Mechanistic Insights for Nitromethane Activation into Reactive Nitrogenating Reagents

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Recently, it was found that nitromethane (CH$_3$NO$_2$) can be activated into a useful nitrogenating reagent for the synthesis of amide and nitrile compounds. In this work, the mechanisms of CH$_3$NO$_2$ activation are explored in detail by extensive DFT calculations. In aqueous triflic acid (HOTf) solution, the formal 1,3-H-shift of CH$_3$NO$_2$ into transient CH$_2$=NO$_2$H is identified as the rate-limiting step over a barrier of 29.6 kcal/mol, followed by multistep acid hydrolysis to cleave the C=N bond to form NH$_2$OH$^+$ (and HCOOH) as final product. In contrast, in non-aqueous acetic acid (AcOH) solution with electrophilic Tf$_2$O and nucleophilic HCOOH additives, the C=N bond is cleaved by sequential steps of H$_2$O elimination, electrophilic Tf$_2$O activation, nucleophilic HCOOH addition and acetate/Tf$^-$ exchange, affording AcONH$_3^+$ as more reactive nitrogenating reagent for Beckmann-type reactions.

Amides and nitriles are pervasive in nature and technology as important compounds for the synthesis of materials, agrochemicals, and pharmaceuticals. The Schmidt reaction[1] discovered in 1923 is one of the most efficient nitrogenation approaches to access amides and nitriles from aldehydes and ketones with HN$_2$ and alkyl azides that are however volatile, highly toxic, and potentially explosive. The even earlier Beckmann rearrangement[2] starting from oxime substrates usually prepared with ketone and hydroxylamine (NH$_2$OH) is a well-known alternative approach to secondary amides. Because of the strongly electron-withdrawing nitro (NO$_2$) group, nitromethane (CH$_3$NO$_2$) is often used as carbon pro-nucleophile[3] as well as a common solvent. Recently, the reactivity of CH$_3$NO$_2$ as nitrogen donor has been developed further using the mixture of either KI, tBuOOH, CsOAc and AcOH[4] or Tf$_2$O, HCOOH and AcOH[5] as activating reagents. The transient nitroxyl species (HNO) was tentatively proposed as the crucial intermediate in such reactions, likely formed from the classical Nef reaction (i.e., acid hydrolysis of CH$_3$NO$_2$– salt to form H$_2$CO and HNO$_2$).[6] In particular, the cascade activation of CH$_3$NO$_2$ with Tf$_2$O, HCOOH and AcOH can be used in one-pot reactions with ketones and aldehydes to effect “Schmidt-type” formation of amides and nitriles (Scheme 1). The acetylated hydroxylamine salt (AcONH$_3^+$) was suggested as the actual nitrogen donor resulted from HNO reduction with HCOOH.[7] On the other hand, the Mayer reaction[8] (acid hydrolysis of CH$_3$NO$_2$) in aqueous solution is well-known to yield the NH$_2$OH$^+$ salt (along with HCOOH)[9] that may react further with ketone substrates into amides via Beckmann rearrangement.

In this work, extensive DFT calculations at the PW6B95-D3 + COSMO-RS//TPSS-D3 + COSMO level in AcOH solution (see below for computational details) are conducted to gain a deep mechanistic insight into the acid-catalyzed CH$_3$NO$_2$ activation,[10] especially the formation of AcONH$_3^+$ salt and its further reaction with typical ketone substrate PhMeC=O in non-aqueous solution.[11] Our DFT calculations show that the acid-catalyzed, endergonic conversion of CH$_3$NO$_2$ into its aci-form CH$_2$=NO$_2$H is the rate-limiting step over a free energy (enthalpy) barrier of 29.6 (24.7) kcal/mol, consistent with the experimentally observed kinetic isotope effects (K$_H$/K$_D$ = 3.6$^{[11]}$) and an enthalpy barrier of 23.3 ± 1.3 kcal/mol. The C=N bond can be efficiently cleaved by subsequent multistep acid hydrolysis, either with nucleophilic H$_2$O to form NH$_2$OH$^+$ or with electrophilic Tf$_2$O and nucleophilic HCOOH in AcOH solution to form AcONH$_3^+$ salt. Moreover, compared with the usual NH$_2$OH$^+$ reagent, enhanced Beckmann-type reactivity of AcONH$_3^+$ with PhMeC=O is clearly revealed by our DFT calculations, highlighting the important role of acetyloxy group as efficient proton shuttle and leaving group.

