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Reaction of Selectfluor (F-TEDA-BF_4) with chloromethylated-DABCO monocation salts (X = BF_4, NTf_2) and other nitrogen bases (Et_3N; piperidine; basic ionic liquid); unexpected formation of symmetrical $[N-H-N]^+$ trication salts

Kenneth K. Laali *, Arezu Jamalian, Chunqing Zhao

Department of Chemistry, University of North Florida, 1 UNF Drive, Jacksonville, FL 32224, USA

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ABSTRACT

Selectfluor reacts with N-chloromethylated DABCO monocation BF_4 or NTf_2 salts in MeCN (rt to 80 °C) to give symmetrical $[N-H-N]^+$ trication salts. The same dimeric adducts are formed via the reaction of Selectfluor with Et_3N, piperidine, or a basic-IL (imidazolium with an alkyl-piperidine tether). The resulting stable salts were studied by multinuclear NMR, $^{15}N/^{1}H$ HMBC, electrospray-MS, and by chemical reactivity. This hitherto unreported reactivity behavior contrasts the well documented 'transfer fluorination' by Selectfluor to quinuclidine and the quinuclidinic nitrogen of cinchona alkaloids.

With its broad-based application as an efficient and selective N–F fluorinating agent and as mediator or catalyst for oxidative functionalizations,[1–3] Selectfluor (F-TEDA-BF_4) continues to remain in the spotlight as a valuable reagent and commodity in synthetic chemists' toolbox.[4] Rapid transfer-fluorination by Selectfluor to tertiary nitrogen sites in quinuclidine, pyridine, and 2,4,6-trimethoxypyridine at room temperature is documented in the literature,[5] and was applied to the development of enantioselective N–F fluorinating agents based on cinchona alkaloid.[6]

In the context of a project in our laboratory on the development and application of task-specific ionic liquids (ILs) we sought to develop a base-catalyzed fluorination method for certain enolizable ketones and diketones using Selectfluor **1**, and employing a piperidine-appended imidazolium-IL **2** in MeCN solvent (Fig. 1). A white solid precipitate appeared quickly and continued to increase on prolonged mixing and subsequent heating (80 °C). The same observations were made in the absence of the carbonyl compound, simply by mixing Selectfluor with **2** in MeCN.

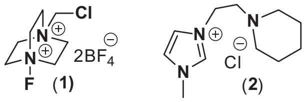

Figure 1. Selectfluor **1** and Basic-IL **2**.

When the basic-IL was replaced with piperidine slow formation of the white solid was again observed after overnight stirring at rt which increased upon further mixing at 80 °C. The formation of the same precipitate was observed by reacting **1** with Et_3N instead of piperidine (the reaction was allowed to continue at 80 °C for 2 days). The isolated solid precipitate had good solubility in water, and NMR studies were performed in D_2O. The ^1H NMR exhibited the usual methylene protons and the CH_2Cl signals observed for Selectfluor, but they were all upfield shifted. The ^{19}F NMR showed that the 46.7 ppm signal (N–*F* of Selectfluor) was no longer present and the ^{19}F spectra consisted only of BF_4 (δ −150.35/−150.36) along with a signal at δ −130.0 ppm.[7]

More material was recovered by removing MeCN under vacuum. The ^1H NMR spectra of the isolated crude residue showed it to be mainly the same compound, but signals stemming from the employed base were also present (Et_3N[8] moiety or piperidine moiety).

The ^{19}F NMR spectrum of the MeCN insoluble and MeCN soluble salts showed [BF_4] along with the signal at −130 ppm but in variable ratios.

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* Corresponding author. Tel.: +1 904 620 1503; fax: +1 904 620 3535.
E-mail address: kenneth.laali@UNF.edu (K.K. Laali).

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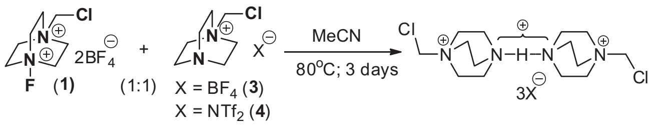

Figure 2. Reaction of Selectfluor with DABCO-monocation salts.

In subsequent work, the 1:1 reactions between Selectfluor and the monocations salts **3** and **4** were studied in MeCN.

