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Total Synthesis and Characterization of 7-Hypoquinuclidonium Tetrafluoroborate and 7-Hypoquinuclidone BF3 Complex

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Total Synthesis and Characterization of 7-Hypoquinuclidonium Tetrafluoroborate and 7-Hypoquinuclidone BF₃ Complex

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ABSTRACT: Derivatives of the fully twisted bicyclic amide 7-hypoquinuclidone are synthesized using a Schmidt-Aubé reaction. Their structures were unambiguously confirmed by X-ray diffraction analysis and extensive spectroscopic characterization. Furthermore, the stability and chemical reactivity of these anti-Bredt amides are investigated. 7-hypoquinuclidonium tetrafluoroborate is shown to decompose to a unique nitrogen bound amide-BF₃ complex of 7-hypoquinuclidone under anhydrous conditions and to react instantaneously with water making it one of the most reactive amides known to date.

INTRODUCTION

The importance of the amide bond cannot be overstated.¹ Typical amides are planar structures,² however, amide bonds can be highly twisted such as in bicyclic bridgehead lactams.³ The distortion of the orbitals from planarity and the pyramidalization of the nitrogen from sp² toward sp³ dramatically affect the stability and reactivity^{3,4} of anti-Bredt amides.⁵ In 2006, our group published the first unambiguous synthesis and characterization of 2quinuclidonium tetrafluoroborate 1 (Figure 1).⁶ Most recently Kirby and co-workers reported on the synthesis and characterization of the "most reactive" twisted amide, an 1-aza-2-adamantone HBF₄ salt $\mathbf{2}$,⁷ which provoked us to explore the synthesis of an even more reactive amide.



Figure 1. Stoltz's 2-Quinuclidonium tetrafluoroborate (1), Kirby's "most reactive amide" 2 and Hall's attempted synthesis of 7-hypoquinuclidone 4 from piperidine-4-carboxylic acid (3).

Of interest to us was a 1958 paper, in which Hall failed to synthesize 7-hypoquinuclidone 4 by heating piperidine-4-carboxylic acid (3) in a free flame (Figure 1). Instead, sublimation of the amino acid was observed.⁸ The highly strained structure of a [2.2.1] bridged bicyclic lactam was ACS Paragon Plus Environment

also proposed as an intermediate in a model system toward the synthesis of perophoramidine.⁹ Most recently, the structure, energetics and protonation of 7hypoquinuclidone 4 were investigated by DFT calculations¹⁰ and the molecule has been suggested to be too strained to be isolated.^{10c}

RESULTS AND DISCUSSION

Based on the knowledge and experience in our research group with the synthesis of 2-quinuclidonium tetrafluoroborate 1, we proposed a synthesis of 7-hypoquinuclidone 4 using an intramolecular Schmidt-Aubé reaction¹¹ leading to ketoazide 8 as the key fragment (Scheme 1).



Scheme 1. Synthesis of protected piperidine 4-carboxylic acid methylester 9 - first proof for the existence of 7hypoquinuclidone 4.

Synthesis. The synthesis commenced from literature known cyclobutanone N,N-dimethylhydrazone 5¹², which was alkylated with TBS protected 2-bromoethanol (Scheme 1).^{13,14} The corresponding intermediate was fully deprotected under acidic conditions to afford hydroxy ketone 6 in 45% yield. Tosylation of the alcohol and substitution with sodium azide gave access to substrate 8 for the intramolecular Schmidt-Aubé reaction. Since it was uncertain, if this highly strained and fully twisted lactam 4.H+ would even exist, we decided to solvolyze this hypothetical intermediate 4.H+ in situ with methanol as the nucleophile. Moreover, the reaction was performed under Fischer esterification conditions to ensure protection of the corresponding amino acid, in case 4•H⁺ would have been hydrolyzed with traces of water. Thus, treatment of ketoazide 8 with triflic acid¹⁵ followed by solvolysis/esterification with methanol and tosyl protection of the amine furnished N-tosyl piperidine 4-carboxylic acid methyl ester (9) in 56% yield over 3 steps after column chromatography.¹⁶ It should be noted that the corresponding protected azetidine 10 was not observed at all (it would originate from migration of the other single bond in the Schmidt-Aubé reaction).17