As shown in Figure 1, in AcOH solution with a nucleophilic H$_2$O molecule explicitly included in the calculation, CH$_3$NO$_2$ can be protonated at one nitrogen oxysite by strong acid HOTf, followed by deprotonation at the methyl site with anion Tf$^-$; such acid-catalyzed conversion of CH$_3$NO$_2$ into CH$_2$=NO$_2$H is 11.8 kcal/mol endergonic over a free energy barrier of 29.6 kcal/mol (via the transition state TS1). Further proton transfer from HOTf to CH$_2$=NO$_2$H is −2.7 kcal/mol exergonic affording cation CH$_2$=N(OH)$_2$$^+$. Nucleophilic H$_2$O-activation at the C-site of CH$_3$N=O(OH)$_2$$^+$ is −0.5 kcal/mol exergonic over a low free energy barrier of 13.9 kcal/mol (via TS2$^*$) forming the cation HOCH$_2$=N=O(OH)$_2$$^+$. Following facile 1,2-H-shift-promoted H$_2$O elimination from the N-site (via TS3$^*$), affording the cation HOCH$_2$=NOH$^+$ in a highly exergonic step. Further acid-catalyzed multistep hydrolysis is −5.9 kcal/mol exergonic over a moderate barrier of about 19.0 kcal/mol to cleave the C=N bond, eventually leading

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to HCOOH and NH$_4^+$ as final product. The overall acid hydrolysis of CH$_3$NO$_2$ is $-46.5$ kcal/mol exergonic over an effective free energy (enthalpy) barrier of 29.6 (24.7) kcal/mol (rate-limited by TS1) to form NH$_4$OH as useful reagent for

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**Scheme 1.** Acid-catalyzed CH$_3$NO$_2$ activation in aqueous and non-aqueous solutions: (A) some previous proposals; (B) our DFT-computed mechanisms.

**Figure 1.** DFT-computed free energy paths (in kcal/mol, at 298 K and 1 M) for HOTf-catalyzed acid hydrolysis of CH$_3$NO$_2$ in AcOH solution with excess H$_2$O. Besides the cationic channel (black line) leading to NH$_4$OH, competing neutral channel (blue line) via HOCH$_2$N(OH)$_2$ is also possible in dilute acid solution and may even dominate if energetic CH$_2$NO$_2$ salts are used (red line) in Nef reaction in weak acidic or basic solution.
As shown in Figure 2, in non-aqueous AcOH solution with excess TfO and HCOOH additives, the acid hydrolysis of CH3NO2 proceeds somewhat differently. Our DFT calculations show that TfO is kinetically 2.0 kcal/mol less active than HOTf in promoting the formation of CH2=NOH (see ESI). The aci-form species CH2=NOH can be easily protonated by HOTf at the OH site over a lower barrier of 14.4 kcal/mol (via TS5) to eliminate H2O, followed by facile and highly exergonic deprotonation from C-site of CH2=NOH to form HCNO. Further electrophilic activation with TfO at the O-site (via TS6) followed by nucleaseic HCOOH addition at the C-site (via TS7) is −12.5 kcal/mol exergonic over a sizeable barrier of 24.5 kcal/mol to form HCOOCH−HOTf+. For comparison, the competing protic activation of HCNO with HOTf at the O-site followed by a nucleaseic TfO− addition at the C-site (via TS8) is only −1.6 kcal/mol exergonic over a slightly lower barrier of 23.8 kcal/mol to form the neutral adduct TfOCH=NOH, effectively increasing the barrier of electrophilic HCNO activation by 1.6 kcal/mol. Further nucleaseic HCOOH addition may cleave the C=N bond of HCOOCH=HOTf+ to form neutral TfONH2 along with HC(O)OH, after TfO− deprotonation, which is kinetically feasible over a barrier of 23.6 kcal/mol (via TS8+) but still 6.5 kcal/mol exergonic. Further reaction between TfONH2 and AcOH is −14.7 kcal/mol exergonic over a barrier of 22.7 kcal/mol (via TS9) to form the AcONH3+ salt; in this way, the C=N cleavage of HCOOCH=HOTf+ eventually becomes −8.2 kcal/mol exergonic over a sizeable barrier of 29.2 kcal/mol, slightly lower than that (29.6 kcal/mol at TS1) required for the HOTf-catalyzed conversion of CH3NO2 to CH2=NOH. Note that neutral AcONH3 was already synthesized in 1958 from the reaction of NH2OH·HCl, NaOH and p-nitrophenyl acetate in 

