Experimental determination of the gas phase proton affinities of the conjugate base anions of 2-iodoxybenzoic acid (IBX) and 2-iodosobenzoic acid (IBA)†‡

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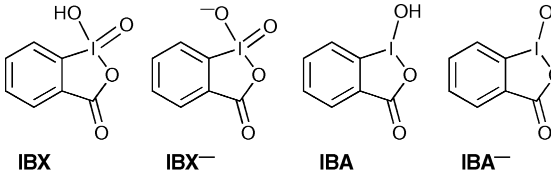
The gas phase anion proton affinities of the periodinane anions IBX^- and IBA^- were examined using mass spectrometry-based experiments, and estimated as 1300 ± 25 and 1390 ± 10 kJ mol^{-1}, respectively. The experimental results were supported by theoretical calculations, which yielded proton affinities of 1336 and 1392 kJ mol^{-1} for IBX^- and IBA^- respectively, at the B3LYP/aug-cc-PVDZ level of theory.

Introduction

Despite the widespread use of 2-iodoxybenzoic acid (IBX, Scheme 1) as an oxidant in organic synthesis,[1] its pK_a was unknown until a recent experimental and theoretical study.[2] In that work, theoretical calculations were also used to predict the gas phase anion proton affinities [defined as the $\Delta_r H$ of eqn (1)] of the deprotonated forms of IBX (denoted IBX^-), and its reduced form, 2-iodosobenzoic acid (denoted IBA^-, Scheme 1). Very similar anion proton affinities were reported for both species (1408 kJ mol^{-1} and 1405 kJ mol^{-1} respectively, at the B3LYP/LANL2dz+p level).[2]

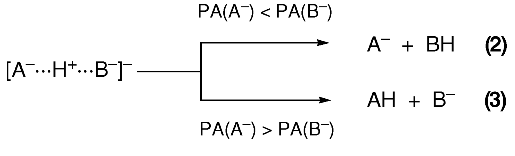
$$AH \rightarrow A^- + H^+ \quad \text{proton affinity}(A^-) = \Delta_r H \qquad (1)$$



Scheme 1 IBX, IBA and their conjugate base anions.

However, these results seem counterintuitive, as the anion proton affinity of IBX^- is expected to be less than that of IBA^- due to the resonance stabilization afforded by the additional oxygen atom in the former (Scheme 1). For example, the series of sulfur oxyanions follow the expected trends in gas phase acidity with increasing resonance stabilization *i.e.* $MeSO_2(OH)$ (strongest acid) > $MeSO(OH)$ > $MeS(OH)$ (weakest acid).[3]

These observations prompted closer investigation of the theoretical data in the previous work, which revealed an error in the quoted B3LYP/LANL2dz+p proton affinity of IBX^- due to incorrect addition of zero-point vibrational energy.[2] The reported value should have been 1346 kJ mol^{-1}, and not 1408 kJ mol^{-1}. This revised value is in much closer agreement with expectations *i.e.* the proton affinity of IBX^- (1346 kJ mol^{-1}) is lower than that of IBA^- (1405 kJ mol^{-1}), meaning that IBX is a stronger acid than IBA. However, the earlier calculations cannot be considered definitive, so it seemed critical to determine the proton affinities of IBX^- and IBA^- experimentally, and to recalculate their proton affinities at higher levels of theory in light of the new experimental results. Here we report such studies. The experimental measurements used a combination of mass spectrometry-based experiments in a quadrupole ion-trap[4] involving ion–molecule reactions and Cooks' kinetic method.[5,6] The latter experiments involved examining the competitive fragmentation of a series of proton-bound dimers containing either IBX^- or IBA^- and a reference base of known proton affinity [eqn (2) and (3); Scheme 2]. For example, the relative anion proton affinities of IBX^- and A^- can be established by fragmentation of the proton-bound dimer $[IBX^- \cdots H^+ \cdots A^-]^-$ to determine the relative abundances of the competitive dissociation pathways to form IBX^- and A^-.[5,6] Here we employ the kinetic method in its simplest form, based on the assumption that difference in entropy between the two competitive dissociation channels is negligible. A more detailed study would require the effect of collisional energies on branching ratios to be examined in order to investigate this,[5] but this is difficult in the ion-trap instrument and beyond the scope of the present work.