The **1**+**3** mixture (1:1 molar ratio) gave the same white precipitate in higher yield (adduct **a**) with identical ^{1}H and ^{13}C NMR to those of earlier cases, consistent with a symmetrical dimeric adduct (Fig. 2). Stacked plots showing gradual proton shielding in the sequence Selectfluor < adduct < **3** and Selectfluor < adduct < **4** (see Fig. 3). More of the white solid material was recovered by removal of solvent under vacuum (adduct **b**) with essentially the same ^{1}H and ^{13}C NMR but with slight variations in chemical shifts. The ^{19}F NMR showed the signals for BF_4 (major) along with the signal at −130 ppm (minor).

Collectively, the data suggested that less soluble adduct that precipitated out of MeCN and the more soluble adduct that was isolated after removal of solvent have the same cationic constitution, varying only in the 'make-up' of their counterions.

A similar reaction between **1** and the monocation salt **4** resulted in the formation of two structurally similar adducts, a brownish-white solid (adduct **c**) that precipitated out of MeCN, and a brown residue which was recovered after removing the solvent (adduct **d**). The two adducts exhibited the same ^{1}H and ^{13}C NMR spectra (with slight chemical shift variations due to counter ion effects). The ^{19}F NMR spectrum of adduct **d** exhibited resonances for BF_4 (−150.5/−150.4) and for CF_3 (−79.3) in 6 to 8 ratio, consistent with $[N(SO_2CF_3)_2][2BF_4]$. For adduct **c** however, the ratio suggested a complex counterion 'richer in BF_4' since the −150 ppm signal was considerably more intense than expected for $[N(SO_2CF_3)_2][2BF_4]$.

Since attempts to obtain suitable crystals for X-ray analysis from these adducts were unsuccessful, they were subjected to electrospray-MS analysis by direct infusion. Electrospray mass spectra of **1**, **3**, and **4** were also recorded for comparison. The significant ions detected by ES-MS and their assignments are shown in Chart 1. The ES-MS of parent Selectfluor **1** gave an intense *m*/*z* 267 ion and a cluster ion (at *m*/*z* 621.7). The BF_4-monocation salt **3** gave a prominent ion at *m*/*z* 161 and a two cation/one anion cluster (*m*/*z* 409/411), and the NTf_2-monocation salt **4** exhibited the