With a first proof for the existence of 7-hypoquinculidone in hand, ketoazide **8** was treated with tetrafluoroboric acid in diethylether, which led to immediate gas evolution and precipitation of a colorless solid (97% mass recovery). NMR experiments revealed the presence of three species in a 77:15:12 ratio: the protonated amide 7-hypoquinuclidonium tetrafluoroborate $4 \cdot HBF_4$, the hydrolysis product **11** and, unexpectedly, the BF₃ complex of 7-hypoquinuclidone $4 \cdot BF_3$ (Scheme 2).



Scheme 2. Total synthesis of 7-hypoquinuclidonium tetrafluoroborate $4 \cdot HBF_4$ and 7-hypoquinuclidone BF_3 complex $4 \cdot BF_3$.

Since the formation of $4 \cdot BF_3$ was at first mysterious and somehow unexpected, we were wondering, if traces of BF₃ etherate are present in our commercial 50-54% HBF₄ solution, which would catalyze the Schmidt-Aubé reaction.¹⁸ The inherent instability of HBF₄ in acidic solutions was further supported by voltammetric investigations, which indicated decomposition of HBF₄ to a BF₃solvent complex and HF.¹⁹ To check this hypothesis, ketoazide **8** was subjected to two equivalents of BF₃ etherate instead of HBF₄ with the ultimate goal to selectively prepare $4 \cdot BF_3$. However, neither gas evolution nor consumption of the starting material was observed, even at room temperature. Subsequently, a catalytic amount of HBF₄ was added with the idea that the proton of the Brønsted acid would be formally released after formation

of product 4-BF₃. In contrast, the catalytic amount of acid was consumed instantaneously with concomitant gas evolution and precipitation of a solid. Thereafter, the reaction did not proceed any further without adding a stoichiometric amount of HBF₄ (two equivalents in total). After stirring overnight, we isolated instead of 4.BF3 the hydrolyzed amino acid 11 as the major product (73%) along with 15% of $4 \cdot HBF_4$ and a third unknown species (ca. 12%) according to ¹H-NMR spectroscopy.²⁰ When the spectrum was recorded again the next day, the later two species had converted to 11 in a quantitative fashion. At this point, it was still unclear how 4.BF3 was formed, but we gained first evidence for the inherent instability of 4.HBF4 toward hydrolysis in dry CD3CN leading to the expected hydrolysis product isonipecotic acid tetrafluoroborate (11).

Proof of Structure and Spectroscopic Data. 7-Hypoquinuclidonium tetrafluoroborate (4•HBF₄) was isolated as a stable, colorless solid, which can be stored in a -40 °C freezer of a nitrogen filled glovebox for several weeks without decomposition. However, as soon as the solid is dissolved in any rigorously dried solvent, decomposition starts immediately, even upon handling in the dry atmosphere of a glovebox (N₂). For this reason, all of our attempts failed to grow single crystals of 4•HBF₄ via precipitation, recrystallization or vapor diffusion method between -40 °C and 23 °C. Fortunately, decomposition was slow enough to characterize 4•HBF₄ spectroscopically in CD₃CN solution by multinuclear ¹H-, ¹¹B-, ¹⁹F-, ¹³C-, ¹⁴N-, ¹⁵N-NMR spectroscopy in a J. Young NMR tube and as a solid by attenuated total reflectance infrared spectroscopy (ATR-IR, Table 1). By contrast, 4•HBF₄ was hydrolyzed instantaneously in the matrix of the fast atom bombardment high-resolution mass spectrometer (FAB-HRMS) and in the electrospray ionization chamber (ESI) of a linear ion trap mass spectrometer (LTQ-CID-MS). The mass spectra for 4•HBF₄ were identical to those recorded for the hydrolysis product **11**. A very characteristic 1:1:1 triplet at 7.76 ppm was observed for the NH⁺ group in the ¹H-NMR spectrum of **4**•**HBF**₄ (Figure 2) showing a ¹H-¹⁴N coupling (J = 63 Hz, I = 1, Table 1). This indicated a highly symmetric environment around the nitrogen, since otherwise the ¹H-¹⁴N splitting pattern would not be resolved due to significant quadrupolar line broadening.²¹



