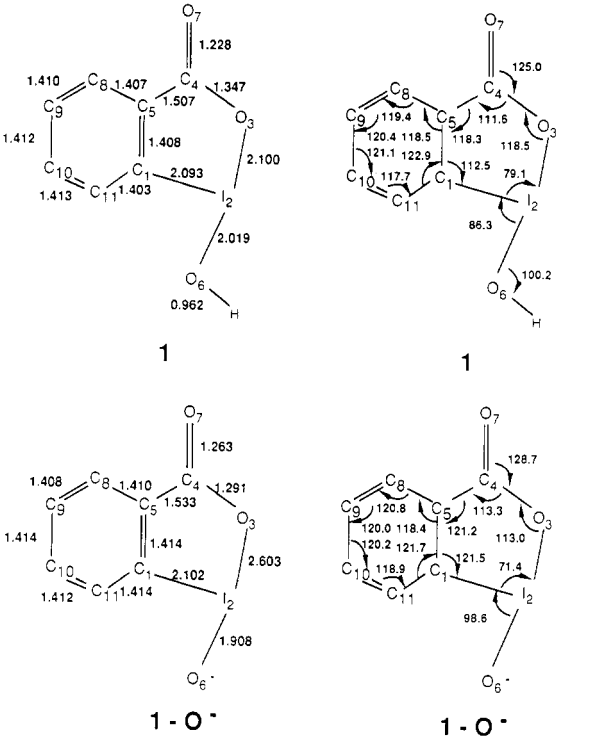

Figure 3. Calculated bond lengths and angles for the non-hydrogen atoms in the conjugate acid/base pair **1/1-O⁻**. The calculations are described in the text. Full sets of Cartesian coordinates are available in the supplementary material.

Table I. Calculated Natural Net Charges[a]

atom	1	1-O⁻	2[b]	2-O⁻[b]	4	4-O⁻
C_1	−0.28	−0.29	−0.43	−0.47	−0.43	−0.46
I_2	1.52	1.31	1.48	1.25	1.45	1.21
O_3	−0.95	−0.93	−0.94	−0.94	−0.96	−0.95
C_4	0.98	0.99	0.94	0.95	0.97	0.98
C_5	−0.19	−0.17	−0.27	−0.29	−0.30	−0.30
O_6	−1.15	−1.14	−1.14	−1.12	−1.13	−1.10
O_7	−0.70	−0.85	−0.68	−0.84	−0.69	−0.85
C_8	−0.14	−0.17			−0.35	−0.38
C_9	−0.19	−0.22				
C_{10}	−0.17	−0.21				
C_{11}	−0.19	−0.21				

[a] See Figures 3 and 4 for the numbering of the atoms. See text for details of the calculations. [b] Data obtained previously, see ref 6. The numbering scheme follows that presented in Figures 3 and 4; see also Figure 5 in ref 6.

(25) Kusuyama, Y. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1944.
(26) All rate constants are taken from the maxima of full rate constant versus [CTACl] profiles.
(27) Alltech C18 5-μm reversed-phase column, operated at 300 psig, with 95:5 MeOH/H_2O eluent at 0.5 mL/min and UV detection at 254 nm. The retention times (min) of **5**, **4**, and **7** were 3.72, 5.65, and 5.85 min, respectively.
(28) $k = 1.89 \times 10^{-4}$ L/(M·s) for **1** and 6.9×10^{-4} L/(M·s) for **2**.
(29) Dupuis, M.; Spangler, D.; Wendoloski, J. GAMESS NRCC Software Catalogue, Vol. 1, Program No. QG01, 1980. Schmidt, M. W.; Boatz, J. A.; Baldridge, K. K.; Koseki, S.; Gordon, M. S.; Elbert, S. T.; Lam, B., private communication. Stevens, W. J.; Krauss, M., private communication.
(30) (a) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284. (b) Stevens, W. J.; Basch, H.; Krauss, M. J. *Ibid.* **1984**, *81*, 6026. (c) Huzinaga, S.; Andzelm, J.; Klobukowski, M.; Radzio-Andzelm, E.; Sakai, Y.; Tatewake, H. *Gaussian Basis Sets for Molecular Calculations*; Elsevier: Amsterdam, 1984.