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Figure 2. DFT-computed free energy paths (in kcal/mol, at 298 K and 1 M) for HOTf-catalyzed hydrolysis of CH3NO2 in AcOH solution with electrophilic TfO and nucleaseic HCOOH additives. Nucleaseic H2O addition is mostly inhibited by rapid reaction with excess TfO. In addition to the electrophilic activation of HCNO with TfO (black line), competing protic activation with HOTf (blue line) is kinetically faster but thermodynamically much less favorable.
ethanol solution. In contrast, similar reaction between TfONH$_2$ with HCOOH is kinetically 8.3 kcal/mol less efficient (via TS10) due to less nucleophilic HCOO$^-$ unit.

This proposed cationic mechanism in non-aqueous solution is fully consistent with recent experiments concerning the cooperative CH$_3$NO$_2$ activation with Tf$_2$O/HCOOH/AcOH, but suggests totally different roles of excess Tf$_2$O and HCOOH additives. Our DFT calculations show that excess Tf$_2$O plays a dual role in absorbing released H$_2$O (forming HOTf over a barrier of 24.7 kcal/mol, faster than the initial conversion of CH$_3$NO$_2$ to CH$_2$=NOH$_2$) and in activating HCNO for further nucleophilic HCOOH addition that is crucial for the CN bond cleavage. The competing neutral channel leading to HNO should be favored in dilute aqueous solution under weak acid or even basic conditions, but is mostly inhibited in non-aqueous solution of strong acids with excess anhydrides. Our DFT calculations suggest that the additive HCOOH should act as suitable nucleophile as well as proton source to cleave the C=N triple bond of Tf$_2$O-activated HCNO intermediate rather than the recently proposed$^{[3]}$ role of HNO reducing reagent. Moreover, our DFT calculations show that the nucleophilic trapping of intermediate HCNO$_2$H$^+$ and HCNOTf$^+$ cations is kinetically at least 14 kcal/mol more favorable than the corresponding reduction with HCOOH (see ESI Table S2). This is crucial for the design of novel CH$_2$NO$_2$ activation protocol.

As shown in Figure 3, the AcONH$_3^+$ salt can indeed be involved in Beckmann-type reaction with typical ketone substrate PhMeC=O. The reaction is initiated by C=O oxygen protonation with AcONH$_3^+$, followed by nucleophilic N-to-C addition over a low barrier of 11.6 kcal/mol (via TSA$^+$) to form the transient adduct A$. Subsequent H$_2$O-elimination from A$^+$ is aided by acetyloxy group mediated proton transfers via intermediate B$, and from NH$_3$ to the alcohol OH group, which is $\sim 1.2$ kcal/mol exergonic over a moderate barrier of 21.2 kcal/mol (TSC$^+$) with respect to initial reactants to form the cation C$^+$ containing a new C=N double bond. Facile AcOH-elimination from C$^+$ is then induced by intramolecular proton transfer from NH to the acetyloxy group, which is $\sim 32.5$ kcal/mol exergonic over a low barrier of only 10.4 kcal/mol (TS$^+$) to form the nitritium ion D$^+$ (MeC=NH$^+$) that is commonly involved in Beckmann rearrangements.$^{[11]}$ In aqueous solution, sequential nucleophilic H$_2$O addition and protonation at the C- and N-sites of the C=N bond of D$^+$ eventually lead to the O-protonated amide product F$^+$ in a highly exergonic step over a moderate barrier of 20.4 kcal/mol (via H$_2$O-adduct E$^+$). In contrast, direct 1,2-Ph-shift within B$^+$ may also lead to F$^+$ via single transition structure TSF$^+$, which is however kinetically 7.8 kcal/mol less favorable. The cation F$^+$ is stable in acidic solution and cannot be deprotonated by anion TfO$^-$ or ketone substrate. Indeed, quenching with aqueous NaOH or NaHCO$_3$ is still required to obtain MeCONHPh as the final neutral amide product.$^{[11]}$ The overall reaction is thus rate-limited by the acetyloxy-aided H$_2$O-release over a moderate barrier of 21.2 kcal/mol (via TSC$^+$).