Scheme 2 Relative proton affinities by Cooks' kinetic method.

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‡ Electronic supplementary information (ESI) available: Mass spectra for fragmentation of each of the proton-bound dimers mentioned in Table 1. Calculated energies and cartesian coordinates for each of the species mentioned in the text at the B3LYP/aug-cc-PVDZ level. See DOI: 10.1039/b803452d

Results and discussion

The simplest way to determine the relative proton affinities of the anions IBX^- and IBA^- is to examine the fragmentation of their proton-bound dimer, *i.e.* $[IBA^- \cdots H^+ \cdots IBX^-]^-$, which was readily formed upon electrospray ionization of an H_2O–CH_3CN solution containing both IBX and IBA. Collision-induced dissociation of the proton-bound dimer $[IBX^- \cdots H^+ \cdots IBA^-]^-$ resulted in the observation of only IBX^-, clearly highlighting that IBA^- has a higher proton affinity than IBX^- (Fig. 1a, Scheme 2).

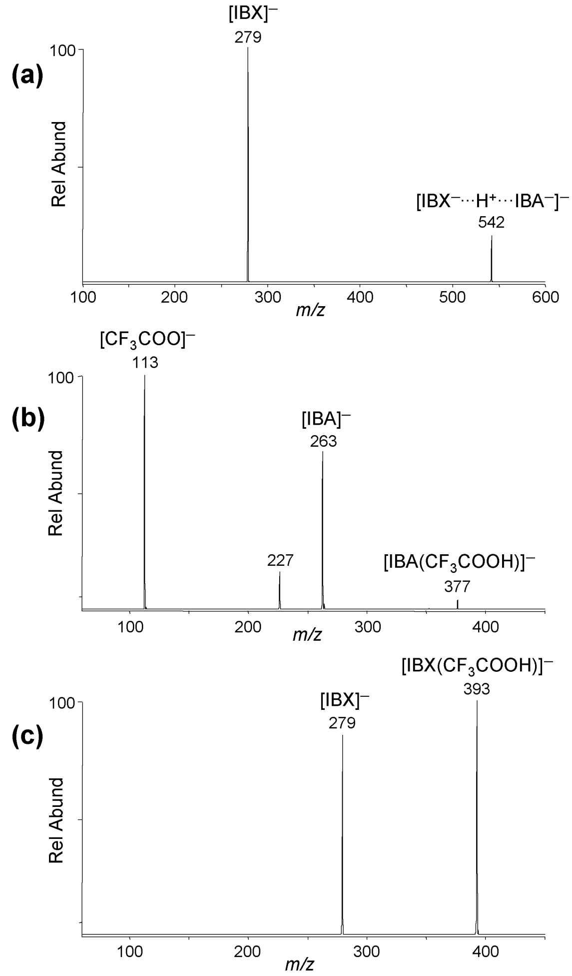

Fig. 1 (a) Fragmentation of the proton-bound dimer $[IBA^- \cdots H^+ \cdots IBX^-]^-$ (*m/z* 542) give IBX^- (*m/z* 279). No IBA^- (*m/z* 263) was observed; (b) ion–molecule reaction of IBA^- (*m/z* 263) with CF_3COOH to give CF_3COO^- (*m/z* 113). The peak at *m/z* 227 is assigned to $[(CF_3COO)CF_3COOH]^-$ formed in a secondary association reaction between product CF_3COO^- and CF_3COOH; and (c) ion–molecule reaction of IBX^- (*m/z* 279) with CF_3COOH to give $[(IBX)CF_3COOH]^-$ (*m/z* 393). No proton transfer to give CF_3COO^- (*m/z* 113) was observed.