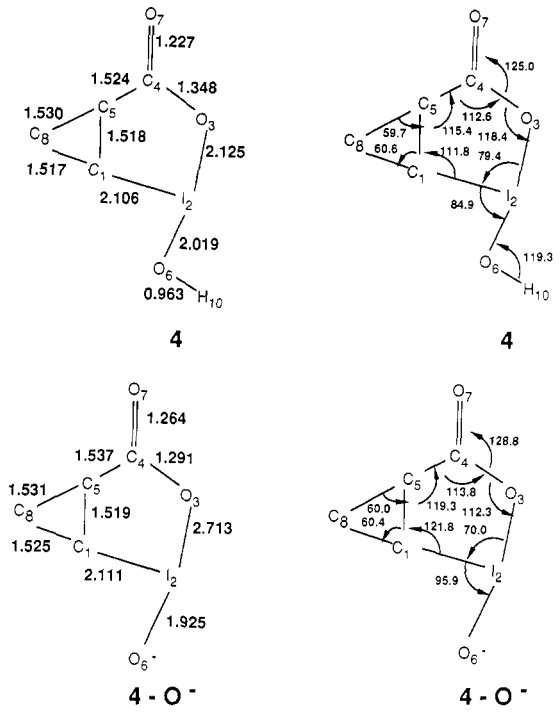

Figure 4. Calculated bond lengths and angles for the non-hydrogen atoms in the conjugate acid/base pair **4**/**4-O⁻**. The calculations are described in the text. Full sets of Cartesian coordinates are available in the supplementary material.

restrictions (C_1) for **4**/**4-O⁻**) in cartesian coordinate space using the basis sets and effective core potentials described above and Schlegel's scheme[31c] with analytical gradients but finite-difference second derivatives. These computational procedures were also used by us in the detailed analysis of the bonding and reactivity of **2**/**2-O⁻**.[6]

Optimized geometries for the conjugate acid/base pairs **1**/**1-O⁻** and **4**/**4-O⁻** are displayed in Figures 3 and 4, respectively. In Table I we collect several net atomic charge values of particular interest from the population analyses. Where proper comparisons can be made to our previous structures for **2**/**2-O⁻**,[6] incorporation of the cyclopropane (**2** → **4**) or the phenyl (**2** → **1**) ring does not appear to have induced dramatic distortions into the five-membered iodoxolone heterocycle. In particular, the local geometries around C_4 are virtually transferable between the acids (**1**, **2**, and **4**) or their conjugate bases (**1-O⁻**, **2-O⁻**, and **4-O⁻**). The five-membered rings in **4** and **4-O⁻** deviate slightly from planarity (~0.1 Å from the "best" plane), but larger deviations occur for the exocyclic O_6 and O_7 atoms which depart by up to 0.3 Å from the best plane, in a direction away from C_8.

Structural differences deserving special attention arise in the T-shaped coordination geometry around the formally hypervalent iodine atom. As discussed previously,[6] the O_6–I_2–O_3 triad acts as a "shuttle" for transferring electron density from deprotonated O_6 to the O_7–C_4–O_3 triad, making the latter resemble a carboxylate moiety. The transfer is accompanied by a significant increase in the I_2–O_3 distance, and the I_2–O_3 bond length is computed at 2.71, 2.63, and 2.60 Å in **4-O⁻**, **2-O⁻**, and **1-O⁻**, respectively. These distances are 0.59, 0.53, and 0.50 Å larger than those calculated for the respective I–OH parent molecules. The extent of ring opening (as measured by the I_2–O_3 distance) is particularly large in **4-O⁻** and may contribute to its facile disproportionation (see above).