For comparison, a similar mechanism is also found for the usual Beckmann reaction of NH$_2$OH$^+$ with PhMeC=O in our DFT calculations. The nucleophilic N-to-C addition after the C=O protonation with NH$_2$OH$^+$ is 11.0 kcal/mol endergonic over a moderate barrier of 20.6 kcal/mol (via ts$^+$) to form the transient adduct a$, followed by faster and more exergonic H$_2$O-elimination via AcOH-mediated proton transfer (tsc$^+$) to form the cation c$^+$ containing a new C=N double bond. The formation of c$^+$ from the condensation reaction of NH$_2$OH$^+$ and PhMeC=O is $\sim 3.2$ kcal/mol exergonic. Additional H$_2$O or AcOH molecules are required to mediate the proton transfer steps for further H$_2$O-elimination from c$^+$, which is $\sim 25.1$ kcal/mol exergonic but encounters a sizeable barrier of 24.6 kcal/mol (via the H$_2$O-adduct Da$^+$.OH$^-$) to form the same nitritium ion D$^+$ as also found in the reaction of AcONH$_3^+$ and PhMeC=O. However, without the help of intramolecular acetyloxy group (as found in A$^+$ and C$^+$), protic AcOH or H$_2$O molecules are required to mediate efficient proton transfer within the cations a$^+$ and c$^+$, leading to an 13.9 kcal/mol higher barrier for the formation of D$^+$ that is now the rate-limiting step. The sizeable overall barrier of 24.6 kcal/mol for the reaction of NH$_2$OH$^+$ with PhMeC=O is consistent with the moderate heating required for usual Beckmann rearrangements.$^{[11]}$ This also highlights the important role of the acetyloxy group within AcONH$_3^+$ for higher reactivity (lower overall barrier of 21.2 kcal/mol).

In conclusion, large parts of the mechanism of acid hydrolysis of CH$_3$NO$_2$ both in aqueous HOTf solution and in non-aqueous AcOH solution with Tf$_2$O and HCOOH additives were explored by extensive, highly accurate DFT calculations. The acid-catalyzed conversion of CH$_3$NO$_2$ to its aci-form CH$_3$=NOH$_2$ is found to be the rate-limiting step over a free energy barrier of 29.6 kcal/mol, followed by faster protonation/deprotonation and H$_2$O elimination/addition steps to cleave the C=N bond into HCOOH and NH$_2$OH$^+$ salt products. In AcOH solution with excess Tf$_2$O and HCOOH additives, intermediate HCNO is formed from acid-catalyzed H$_2$O-elimination of CH$_3$=NOH$_2$, followed by electrophilic Tf$_2$O activation and nucleophilic HCOOH addition to cleave the C=N bond to form TfONH$_2$ that can be further stabilized by reaction with AcOH into AcONH$_3^+$ salt. The AcONH$_3^+$ salt shows higher Beckmann-type reactivity than the corresponding NH$_2$OH$^+$ salt for reaction with typical ketone substrates PhMeC=O to form the O-protonated amide product MeC(OH)NHPh$^+$, highlighting the role of acetyloxy group as efficient proton shuttle and leaving group.

