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Considerations of the mechanism of reductive deamination of primary amines with HNF_2

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Abstract

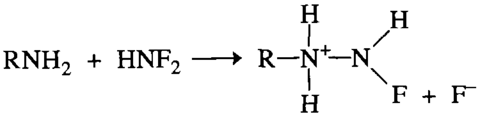
A possible mechanism for the reductive deamination of primary amines ($RNH_2 \rightarrow RH$) by HNF_2 is presented. The initial step involves bimolecular displacement of F from HNF_2 by RNH_2. The subsequent series of intermediates proposed is supported by proton affinity data and literature analogies. The role of fluorine in affecting amine basicity is also delineated.

A number of years ago we noted that exposure of primary amines to HNF_2 resulted in reductive deamination [1].

$$3RNH_2 + HNF_2 \longrightarrow RH + N_2 + 2R\overset{+}{N}H_3 + 2F^-$$

If an optically active amine is used, the reaction proceeds with net retention [2]. Originally [1], we suggested a scheme involving fluoronitrene as a working hypothesis for the conversion of amines to alkanes, N_2 and RNH_3F. An alternative route beginning with S_N2 displacement of F from HNF_2 by RNH_2 was not excluded by the data.

Subsequent observations from several groups [3–5] regarding the reaction chemistry and thermochemistry of HNF_2 lead us to point out that this bimolecular process involving nucleophilic attack by RNH_2 on HNF_2 provides an attractive accommodation of the facts. We therefore suggest the following sequence — and accompanying precedents and commentary — to account for the reductive deamination of amines by HNF_2.



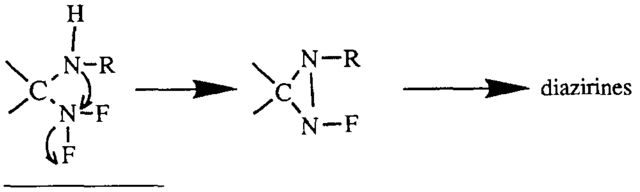
$$RNH_2 + HNF_2 \longrightarrow R{-}\overset{\displaystyle H}{\underset{\displaystyle H}{N^+}}{-}N\begin{matrix}H\\F\end{matrix} + F^- \qquad \text{(step 1)}$$

Step 1, direct substitution, is consistent with the observations of Yap, Craig and Ward [3] who found that HNF_2 is attacked by a number of inorganic anions in a second-order process and that the reactivity pattern parallels the S_N2 order. An exception is OH^-. This is the base used by le Noble and Skulnik [4] in a study ($\Delta V^\ddagger$) of the hydrolysis of HNF_2. Their evidence indicates that NF is generated by α-elimination of HF from HNF_2. These results may be reconciled by the hard and soft acids and bases (HSAB) approach to reactivity [6]: the relatively soft anions used by Yap *et al.* would be expected to participate readily in S_N2 reactions with HNF_2, whereas the relatively hard (charged) strong base OH^- would prefer to abstract a proton from HNF_2. The uncharged, weak base RNH_2 is softer than OH^- and therefore amines would be expected to act as nucleophiles toward HNF_2 rather than as bases.

By analogy to many other examples of positively charged hydrogen-assisted X—F bond polarization and resulting heterolytic cleavage [7], we suggest that step 1 is autocatalytically assisted† by the RNH_3^+ reaction product. Noting that HNF_2 and OF_2 are isoelectronic, we recall the invocation of the isoelectronic reaction [7] to explain the literature reaction [9]

$$3RNH_2 + OF_2 \longrightarrow RNO + 2RNH_3^+F^-$$

Graham's synthesis [10] of diaziridines represents an intramolecular case where an amine displaces a fluorine atom on another nitrogen atom, again with N—F bond cleavage assisted by polarization.



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†For other examples of Lewis and/or Brønsted acid autocatalytic fluoride-displacement reactions, see ref. 8.

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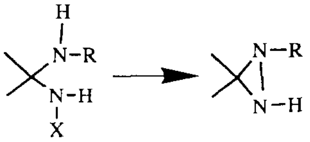
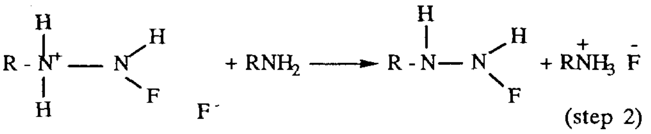
Analogous displacements on nitrogen are known to lead to diaziridine formation [11].



$X=Cl, OSO_3^-$

Evidence presented by Schmitz [11] indicates that such cyclizations occur via the S_N2 route and do not involve a nitrene. Since these intramolecular cases do not utilize a nitrene intermediate, we suggest that the intermolecular counterpart shown in step 1 is likewise an S_N2 process.