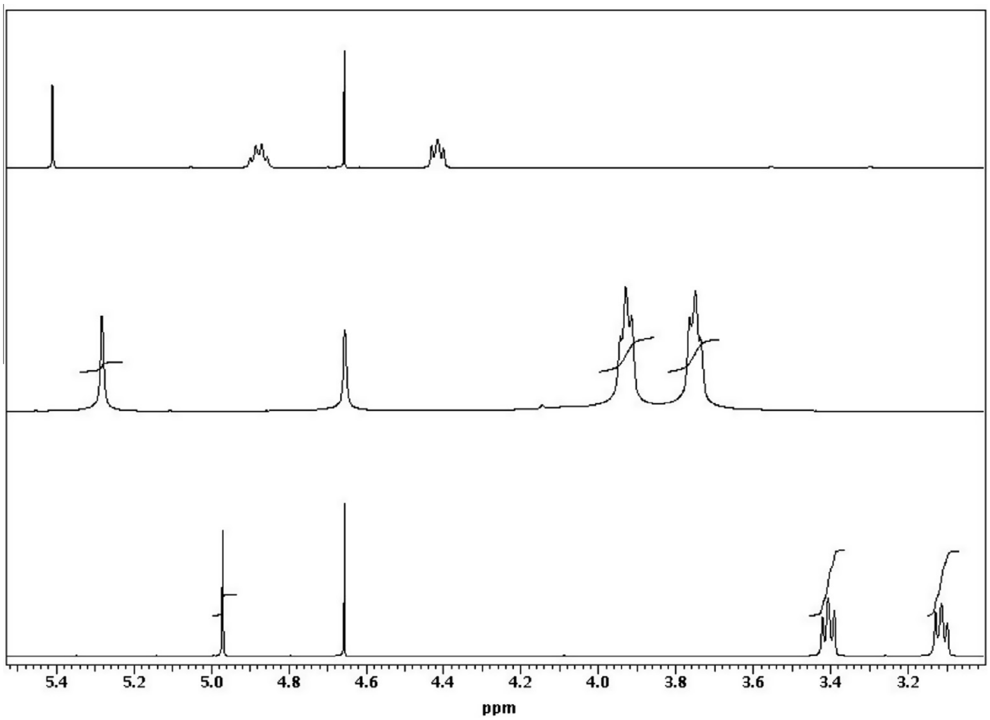

Figure 3. ^{1}H NMR stacked-plot; from top to bottom: Selectfluor (**1**); adduct **a** (**1**+**3**); DABCO-monocation salt (**3**); 4.65 ppm signal is H_2O in D_2O.

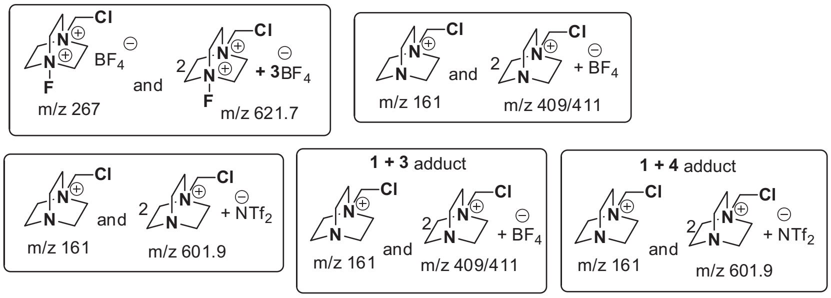

Chart 1. Significant ions detected by ES-MS for **1**, **3**, **4**, and **1**+**3** and **1**+**4** adducts.

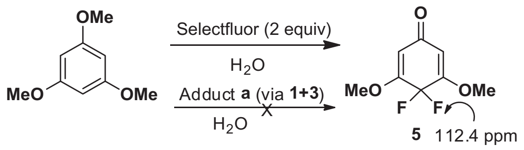

Figure 4. Control reaction with trimethoxybenzene (TMB).

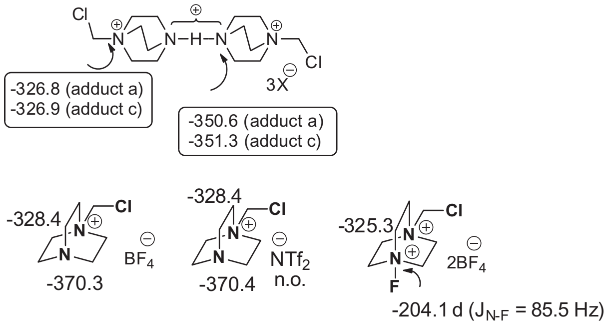

Chart 2. ^{15}N NMR data for the trication salts, monocation salts, and Selectfluor.

monocation (m/z 161) and a two cation-one anion cluster (m/z 601.9) Adducts **a**/**b** (via **1**+**3**) and **c**/**d** (via **1**+**4**) gave the same ions as those of **3** and **4**, respectively, (Chart 1).

Although NMR studies had pointed to cleavage of the N–F bond in the resulting adducts, confirmatory evidence was sought at this point based on chemistry. Reaction of two equivalents of Selectfluor with 1,3,5-trimethoxybenzene (TMB) in water as solvent reported by Banks et al.[9] leading to the difluoro compound **5** was selected for reactivity test (see Fig. 4).

In a control experiment using Selectfluor, compound **5** was formed in 78% yield (by NMR with the rest being unreacted TMB). However, when isolated adduct **a** was allowed to react with TMB under the same conditions, compound **5** was not detected.[10]

Returning to NMR studies, proton relaxation times (T1) were measured for parent **1**, monocation salts **2** and **3**, and for the isolated adducts in D_2O as solvent. It was anticipated that molecular motion in the dimeric adducts should diminish resulting in lower T1 values. However, the changes in relaxation times were not significant enough to reflect suppression of molecular motion in the larger, more sterically crowded, adducts.