In order to establish quantitative anion proton affinities for IBX^- and IBA^-, we next examined their gas-phase reactivity with compounds of known anion proton affinity. Since the previous calculations had predicted anion proton affinities of 1346 kJ mol^{-1} and 1408 kJ mol^{-1} for IBX^- and IBA^- respectively,[2] we examined their ion–molecule reactions with the strong acid trifluoroacetic acid, $PA(CF_3CO_2^-) = 1355 \pm 12$ kJ mol^{-1},[3] which lies between these values. Fig. 1b and c show the ion–molecule reactions of mass selected IBX^- and IBA^- with trifluoroacetic acid. While IBX^- does not react by proton transfer [instead undergoing only a clustering reaction, Fig. 1c, eqn (4)], IBA^- reacts by proton transfer to form $CF_3CO_2^-$ and neutral IBA [Fig. 1b, eqn (5)]. While the observation of clustering for IBX^- does not provide a strict upper limit for the proton affinity of IBX^-, the complete lack of proton transfer is consistent with $PA(IBX^-) < PA(CF_3CO_2^-)$, which is further supported by additional experimental data presented below. This establishes the following anion proton affinity order: $IBA^- > CF_3CO_2^-$ (1355 ± 12 kJ mol^{-1}) $> IBX^-$. These results are consistent with the CID data on the proton-bound dimer $[IBA^- \cdots H^+ \cdots IBX^-]^-$ discussed above, which indicated IBA^- was a stronger base than IBX^- (*i.e.* higher proton affinity). They are also consistent with the revised theoretical predictions from the previous work.[2]

$$IBX^- + CF_3CO_2H \rightarrow [IBX^-(CF_3CO_2H)]^- \qquad (4)$$

$$IBA^- + CF_3CO_2H \rightarrow IBAH + CF_3CO_2^- \qquad (5)$$

Cooks' kinetic method was employed in order to narrow down the anion proton affinities of IBX^- and IBA^- further.[5,6] A series of proton-bound dimers were generated by electrospray of IBX or IBA together with reference compounds with known anion proton affinities (Table 1).[3] The resulting proton-bound dimers were subjected to CID and the relative yields of product anions were determined to provide insight into the relative proton affinity of the two species. For example, if the fragmentation of $[IBX^- \cdots H^+ \cdots A^-]^-$ gave only IBX^-, then the proton affinity of IBX^- is less than that of A^-. Alternatively, if only A^- is observed, then the proton affinity of IBX^- is higher than that of A^-.

The results of the CID spectra on a range of proton-bound dimers are summarized in Table 1, and relevant spectra are included in the Supplementary Information‡. In a few cases dehydration of the proton bound dimer was observed to be in competition with dissociation (*e.g.* HSO_4^- with IBX^- and $H_2PO_4^-$ with IBX^- and IBA^-, see Supplementary Information‡) but these

Table 1 Results from Cooks' kinetic method experiments for dissociation of proton bound dimers between IBX^- or IBA^- and reference bases (A^-) of known anion proton affinity.[a] Branching ratios are reported as $\ln(A^-/B^-)$ where A^- corresponds to the intensity of the reference base peak and B^- corresponds to the intensity of either IBX^- or IBA^-[b]