(step 2)

The proton transfer represented in step 2 is reasonable in view of the following observations. In the gas phase, alkyl amines RR'NH and the related hydrazines $RR'NNH_2$ have seemingly nearly identical basicities: more precisely, the proton affinities* of the amines NH_3, CH_3NH_2 and $(CH_3)_2NH$ are 204.0, 214.1 and 220.6 kcal mol^{-1}, and of the corresponding hydrazines are 204.7, 214.1 and 219.9 kcal mol^{-1}. Hence, proton transfer between $RNHNH_2$ and RNH_2 should be thermoneutral. Intuitively, the replacement of an H atom on the NH_2 of the hydrazine by the electron-withdrawing fluorine should result in decreased basicity. For example, contrast the proton affinity of $(CH_3)_3N$ with that estimated for $(CH_3)_2NCH_2F$.

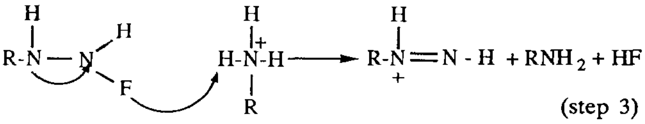
(a) Linearly interpolate the proton affinities of $(CH_3)_3N$, 225.1 kcal mol^{-1} and $(CH_3)_2NCF_3$, 193.8 kcal mol^{-1}, resulting in 214.7 kcal mol^{-1}.

(b) Use the literature proton affinity of $(CH_3)_2NCH_2CF_3$, 215.0 kcal mol^{-1}, and interrelate with $(CH_3)_2NCH_2F$ by either equation shown below from ref. 13:

$$PA(XCF_3) = 0.920PA(XF) + 13.597 \quad (n=14,\ r=0.9934)$$

$$PA(XCF_3) = PA(XF) - 1.81 \quad (\pm 3.16)$$

These two equations result in a predicted proton affinity for $(CH_3)_2NCH_2F$ of 218.9 and 216.8 kcal mol^{-1}, respectively. A value of 217 ± 2 kcal mol^{-1} is thus credible, and is certainly significantly less than that of the parent, unfluorinated, trimethylamine. We thus conclude that RNHNHF is expected to be meaningfully less basic than RNH_2 for any R group of interest.



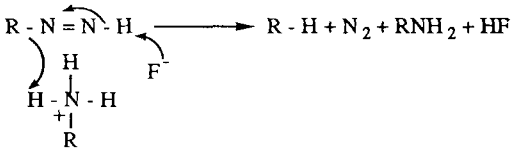
(step 3)

The elimination in step 3 is another example of X—F bond polarization, and then heterolytic cleavage, by positively charged hydrogen. This reaction is 'driven' by formation of the comparatively strong nitrogen–nitrogen double bond and loss of the comparatively weak nitrogen–nitrogen single bond†. It is no doubt superfluous to comment that both here and elsewhere in our mechanism the RNH_2 and HF products of any step combine to form RNH_3^+ F^-.

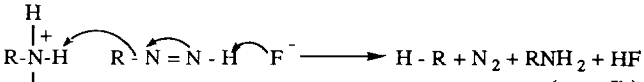
$$R\text{-}\overset{H}{\underset{+}{N}}{=}N\text{-}H + RNH_2 \longrightarrow R\text{-}N{=}N\text{-}H + R\overset{+}{N}H_3$$

(step 4)

Consistent with step 4 is the finding that the dialkyldiazene $CH_3N{=}NCH_3$ is considerably less basic than CH_3NH_2 (206.9 versus 214.1 kcal mol^{-1}). Since methylation generally increases proton affinities (cf. ref. 12), we thus conclude that CH_3NNH is considerably less basic than CH_3NH_2, and assuming there is nothing 'special' about methyl, RNNH is likewise less basic than RNH_2.



(step 5a)



(step 5b)

Step 5a depicts an elimination involving a tight RNH_3^+ F^- ion pair which would be expected to favor retention of configuration, the major stereochemical route. The separated ion-pair model shown in step 5b provides a route for the minor inversion pathway that results in 'H—R' instead of R—H.

We therefore conclude that steps 1–5 constitute a reaction scheme consistent with the available data on reductive deamination of primary amines by HNF_2 and is consonant with the reaction chemistry of other nonmetal fluorides.

References

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*All proton affinity (*PA*) data in the current study have been taken from the evaluated data compendium and review [12].

†This is one of the 'bonding rules' for compounds of nitrogen, oxygen and fluorine, cf. ref. 14.

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