Figure 2. Detail of the ¹H-NMR spectrum of $4 \cdot HBF_4$ showing the distinctive 1:1:1 triplet of the protonated amide.

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Table 1. Selected spectroscopic properties for twisted amides 4•HBF₄ and 4•BF₃ and for the hydrolysis product isonipecotic acid tetrafluoroborate (11).

Compound ^a	4•HBF ₄	4•BF ₃	11
$\delta^1 H$ of NH_x	7.76 (t, ¹ J _{1H14N} = 63 Hz)	-	6.90-6.12 (m, ¹ J _{1H14N} = ~55 Hz)
δ^{13} C of C=O	174.7	179.8	169.7
$\delta^{11}B$	-1.2 (s)	–0.3 (q, ¹ J _{11B19F} = 13.8 Hz)	-1.2 (s)
$\delta^{19}F$	–151.3 (s)	-154.9 (q, ¹ J _{19F11B} = 13.9 Hz)	–151.2 (s)
$\delta^{14}N$	34.8 (d, ¹ J _{14N1H} = 62.8 Hz)	39.3 (s)	-4.9 (m, ${}^{1}J_{14N1H}$ = not resolved)
$\delta^{15}N^b$	78.6 (¹ J _{15N1H} = ~88 Hz)	-	38.8 $({}^{1}J_{15N1H} = ~77 \text{ Hz})^{c}$
IR, v_{max} C=O, cm ⁻¹	1877 ^d	1860 ^d	1814 ^e

^a All NMR spectra were recorded in CD₃CN. ^b Due to the low abundance of this isotope, the chemical shifts and coupling constants were determined by ¹H-¹⁵N and ¹H{¹⁵N}-¹⁵N correlation experiments. ^c A vicinal proton coupling constant of ²J_{1H1H} = 10.8 Hz was observed. ^d Measured using an ATR-IR in an argon filled glovebox. ^e Neat film on a NaCl plate.

These findings for 4•HBF₄ were further confirmed by the observed doublets in the ¹⁴N- and ¹⁵N-NMR spectra (Table 1). The carbonyl infrared absorption band of **4**•**HBF**₄ was observed at 1877 cm⁻¹ (ATR), which is the highest value we have ever observed for an organic molecule, even higher than acid chlorides or anhydrides. This value suggests a rather short and strong C=O bond in a highly strained molecule. These conclusions were in line with our DFT calculations for the structure of 4•HBF₄ (see Table 21 in the SI).²² Moreover, since we did not observe any other C=O bands nor overlapping IR signals originating from the other two species (4.BF3 and 11), the recorded IR spectrum of 4•HBF₄ was evidence for high purity of the isolated crude solid after the reaction. The observed mixture in the ¹H-NMR spectrum of $4 \cdot HBF_4$, 4-BF₃ and 11 (Scheme 2) most likely resulted from decomposition by dissolving the solid in CD₃CN and in the time until the NMR spectra were recorded.

A single crystal of $4 \cdot BF_3$ suitable for X-ray diffraction analysis was grown over four weeks by slow diffusion of diethyl ether into a solution of the crude twisted amide $4 \cdot HBF_4$ in acetonitrile at -40 °C in the glove box (N₂). The crystal structure of $4 \cdot BF_3$ is depicted in Figure 3.



Figure 3. X-ray structure of 7-hypoquinuclidone BF_3 complex $4 \cdot BF_3$ (ellipsoids at the 50% probability level, oxygen = red,

nitrogen = blue, boron = pink, fluorine = yellow, carbon = dark gray, hydrogen = white).