To gain more insight into the adduct structures in comparison to those of Selectfluor **1** and the monocation salts **3** and **4**, they were studied by ^{15}N NMR and by $^{15}N/^{1}H$ HMBC (Chart 2). For the monocation salts **3** and **4**, ^{15}N NMR spectra could be recorded in either MeCN-d_3 or D_2O (see Supplementary material) and both ring nitrogens were detected (the nitrogen signal for [NTf_2] in **4** was not detected).[11] To our knowledge, ^{15}N NMR data for Selectfluor **1** have not been reported. To obtain natural abundance ^{15}N NMR spectrum for Selectfluor, longer pulse delay had to be employed in order to detect the N–F nitrogen (Fig. 5). The N-CH_2Cl was observed at −325.3 ppm and the N-F signal was detected at −204.15 ppm, appearing as a doublet with a J_{N-F} of 85.5 Hz.

Despite the fact that highly concentrated samples of the adducts had been prepared in D_2O for the ^{15}N NMR study, only the N-CH_2Cl nitrogens were observed in 1D ^{15}N NMR. This problem was overcome via $^{15}N/^{1}H$ HMBC spectra (Fig. 6 and Supplementary information) that also confirmed the relative assignment of the nitrogen signals (only the deshielded nitrogen signal gave a cross peak with CH_2Cl).

The combined data support the formation of symmetrical $[N-H-N]^+$ dimeric trication salts. There is a precedent for the formation of $[N-H-N]^+$ monocation salts of DABCO via the reaction of

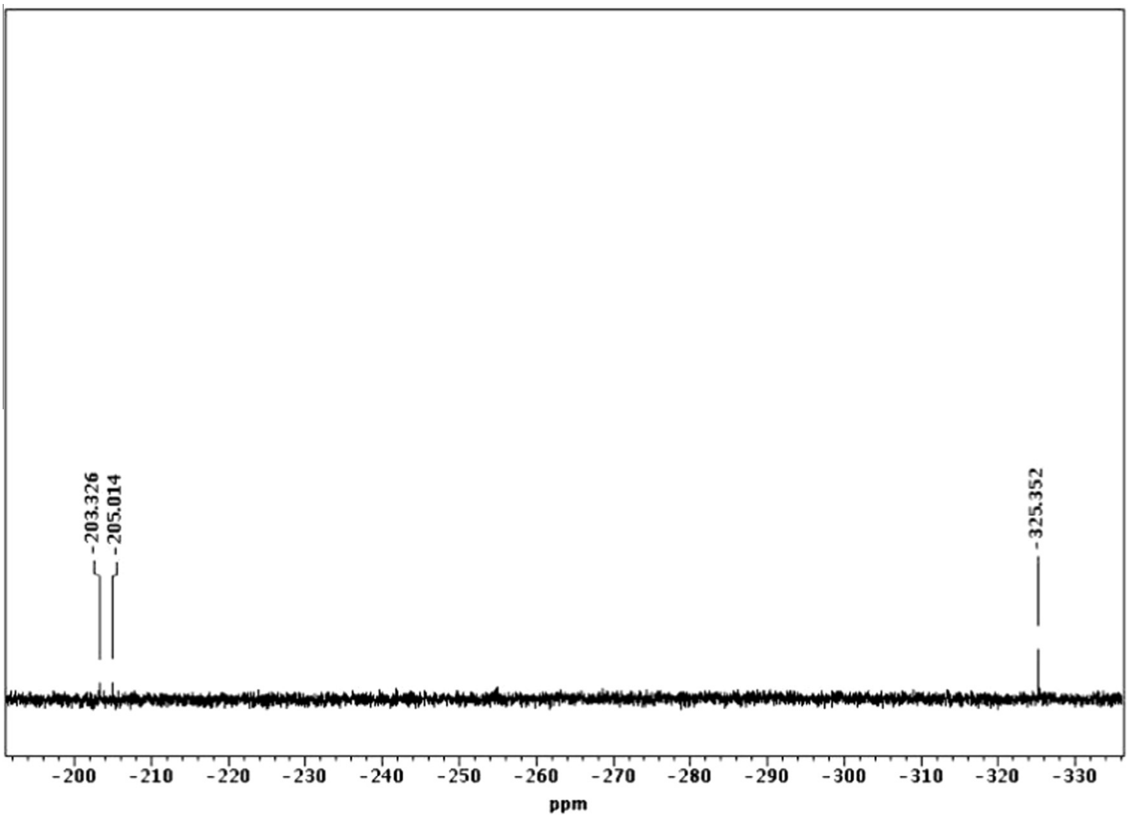

Figure 5. ^{15}N NMR spectrum of Selectfluor.