In unison with the I_2–O_3 distance alterations, the I_2–O_6 distances diminish in sequence from 1.925 Å in **4-O⁻**, through 1.917 Å in **2-O⁻**, to 1.908 Å in **1-O⁻**, representing changes relative to the neutral acids of 0.09, 0.10, and 0.11 Å, respectively. The I_2–O_6 bond lengths are just below the sum of the covalent radii (~2.0 Å) and well above the values corresponding to an I=O double bond formulation (~1.6 Å).[2a,32] According to the description of the bonding characteristics developed for **2-O⁻** and its desoxo analogue,[6] the bonding around I_2 involves a mixture of two resonances (Lewis) structures, **8** and **9**:

$$O_6\text{-}I_2^{+}\ :\!\bar{O}_3 \longleftrightarrow O_6\text{-}I_2\text{-}O_3$$
8 **9**

Structure **8** represents an extreme form of the delocalized 3c–4e bonding illustrated by **9**. The two important molecular orbitals in **9** ("fully bonding" and "nonbonding" combinations) have localized into an I_2–O_6 σ-bond orbital and an O_3 in-plane lone pair. Both resonance structures have three lone pairs localized on O_6, which are responsible for the strong nucleophilicity of these iodosocarboxylates. Structure **8** is the dominant canonical form, but the contribution of **9** increases in the series **4-O⁻** < **2-O⁻** < **1-O⁻** as both the I_2–O_6 and I_2–O_3 bond lengths decrease. A decrease in the I_2–O_6 bond length is indicative of an increase in basicity at the O_6 atom.[2b]

Another trend suggesting increased basicity in the **4-O⁻** to **1-O⁻** series may be discerned from inspection of the natural atomic net charges in Table I. Where comparisons among the systems are appropriate, there are clearly no dramatic differences to be observed, in accordance with the small structural changes noted above. However, the net charge on O_6 increases slightly from −1.10 in **4-O⁻**, through −1.12 in **2-O⁻**, to −1.14 in **1-O⁻**. The computed ionization energy for the reaction **4** → **4-O⁻** is 333 kcal/mol and is similar to the values obtained for the ionizations of **2** or **1** (330 kcal/mol),[6] in accord with their similar pK_a's, reported above. Thus, the most reactive species toward PNPDPP (**1-O⁻**) has the largest computed electron density on O_6, as well as the shortest I_2–O_3 and I_2–O_6 bond lengths. The small differences in reactivity between the conjugate bases of **1**, **2**, and **4** may thus be related to subtle structural and bonding differences.

Table II. Some Properties of 1-Oxidoiodoxol-3(1*H*)-ones

property	**1-O⁻**	**2-O⁻**	**4-O⁻**
I_2–O_3, Å[a]	2.603	2.632	2.713
I_2–O_6, Å[a]	1.908	1.917	1.925
O_6, net atm chg[b]	−1.14	−1.12	−1.10
k_ψ^{max}, s⁻¹[c]	0.064	0.010	0.0044
k_{dis}, L/(M·s)[d]	0.00019	0.00069	0.027

[a] Calculated bond lengths; see above and ref 6. [b] Calculated net atomic charges; see above and ref 6. [c] Pseudo-first-order rate constants for the cleavage of PNPDPP in pH 8 micellar aqueous CTACl. Data were taken at the maxima of rate constant–[surfactant] profiles; see above and ref 6 for conditions. [d] Second-order rate constants for disproportionation in water at pH 8; see above for details.