In all our attempts to crystallize the protonated twisted amide 4•HBF₄, we could only isolate crystals of the BF₃ complex 4•BF₃, which apparently is the more stable compound of the two amides (Figure 3). To our knowledge, the BF3 complex of 7-hypoquinuclidone 4.BF3 is the first and only nitrogen bound BF3-amide complex reported to date. A single molecule of 4.BFa was observed in the unit cell of the crystal with a high degree of symmetry (mirror plane through the F-B-N-C=O axis). The compound clearly belongs among the most twisted amides with a torsion angle τ of 90.0°. The nitrogen is highly pyramidalized with an out-of-plane parameter χ_N of 69.8°, while the carbonyl carbon is exactly planar and sp² hybridized ($\chi_c = 0.0^\circ$). The observed length of the N-C(O) bond is 1.526 Å, 1.186 Å for the C=O bond and 1.606 Å for N-B bond, respectively. These parameters were all in close agreement to the calculated structure of **4**•BF₃ (see Table 21 in the SI and compare with parameters of other twisted amides and more calculated structures). Selected spectroscopic parameters of 4.BF3 are summarized in Table 1. The ¹³C chemical shift of the carbonyl group in 4-BF₃ is 5 ppm more downfield than in 4•HBF₄, which is also true for the ¹⁹F chemical shift at -154.9 ppm. In the later case, the ¹J coupling to ¹¹B (I =3/2) was observed as a 1:1:1:1 guartet with a coupling constant of 14 Hz.²³ The reverse coupling to ¹⁹F ($I = \frac{1}{2}$) was visible at -0.3 ppm as a 1:3:3:1 quartet in the ¹¹B-NMR spectrum, however without any coupling to ¹⁴N.²⁴ The carbonyl stretching vibration for 4.BF3 was observed at 1860 cm⁻¹, which is a slightly lower frequency than for 4•HBF₄. This trend is in line with a slightly longer C=O bond for 4.BF3 than for 4.HBF4 according to our DFT calculations (see Table 21 in the SI).

The formal hydrolysis product of $4 \cdot HBF_4$, isonipecotic acid tetrafluoroborate (11), was fully characterized by spectroscopic methods (Table 1) and the structure was unambiguously confirmed by X-ray diffraction analysis (see

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the SI). As for the protonated twisted amide $4 \cdot HBF_4$, spin couplings of ${}^{1}H^{-14}N$ and ${}^{1}H^{-15}N$ were observed with coupling constants of 55 Hz and 77 Hz, respectively. Remarkably, the C=O IR stretching frequency at 1814 cm⁻¹ (NaCl) was rather high for a carboxylic acid.

Chemical Behavior. As described earlier in this paper, the protonated amide $4 \cdot HBF_4$ was much more sensitive to nucleophiles than the BF₃ complex $4 \cdot BF_3$. $4 \cdot HBF_4$ decomposed very quickly in solution, even in rigorously dried solvents and with careful handling in the glovebox. For this reason, the NMR spectra of dissolved $4 \cdot HBF_4$ had to be recoded as fast as possible, since the signals corresponding to $4 \cdot HBF_4$ disappeared very quickly and several new species were formed over time. In contrast, solutions of the corresponding BF₃ complex $4 \cdot BF_3$ were fairly stable according to NMR spectroscopy. This raised the question, if the BF₃ complex $4 \cdot BF_3$ is the decomposition product of the very labile amide $4 \cdot HBF_4$ in dry solution, which would also explain, why we could grow crystals of $4 \cdot BF_3$ out of a solution of $4 \cdot HBF_4$.

To answer these questions, we studied the decomposition and reactivity of both twisted amides $4 \cdot BF_3$ and $4 \cdot HBF_4$ in CD₃CN in the presence or absence of D₂O over time using a series of ¹H-NMR measurements with 1,3,5-trichlorobenzene as the internal standard (Scheme 3, see the SI for more details).