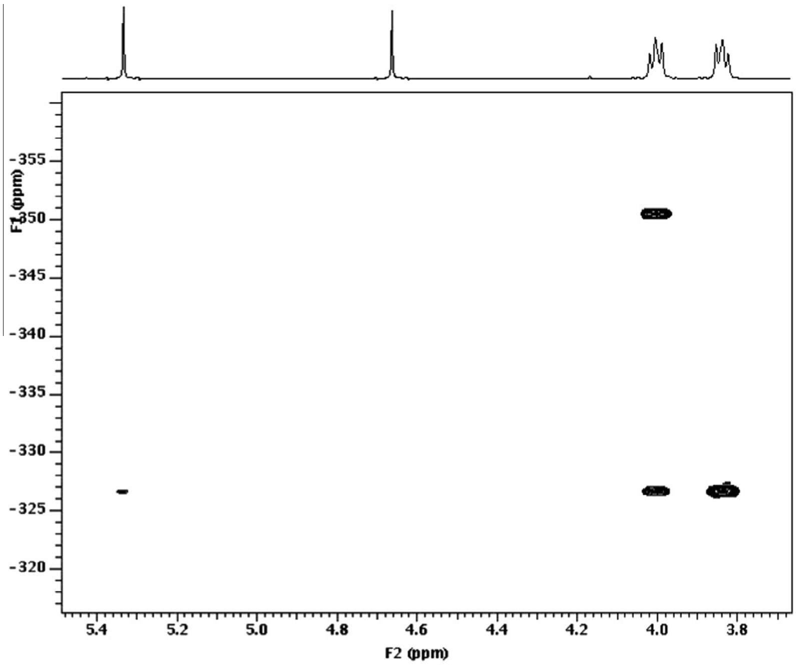

Figure 6. $^{15}N/^{1}H$ HMBC spectrum of adduct **a** (via **1**+**3**).

DABCO-HCl and DABCO,[12] and the crystal structure of its $[B(Ph)_4]$ salt has been reported.[12] Similarly, DABCO-HBF_4, DABCO-$HClO_4$, and DABCO-$HReO_4$ salts have been prepared and studied. These compounds form hydrogen bonded networks and have unusual dielectric properties.[13]

Formation of $[N-H-N]^+$ trication salts in the present study likely originates from the hydrolysis of $[BF_4]$ to generate HF in situ.[14] Formation of the same adducts by reacting Selectfluor with nitrogen bases in MeCN could be accounted for by slow N^+–F cleavage (homolytic or heterolytic) and formation of N^+–H. The resulting tricationic species are structurally analogous to $[N-X-N]^+$ trication salts formed via the reaction of the monocation salt **3** with $AgBF_4/X_2$ (X = Br, Cl).[15]

Synthesis of symmetrical $[N-H-N]^+$ trication salts via the reaction of Selectfluor with chloromethylated-DABCO/BF_4 or/NTf_2 monocation salts, or by self-coupling when treated with nitrogen bases in MeCN, represents a hitherto unreported reactivity channel that is significantly different from the well documented transfer-fluorination observed with quinuclidine and quinuclidinic bases.[5,6] Additional studies are needed including attempts to grow suitable crystals for X-ray analysis through anion metathesis protocols.

Acknowledgements

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Supplementary data

Supplementary data (experimental procedures, NMR data, and selected ^{15}N NMR and $^{15}N/^{1}H$ HMBC spectra (Figs. S1–S5)) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.10.071.

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7. The likely candidate for the −130 ppm signal is BF_3, or more logically BF_3/MeCN, but it is unclear how it is associated with the trication salt.
8. Two sets of N-*Et* groups were present in the ^{1}H NMR spectrum (D_2O) of the recovered residue via the reaction of **1** with Et_3N in about 1:1.2 ratio.
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11. ^{15}N NMR chemical shift of $AgNTf_2$ has been reported at 141.7 (from NH_3) which is equivalent to −240.3 ppm from $MeNO_2$; see Levya-Perez, A.; Corma, A.; Cabrero-Antonino, J. R. *Chem. Eur. J.* **2013**, *19*, 8627–8633.
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