Conclusions. *cis*-Iodosocyclopropanecarboxylic acid, **3**, can be prepared by mild basic hydrolysis of the unusually stable iodocyclopropane dichloride, **6**. However, the iodoso acid preferentially exists in the heterocyclic methanohydroxyiodoxolone form, **4**. There is no spectral evidence for detectable **3** in "equilibrium" with **4**. In accord with its hydroxyiodoxolone formulation, **4** is weakly acidic (pK_a ~ 7.5), and its conjugate base, **4-O⁻**, is a potent O-nucleophile that readily cleaves *p*-nitrophenyl diphenyl phosphate in aqueous cationic micellar solution. Ab initio molecular orbital calculations clearly manifest the iodoxolone-like structure, **4**, as the global minimum. Close examination of the calculated structures for the methano (**4**, Figure 4), parent (**2**, ref 6), and benzo (**1**, Figure 3) 1-hydroxyiodoxol-3(1*H*)-ones reveals subtle differences that may be reflected in their comparative reactivities. Thus, along the series **1-O⁻**, **2-O⁻**, **4-O⁻**, the I_2–O_3 and I_2–O_6 bond lengths increase, the net atomic charges on (nucleophilic) O_6 decrease, but the tendencies toward disproportionation increase; see Table II.

It is tempting to view the I_2–O_3 bond length as the key structural feature, for it is this parameter that "measures" the degree to which

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these compounds resemble either the hydroxyiodoxolone or iodosocarboxylic acid structural extremes. The latter, "open" structure will have minimal nucleophilicity and maximum kinetic instability vis-à-vis disproportionation; the "closed" hydroxyiodoxolones will express maximum nucleophilicity and kinetic stability. This paradigm is richly suggestive of new approaches to the rational design of stronger 1-oxidoiodoxolone nucleophiles. It is necessary to impose structural factors that will force greater closure on the I_2–O_3 bond. Appropriate experimental tests of this proposition are now in progress.

Experimental Section

General Methods. Melting points and boiling points are uncorrected. NMR spectra were determined on Varian T-60, VXR-200, or XL-400 instruments. Chemical shifts are reported relative to internal Me_4Si (60 MHz) or $CHCl_3$ (200 and 400 MHz). IR spectra were recorded on a Perkin-Elmer 727B spectrometer or on a Mattsun Cygnus 100 FT instrument. Analytical GC employed a Varian Model 3700 flame-ionization unit (injection temperature, 250 °C; detection temperature, 300 °C; N_2 flow, 25 mL/min) fitted with a 12-m × 0.22-mm bonded-phase SE-30 vitreous silica capillary column. UV spectra were determined with a Hewlett-Packard Model 8451A diode array spectrophotometer. Mass spectra were determined with a VG 7070 (United Kingdom) mass spectrometer. TLC analyses were carried out on Aldrich precoated polyester silica gel plates with fluorescent indicator. pK_a titrations employed a Brinkman 636 "Titroprocessor" automatic titrimeter, and the pK_a was read directly from the "half end point" of the classical titration curve (Figure 1). Microanalyses were performed by Robertson Laboratory, Madison, NJ.

Materials. PNPDPP was prepared and purified by literature methods.[33] CTACl was obtained from Eastman, recrystallized several times from methanol/ether, and dried under vacuum. Commercially available chemicals were used as received without further purification, unless otherwise noted. Anhydrous solvents were obtained by distillation, immediately prior to use, from sodium/benzophenone ketyl (diethyl ether), barium oxide (dimethylformamide), magnesium methoxide (methanol), or phosphorus pentoxide (chloroform, chlorobenzene).

4,5-Methano-1-hydroxyiodoxol-3(1*H*)-one, 4 [*cis*-Iodosocyclopropanecarboxylic Acid, 3]. This compound was prepared by the sequence of steps outlined in Chart I.

(*Z*)-3-Iodopropenoic Acid. In a typical preparation, 17.5 g (250 mmol) of propiolic acid (Aldrich) was added over 25 min to a stirred solution of 7.8 g of cuprous iodide catalyst in 51.2 g (0.4 mol) of 57% aqueous hydriodic acid (Aldrich); a temperature of 8–10 °C was maintained by cooling. After storage at 0 °C overnight, a yellow precipitate had formed. This solid was filtered and dissolved in ~250 mL of chloroform. The chloroform solution was washed with ~30 mL of water, ~30 mL of aqueous sodium thiosulfate solution, and then again with ~30 mL of water. After drying ($MgSO_4$), solvent was stripped and the resulting yellow solid was recrystallized twice from hexane (crystals were obtained by rapid cooling in an ice–salt bath). We thus obtained 35 g (0.177 mol, 70.8%) of pure, slightly yellow (*Z*)-3-iodopropenoic acid, mp 67–68 °C; lit.[1,20] mp 67 °C. After two recrystallizations, the product was 99% pure *Z* isomer by capillary GC at 100 °C; R_t = 2.37 min (*E* isomer), 2.86 min (*Z* isomer).