Scheme 3. Reactivity for **4**•**HBF**₄ and **4**•**BF**₃ in solution and determination of their half-lives.

4•**BF**₃ was fairly stable in wet CD₃CN with a half-life of 87 minutes (9.6 equivalents of D₂O, 10.6 μM) yielding a complex mixture of products along with amino acid **11** (Scheme 3). By contrast, the protonated amide **4**•**HBF**₄ was hydrolyzed instantaneously upon addition of 5 equivalents of D₂O ($t_{1/2} = <1 \text{ min}, 87.4 \mu$ M) to give amino acid **11** as the major product. Compared to the half-lives of 2quinuclidonium tetrafluoroborate **1** ($t_{1/2} = 135 \text{ min}, 84 \mu$ M, 5 equiv)^{6a} and *Kirby's* "most reactive amide" **2** ($t_{1/2} = 8.4$ min, 84 μ M, 5 equiv D₂O, Figure 1),⁷ 7hypoquinuclidonium tetrafluoroborate $4 \cdot HBF_4$ is now the most reactive twisted amide prepared to date. In addition, $4 \cdot HBF_4$ decomposed in dry CD₃CN with a half-life of 119 minutes (117 μ M). At the same time, saturation growth of the BF₃ complex $4 \cdot BF_3$ was observed over time, which strongly indicated that $4 \cdot BF_3$ is indeed formed from $4 \cdot HBF_4$ in dry CD₃CN solution. It should be noted that several other unidentified species were observed together with $4 \cdot BF_3$. However, amino acid 11 was not detected at all due to the absence of water.

When the twisted amides 4•HBF₄ and 4•BF₃ and the amino acid 11 were characterized by FAB-HRMS, we found identical spectra due to fast hydrolysis in the matrix, but also a common dehydration fragment with m/z 112.1 corresponding to the protonated twisted amide 4•H⁺ or its ring-chain tautomer as an oxocarbonium ion (Scheme 4). Since we previously observed dehydration of the hydrolyzed twisted amide 1 (Figure 1) via collision induced dissociation (CID),^{6b} this raised the question if **11** was dehydrated to 4•H⁺ by FAB ionization in the matrix or in the gas phase. To investigate this, we isolated the ammonium ion of 11 with m/z 130.1 in the ion trap of the LTQ-MS. Upon collisional excitation (MS²-CID), we did indeed observe dehydration giving an ion $4 \cdot H^+$ with m/z 112.1 in the mass spectrum (see the SI for the spectra). When isolation and excitation of 4.H+ was continued in a multistage MS experiment (MS³), a formal loss of CO (M-28) corresponding to an ion with m/z 81.4 was observed.



Scheme 4. Gas phase and thermal reactivity of isonipectotic acid derivatives.

Inspired by Kirby's observation for thermal cyclization to adamantane type twisted amides in the gas phase,⁷ we attempted to cyclize amino acid **11** and the commercially available Boc protected derivative **12** by gas chromatography (Scheme 4). However, all attempts failed and no ions were observed at all.

Definition of Bending Angle ξ . We observed significant bending of the carbonyl oxygen towards the nitrogen in the crystal structure of $4 \cdot BF_3$ (Figure 3) and we found that this phenomenon was significantly underestimated in our calculated structure of $4 \cdot BF_3$ (see Table 21 in the SI). Since there wasn't any parameter available in the literature

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Figure 4. Definition of the bending angle ξ and the dominant orbital interactions of the p-type lone pair of the C=O oxygen.