Acid, AH	PA (A^-)	$\ln(A^-/IBX^-)$	$\ln(A^-/IBA^-)$
$CF_3SO_2(OH)$	1278 ± 9	>5	n/a
H_2SO_4	1282 ± 13	>5	n/a
$2,4\text{-}(NO_2)_2C_6H_3OH$	1323 ± 9	−4.7	n/a
$C_3F_7CO_2H$	1347 ± 9	−1.4	>5
CF_3CO_2H	1355 ± 12	<−5	>5
p-$(NO_2)C_6H_4OH$	1372 ± 9	<−5	>5
H_3PO_4	1383 ± 21	<−5	3.7
$(CF_3)_3COH$	1387 ± 9	n/a	2.5
o-$(NO_2)C_6H_4CO_2H$	1388 ± 9	n/a	1.4
p-CN-C_6H_4OH	1390 ± 9	n/a	−0.7
p-CHO-C_6H_4OH	1393 ± 9	n/a	−2.6
m-$(NO_2)C_6H_4OH$	1399 ± 9	n/a	<−5
$C_6H_5CO_2H$	1423 ± 9	n/a	<−5

[a] Anion proton affinities (kJ mol^{-1}) are from ref. 3. [b] Mass spectra are included in the supporting information‡.

side reactions are not expected to alter interpretation of the experimental results.

The experiments indicate that the proton affinity of IBX$^-$ is in the range of 1280–1320 kJ mol^{-1}, and that of IBA$^-$ of 1385–1395 kJ mol^{-1}. The proton affinity range for IBX$^-$ was difficult to narrow down further experimentally due to the absence of suitable reference bases of appropriate proton affinity and/or difficulties in forming the required proton bound dimers. For example, we have attempted to form proton bound dimer complexes with 2,4,6-trinitrophenol (anion proton affinity = 1298 ± 9 kJ mol^{-1}) and with HI (1315 ± 1 kJ mol^{-1}), but were not successful. In addition, the results for proton bound dimers of IBX$^-$ with 2,4-$(NO_2)_2C_6H_3O^-$ and $C_3F_7CO_2^-$ do not exhibit smooth changes in branching ratios with proton affinity (Table 1). This discrepancy might be due to limitations in the assumption of negligible differences in entropy between the competing dissociation channels.[5,6] However, the results for IBX$^-$ with 2,4-$(NO_2)_2C_6H_3O^-$ are clearly consistent with PA(IBX$^-$) < PA(2,4-$(NO_2)_2C_6H_3O^-$), and so an upper limit of ~ 1320 kJ mol^{-1} is adopted for PA(IBX$^-$).

The experimental ranges described above suggest estimates for the proton affinity of IBX$^-$ as 1300 ± 25 kJ mol^{-1} and for IBA$^-$ as 1390 ± 10 kJ mol^{-1}. These estimates are in reasonable agreement with the theoretical predictions from the previous study of 1346 and 1406 kJ mol^{-1}, respectively.[2]

The new experimental data prompted additional theoretical calculations, which are summarized in Table 2 and detailed in the supporting information‡.[7–9] Gas-phase proton affinities were calculated for IBX$^-$ and IBA$^-$ at the B3LYP level using a number of different basis sets.

In addition, calculations were also carried out for the test molecule IO$^-$, for which the proton affinity has been experimentally determined as 1480 ± 8 kJ mol^{-1}.[3] As expected, calculations on the test molecule IO$^-$ indicated that the use of diffuse functions is necessary for reasonable agreement between experiment and theory (Table 2).

Both IBX$^-$ and IBA$^-$ have multiple oxygen sites at which protonation might conceivably occur (Scheme 1), and the calculated proton affinity of each of the possible protonation sites at the B3LYP/aug-cc-PVDZ level is shown in Fig. 2. The calculations predicted the oxygen *trans* to the carboxylate group to be the most basic site for both species, and the calculated values presented in Table 2 refer to this site. The LANL2DZ**++ and aug-cc-PVDZ calculations (both involving diffuse functions) give good agreement with experimental proton affinities for both IO$^-$ and IBA$^-$. For IBX$^-$, the calculated values using the LANL2DZ**++ and aug-cc-PVDZ basis sets are both slightly higher than the experimental range, but still in reasonable agreement with the experimental data.