IR (KBr, cm^{-1}): 3050 (OH, br), 1710 (C=O), 1600 (C=C), 1400, 1300, 1285. ^1H NMR (60 MHz, δ, $CDCl_3$): 7.5 (AB quartet, J = 8.1 Hz, 2 H, *vinyl*).

Methyl (*Z*)-3-Iodopropenoate. Next, 30 g (0.15 mol) of (*Z*)-3-iodopropenoic acid was refluxed for 24 h with 100 mL of absolute methanol and 5 mL of concentrated sulfuric acid as a catalyst. After this time, methanol was removed under reduced pressure, and the crude methyl (*Z*)-3-iodopropenoate was dissolved in ~300 mL of ether. The resulting brown ethereal solution was washed with water, aqueous sodium bicarbonate solution, aqueous sodium thiosulfate solution (until it was yellow in color), and then again with water. The ethereal phase was dried over sodium sulfate, and then ether was removed under vacuum. The crude *Z* ester, contaminated by ~10% of its *E* isomer, was purified by distillation over a short Vigreux column to give 15.9 g (0.075 mol, 50%) of slightly yellow product that was 99% pure *Z* isomer by GC at 80 °C; R_t = 1.27 min (*E* isomer), 1.48 min (*Z* isomer).

IR (neat, cm^{-1}): 1735 (C=O), 1605 (C=C), 1438, 1330, 1285, 1200, 1175, 1003, 910. ^1H NMR (60 MHz, δ, $CDCl_3$): 3.85 (s, 3 H, OCH_3); 7.2 (AB quartet, J = 8.1 Hz, 2 H, vinyl).

(*Z*)-3-Iodopropenol. Next, in a flame-dried, 150-mL, three-neck flask fitted with a mechanical stirrer, a dropping funnel, and a condenser and maintained under a nitrogen atmosphere, 1.2 g of powdered $LiAlH_4$ (Aldrich) was introduced into 35 mL of dry ether. The mixture was stirred for 15 min, and then 10.6 g (50 mmol) of methyl (*Z*)-3-iodopropenoate in 20 mL of dry ether was added slowly through the dropping funnel. The rate of addition was such that the mixture refluxed gently. After the ester was added, stirring was continued for 45 min. Excess $LiAlH_4$ was decomposed by dropwise addition of ethyl acetate, and the reaction mixture was then added to 50 mL of 15% H_2SO_4 (cooled to 5 °C). The ethereal phase was combined with ethereal extracts (6 × 40 mL) of the aqueous phase, and the combined solution was washed with aqueous sodium carbonate solution, aqueous sodium thiosulfate solution (until it was yellow in color), and finally with water. After drying over magnesium sulfate, solvent was stripped, and the resulting orange oil was chromatographed over silica gel with 6:1 hexane/EtOAc as the eluent. The chromatography was monitored by TLC; the required fraction showed (*Z*)-3-iodopropenol as a spot with R_f = 0.3, using 6:1 hexane/EtOAc as the eluent. (R_f for methyl (*Z*)-3-iodopropenoate is 0.8 under these conditions.) We thus obtained 5.6 g (30 mmol, 61%) of iodo alcohol, which was 98% pure by GC at 80 °C (R_t = 1.06 min).