In 1985, Bürgi and Schmidt investigated C=O bending in lactones and lactams for the first time based on X-ray structures and molecular orbital calculations.²⁶ An anomeric effect was proposed to explain this phenomenon, which involves destabilizing interactions of the p-type lone pair at oxygen with the bonding σ (C-C) orbital and favorable overlap with the antibonding σ^* (C-N) orbital (Figure 4). Thus, C=O bending will reduce the former interaction and increase the later one.²⁶ At the same time, C=O bending is an early sign of C-N bond breakage leading to an oxocarbonium ion similar to $4 \cdot H^+$ (Scheme 4) with concomitant C-N bond elongation.²⁶ In line with our own data (see Table 21 in the SI), significant deviations of calculated ξ values were observed compared to X-ray structures by Bürgi²⁶ and others.^{10c, 27}

Since C=O bending is a significant deformation of the amide bond in anti-Bredt lactams and an additional measure for their stability, we suggest to use the Bürgi-Dunitz-Winkler parameters (χ_C , χ_N , τ , ξ) to describe twisted amides in the future.

CONCLUSIONS

Almost 60 years after Hall's first attempt to prepare 7hypoquinuclidone 4,8 we have successfully accomplished the first total synthesis and complete characterization of the protonated twisted amide 4.HBF4 and its BF3 complex 4-BF₃. The use of a Schmidt-Aubé reaction proved again to be key for success.^{6a} Moreover, the stability and reactivity of both 4•HBF₄ and 4•BF₃ were thoroughly investigated in solution and in the gas phase. These studies revealed that 4•HBF₄ is to our knowledge the most reactive amide prepared to date with a half-life of less than one minute in the presence of water. The reverse reaction to 4•H⁺ was rendered possible in the gas phase by formal dehydration of isonipecotic acid 11 using FAB or CID excitation. Since C=O bending contributes to the stability of twisted amides²⁶ and is still difficult to predict by DFT calculations, 10c, 26, 27 a novel bending angle ξ was defined as

an addition to the already existing Dunitz-Winkler parameters.⁵ Looking ahead, the limits are still open for the synthesis of more or less reactive but structurally unique twisted amides.

METHODS

Standard methods were used for the preparation, isolation, and analysis of all new compounds (for experimental details and complete characterization see the SI).

Preparation of $4 \cdot HBF_4$ and Crystallization of $4 \cdot BF_3$ from keto azide 8. To a solution of 8 (52.0 mg, 0.37 mmol, 1.0 equiv) in Et₂O (0.75 mL) was added at 0 °C HBF₄ (0.10 mL, 0.71 mmol, 1.9 equiv, 50-54% wt/wt in Et₂O). Gas evolution was observed immediately. After stirring for 1 h at room temperature, the starting material was fully consumed and a colorless precipitate had been formed. The solvent was decanted off with a syringe under argon. The solids were washed with Et₂O (3 x 0.8 mL) and dried under high vacuum to afford crude $4 \cdot HBF_4$ (72.0 mg, 97% mass recovery) as a colorless solid. Slow diffusion of Et₂O into a solution of the crude product in acetonitrile at -40 °C over four weeks yielded one single crystal of $4 \cdot BF_8$ (2.0 mg, 3%) as a colorless needle.

ASSOCIATED CONTENT

Experimental procedures, characterization data, crystallographic information files, calculated geometries, and details of kinetic measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) Neither gas evolution nor conversion was observed when 1.5 equivalents of trifluoroacetic acid were used without any triflic acid.

(16) Traces of the protected dimer and trimer of 9 were detected by LC-MS in the crude reaction mixture (see the SI for the spectra), which was an evidence for the polymerizability of 4. Compare with reference (8).

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(22) The calculated bond length for N-C(O) in $4 \cdot HBF_4$ is 1.613 Å, which is longer than in $4 \cdot BF_3$ (measured 1.526 Å and calculated 1.534 Å, respectively).

(23) Unresolved coupling of ¹⁹F to ¹⁰B (l = 3) was observed as well (a septet would be expected). However, the minor signal was overlapping with the more intense peak originating from ¹¹B coupling (ca. 1/3 intensity of the major peak).

(24) The absence of ¹¹B-¹⁴N coupling is in line with heteronuclear NMR experiments on trimethylamine-boron trihalide complexes: Hall Clippard, P.; Cooper Taylor, R. *Inorg. Chem.* **1969**, *8*, 2802.

(25) The sum of the three bond path angles CCN, OCC and OCN is 360°.

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