Table 2 Calculated gas-phase anion proton affinities (kJ mol^{-1}) for IBX$^-$, IBA$^-$ and the test molecule IO$^-$. Experimental data are included for comparison

Basis Set	IO$^-$	IBX$^-$	IBA$^-$
LANL2DZ*	1530	1346[a]	1406[a]
LANL2DZ**++	1489	1322	1383
cc-PVDZ	1568	1384	1445
aug-cc-PVDZ[c]	1476	1336	1392
Experiment	1480 ± 8[b]	1300 ± 25	1395 ± 15

[a] From previous work, see ref. 2. [b] Experimental data from ref. 3. [c] Cartesian coordinates and energies are included in the supporting information‡.

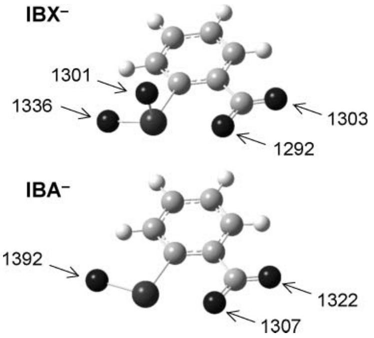

Fig. 2 Calculated structures of the conjugate base anions of IBX (upper) and IBA (lower). Calculated proton affinities (in kJ mol^{-1}, at the B3LYP/aug-cc-pVDZ level) for each of the oxygen sites are shown.

Conclusions

In conclusion, the first experimental investigations into the proton affinities of IBX$^-$ and IBA$^-$ indicated proton affinities of 1300 ± 25 kJ mol^{-1} and 1390 ± 10 kJ mol^{-1}, respectively. Calculated proton affinities are consistent with the experimental data, with predicted values of 1336 and 1392 kJ mol^{-1}, respectively, at the B3LYP/aug-cc-PVDV level. Both theory and experiment suggest that the proton affinity of IBX$^-$ is at least 60 kJ mol^{-1} lower than that of IBA$^-$, as expected based on the increased resonance stabilization in the former.

Future experiments will examine the gas-phase reactivity of IBX$^-$ with a range of neutral reagents relevant to its condensed phase applications. For example, preliminary experiments indicate that IBX$^-$ is unreactive towards methanol, perhaps due to the absence of the I–OH moiety in the deprotonated form that has been implicated in the reaction of neutral IBX with alcohols.[10]

The recent flurry of developmental work into new periodinane oxidation systems, and specifically IBX,[11] for tuning desirable physical properties such as solubility, reactivity or functional group compatibility for synthetic applications, makes physicochemical investigations like those reported here valuable aids to the intelligent design of synthetic reagents.

Experimental

Mass spectrometry

Experiments were carried out using a commercially available quadrupole ion trap mass spectrometer equipped with an electrospray ionization source (Finnigan-MAT model LCQ, San Jose, CA, USA). Solutions of IBX and IBA were made in 1 : 1 H_2O–CH_3CN solution. For ion–molecule reactions, the IBX or IBA was introduced into the gas phase by electrospray and the trifluoroacetic acid was injected directly into the QIT *via* the ion-molecule reaction line, as described previously.[4] Cooks' kinetic method experiments were performed by mixing solutions of IBX or IBA with acids of known anion proton affinity, and then subjected to electrospray ionization.[5] The mixed proton bound dimers were mass selected and subjected to collision induced dissociation with the helium bath gas. Specific collisional activation conditions were: normalized collision energy 16%, mass selection window 3 m/z units.

Theoretical calculations

Calculations were performed using the Gaussian03 program.[7] Calculations were carried out using the aug-cc-PVDZ all-electron basis set for H, C and O and the aug-cc-PVDZ-pp basis set and associated pseudopotentials for I, and basis sets were obtained from the EMSL Basis Set Exchange.[8] Geometry optimizations were performed using density-functional theory with the Becke 3-parameter Lee–Yang–Parr hybrid functional (B3LYP).[9]

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