IR (neat, cm^{-1}): 3350 (br OH), 2990–2950, 1610 (C=C), 1300, 1060, 1025. ^1H NMR (200 MHz, δ, $CDCl_3$): 3.45–3.5 (t, 1 H, O*H*), 4.10–4.20 (dd, $J_{1,2}$ = 5.6 Hz, 2 H, OCH_2), 6.25–6.50 (m, $J_{2,3}$ ~ 7.7 Hz, 2 H, vinyl). The vinyl coupling was consistent with previous reports.[34]

***cis*-1-(Hydroxymethyl)-2-iodocyclopropane.** Next, in a flame-dried flask (fitted with a condenser, under a nitrogen atmosphere), 2.5 g of freshly prepared zinc copper couple[12] in 10 mL of dry ether was irradiated with ultrasound[13] for 4 h. Then, 4.0 g (15 mmol) of methylene iodide was added, and the mixture was sonicated for 15–20 min. The addition of the methylene iodide initiated an exothermic reaction. After this time, 2.1 g (11 mmol) of (*Z*)-3-iodopropenol in 10 mL of dry ether was added dropwise (15 min) at such a rate as to maintain a gentle reflux. The resulting mixture was sonicated for an additional 2 h. The reaction was monitored by GC and stopped when formation of the formal[14] [$(ICyCH_2O)_2CH_2$] became significant. At 80 °C, the GC retention times were R_t = 1.72 min (*cis*-1-(hydroxymethyl)-2-iodocyclopropane) and 4.1 min [$(ICyCH_2O)_2CH_2$]. The gray–purple product mixture was diluted with 40 mL of ether, and an aqueous, saturated ammonium chloride solution (25 mL) was added carefully, dropwise, until the ether layer discharged a black precipitate, which was filtered and washed with 10 mL of ether. The aqueous layer was extracted (three times) with 20 mL of ether. The combined ethereal solution was washed twice with 25 mL of aqueous ammonium chloride solution, followed by two 25-mL portions of aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated under reduced pressure. An orange oil was thus obtained, which was chromatographed over silica gel with 7:3 hexane/ethyl ether as eluent. We obtained 0.67 g (3.3 mmol, 29.8%) of pure, slightly yellow *cis*-1-(hydroxymethyl)-2-iodocyclopropane, which gave a single spot on TLC, R_f = 0.31, using 1:1 hexane/ethyl ether as eluent (the R_f for (*Z*)-3-iodopropenol was 0.46 under these conditions). IR (neat, cm^{-1}): 3350 (br OH), 2930–2880, 1250, 1040. ^1H NMR (400 MHz, δ, $CDCl_3$): 0.63–0.68, 0.90–0.95, 1.28–1.33 (3 m's, 1 H each, cyclopropyl), 2.57–2.62 (m, 1 H, cyclopropyl CHI), 3.44–3.49 ("t," 1 H, OH), 3.88–3.92 (m, 2 H, CH_2OH).

Anal. M^+ (m/e) calcd 197.9541; found, 197.9525.

***cis*-2-Iodocyclopropanecarboxylic Acid, 5.** Next, in a flame-dried flask with a magnetic stirring bar, under nitrogen, 0.60 g (3.03 mmol) of *cis*-1-(hydroxymethyl)-2-iodocyclopropane was stirred for 24 h at 25 °C with 4.7 g (12.5 mmol) of pyridinium dichromate, PDC (Aldrich), dissolved in 10 mL of dry DMF.[15] After this time, the reaction mixture was poured into 80 mL of water, and the solution was acidified with 3 N HCl to pH 2.5. (It was necessary to acidify the mixture; otherwise, the pyridinium salt of the desired acid was isolated.) The water solution was extracted 10 times with 15-mL portions of ethyl ether. The combined ethereal solution was washed twice with 20 mL of water. After drying over $MgSO_4$, solvent was stripped, and the resulting brown, crude *cis*-2-iodocyclopropanecarboxylic acid was recrystallized three times from hexane (crystals were obtained by rapid cooling in an ice–salt bath) to give 0.5 g (2.4 mmol, 78%) of pure, slighly yellow needles of **5**, mp 64.5–66 °C. The compound gave a single spot on TLC, R_f = 0.38, using 2:1 hexane/ethyl ether as eluent. (R_f for the starting alcohol is 0.21 under these conditions.) FT IR (KBr, cm^{-1}): 3040 (br, COOH), 1712 (C=O), 1460, 1425, 1225. The ^1H NMR spectrum is described above.

Anal. Calcd for $C_4H_5O_2I$: C, 22.7; H, 2.4; I, 59.9. Found: C, 22.9; H, 2.5; I, 59.7.

4,5-Methano-1-hydroxyiodoxol-3(1*H*)-one, 4. Iodo acid **5** was converted to the title iodoxolone, **4**, either by chlorination–hydrolysis[7a,17] or by peracetic acid oxidation.[18] In a typical preparation, 200 mg (0.94 mmol) of iodo acid **5** in 6 mL of dry chloroform (cooled to 0 °C and protected from the light and moisture) was treated with an equimolar

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amount of dry chlorine (in dry chloroform), and the mixture was stirred gently. A yellow precipitate was observed after 5 min. Stirring was continued for an additional 1 h, and after this time, the precipitate was filtered, washed with chloroform, and dried under vacuum. We thus obtained 0.22 g (0.78 mmol, 83%) of pure, yellow iodo dichloride **6**; mp 80–82 °C.

FT IR (KBr, cm^{-1}): 3441 (br, OH), 3103–2500 (br, OH) 1712, 1700 (C=O), 1461, 1227, 960, 895, 699, 650. ^1H NMR (400 MHz, δ, DMSO-d_6): 1.05–1.09, 1.42–1.48, 1.78–1.84 (3 m's, 1 H each, cyclopropyl), 2.90–2.95 (m, 1 H, *CH*I).

Anal. Calcd for $C_4H_5Cl_2IO_2$: C, 17.0; H, 1.8; I, 44.9. Found: C, 16.8; H, 1.7; I, 45.1.

Next, 0.200 g (0.71 mmol) of iodo dichloride **6** was reacted with aqueous sodium bicarbonate solution (0.13 g, 1.55 mmol in 10 mL of water). After ~2 min of stirring, the yellow solid dissolved. Stirring was continued for an additional 10 min, and then the mixture was acidified with 1 N HCl to pH 6.0. The aqueous solution was extracted 16 times with 5-mL portions of methylene chloride. The combined methylene chloride extract was dried over magnesium sulfate, and then the solvent was stripped under vacuum to give a semisolid compound, which was triturated five times with ethyl ether (to remove iodo acid **5**). The residual white solid product was dried under vacuum to afford 0.07 g (0.31 mmol, 44%) of pure, hygroscopic, moderately stable iodoxolone **4**, mp 84–86 °C. Iodoxolone **4** slowly decomposes on standing at 25 °C.

FT IR (KBr, cm^{-1}): 3100–2500 (br, OH), 1680 (C=O), 1410, 1350, 762, 697, 582. The NMR spectrum is described above, as is the mass spectrum.

Iodoxolone **4** could also be obtained directly from **5** by oxidation with 35% peracetic acid.[18] In a typical preparation, 0.15 g (0.71 mmol) of **5** was reacted with 0.5 g (2.3 mmol) of 35% peracetic acid at 15 °C. After ~5 min, the iodoacid dissolved and the temperature of the mixture increased to room temperature. The reaction mixture was stirred for an additional 24 h at this temperature; then 20 mL of cold water was added. A precipitate did not appear, so the reaction mixture was lyophilized to give a slightly yellow powder, which was washed five times with ethyl ether (to remove unreacted iodo acid) and then dried under vacuum. We thus obtained 0.096 g (0.42 mmol, 59%) of pure, white **4**, mp 83–85 °C. The IR and NMR spectra of this sample matched those obtained from **4** prepared by chlorination–hydrolysis of **5** (see above). The new sample of **4** showed 98.5% of iodoso activity by $KI/Na_2S_2O_3$ titration.[17]

"Iodoxy" Compound 7. As in Chart I, 0.20 g (0.71 mmol) of freshly prepared, pulverized iodo dichloride **6** was reacted with 3.05 g (2.1 mmol) of 5% aqueous NaOCl solution at room temperature. After ~5 min, the iodo dichloride dissolved, and the yellow solution had become colorless. The reaction mixture was stirred for an additional 24 h. After this time, 25 mL of cold water was added, and the reaction mixture was stirred for 2 h. Since no precipitate formed, the reaction mixture was lyophilized to give a slightly yellow powder, which was washed with 5 mL of ethyl ether and dried under vacuum. We thus obtained 0.079 g (0.32 mmol, 45%) of white hygroscopic **7**, mp 80–82 °C (dec).

FT IR (KBr, cm^{-1}): 3060 (br, OH), 1703 (C=O), 1424, 1197. ^1H NMR (200 MHz, δ, D_2O): 0.90–1.10 (m, 2 H, CH_2), 1.84–1.98 (m, 1 H, CHCO), 3.11–3.24 (m, 1 H, $CHIO_2$). Compound **7** showed 95% of theoretical *iodoxyl* oxidative capacity upon iodometric titration ($KI/Na_2S_2O_3$).[17]

Iodoxy derivative **7** could be also prepared from **4** which disproportionates in MeOH (24 h, room temperature) to iodo acid **5** and iodoxy compound **7**. Evaporation of the solvent gave a yellow powder, which was dissolved in water. The water solution was extracted four times with ethyl ether. In the ethyl ether phase, we found iodo acid **5**, which had melting point and spectral properties that agreed with synthetic **5** (see above). The aqueous phase was lyophilized to give a white powder that was identical with synthetic **7** by TLC on silica gel (R_f = 0.70, MeOH).

Kinetic Studies. The straightforward equipment and methods applied to the kinetics of PNPDPP cleavage have already been described.[34] The results are presented graphically in Figure 2 and discussed above. Individual PNPDPP reactions were generally followed to >90% completion and showed good first-order kinetics ($r > 0.999$). Reproducibilities of rate constants were better than ±4% in duplicate runs.

Disproportionations of **1**, **2**, and **4** were followed by analytical HPLC. In a typical experiment, a 0.01 M solution of the iodoso derivative in pH 8.0 aqueous solution was stirred with a magnetic stirrer. An aliquot was taken, acidified to pH 5.5, diluted with HPLC-grade methanol, and submitted to analysis. HPLC employed a Waters Associates system consisting of two Model 6000 solvent delivery modules, a Model U6K injector, a Model 660 solvent programmer, a Model 440 absorbance detector, and a Waters data module. The HPLC column used was a 25-cm × 4.6-mm Alltech C18 5-μm reversed-phase column, operated at 300 psig, with a solvent mixture of 95% methanol (Baker, HPLC grade) and 5% distilled water, with a flow rate of 0.5 mL/min and UV detection at 254 nm. The retention times of **4**, **5**, and **7**, under these conditions, are included in ref 27. Similarly, the retention times of *o*-iodobenzoic acid, **1**, and the iodoxy derivative are 3.97, 5.82, and 6.27 min, respectively. In the parent iodoxolone series, the retention times were (*Z*)-3-iodopropenoic acid, 3.65 min; **2**, 5.60 min; and the iodoxy derivative, 5.75 min. Quantitative HPLC analytical studies as a function of time gave concentration data from which the disproportionations of **1**, **2**, and **4** were found to be second order. The derived rate constants and half-lives are given in the Results[28] and Discussion section. Complete details and plots of $1/C_0$ versus time will appear in the Ph.D. Thesis of B. Wilk.

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Supplementary Material Available: Tables of Cartesian coordinates for the species **1**, **1-O⁻**, **4**, and **4-O⁻** (2 pages). Ordering information is given on any current masthead page.