Computational Methods

All DFT calculations are performed with the TURBOMOLE 7.3 suite of programs.$^{[12]}$ The structures are fully optimized at the TPSS-D3/def2-TZVP+COOMO (AcOH) level, which combines the TPSS meta-GGA density functional$^{[11]}$ with the BJ-damped DFT-D3 dispersion correction$^{[14]}$ and the def2-TZVP basis set,$^{[15]}$ using the Conductor-like Screening Model (COSMO)$^{[16]}$ for acetic acid solvent (dielectric constant $\varepsilon = 6.19$ and diameter $R_{\text{diss}} = 2.83$ Å). The density-fitting RI-J approach$^{[17]}$ is used to accelerate the calculations. The optimized structures are characterized by frequency analysis (no imaginary frequency for true minima and only one imaginary frequency for transition states) to provide thermal free-energy corrections (at 298.15 K and 1 atm) according to the modified ideal gas-rigid rotor-harmonic oscillator model.$^{[18]}$
More accurate solvation free energies in acetic acid are computed with the COSMO-RS model\cite{19} (parameter file: BP_TZVP_C30_1601.ctd) using the COSMOtherm package\cite{20} based on the TPSS-D3 optimized structures, corrected by $+1.89$ kcal/mol to account for the 1 mol/L reference concentration in solution. For AcOH, an additional correction of $+1.72$ kcal/mol is used to account for its high concentration in solution. To check the effects of the chosen DFT functional on the reaction energies and barriers, single-point calculations at both TPSS-D3\cite{13} and hybrid-meta-GGA PW6B95-D3\cite{21} levels are performed using the larger def2-QZVP\cite{15} basis set. Final reaction free energies ($\Delta G$) are determined from the electronic single-point energies plus TPSS-D3 thermal corrections and COSMO-RS solvation free energies. As noted previously\cite{22} the overall results from both DFT functionals are in good mutual agreement ($0.6 \pm 4.5$ kcal/mol, mean $\pm$ standard deviation for all relative energies) though as expected $2.3 \pm 5.0$ kcal/mol higher reaction barriers are found at the PW6B95-D3 level. In our discussion, the more reliable PW6B95-D3 $+$ COSMO-RS free energies (in kcal/mol, at 298.15 K and 1 mol/L concentration) are used unless specified otherwise. The applied DFT methods in combination with the large

Figure 3. DFT-computed free energy paths (in kcal/mol, at 298 K and 1 M) for the Beckmann-type reactions of (A) AcONH$_3^+$ and (B) NH$_3$OH$^+$ salts with typical ketone substrate PhMeC=O. The AcONH$_3^+$ salt is kinetically 3.4 kcal/mol more reactive with acetyloxy group as efficient proton shuttle and leaving group.
AO basis set provide usually accurate electronic energies leading to errors for chemical energies (including barriers) on the order of typically 1–2 kcal/mol. This has been tested thoroughly for the huge database GMTKN55 which is the common standard in the field of DFT benchmarking.

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**Conflict of Interest**

The authors declare no conflict of interest.

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[1] K. F. Schmidt, *Ber. Dtsch. Chem. Ges.* A, 8 1924, 57, 704–706.
[2] E. Beckmann, *Ber. Dtsch. Chem. Ges.* 1886, 19, 988–993.
[3] a) Z. Li, D. S. Bohle, C.-J. Li, *Proc. Natl. Acad. Sci.* 2006, 103, 8928–8933; b) A. Noble, J. C. Anderson, *Chem. Rev.* 2013, 113, 2887–2939.
[4] a) Z.-J. Yang, C.-Z. Liu, B.-L. Hu, C.-L. Deng, X.-G. Zhang, *Chem. Commun.* 2014, 50, 14554–14557; b) Y. Yan, B. Niu, K. Xu, J. Yu, H. Zhi, Y. Liu, *Adv. Synth. Catal.* 2016, 358, 212–217.
[5] J. Liu, C. Zhang, Z. Zhang, X. Wen, X. Dou, J. Wei, X. Qiu, S. Song, N. Jiao, *Science* 2020, 367, 281–285.
[6] a) W. E. Noland, *Chem. Rev.* 1955, 55, 137–155; b) R. Ballini, M. Petriti, *Adv. Synth. Catal.* 2015, 357, 2371–2402.
[7] a) V. Meyer, C. Wuxier, *Ber. Dtsch. Chem. Ges.* 1873, 6, 1168–1172; b) J. T. Edward, P. H. Ternaine, *Can. J. Chem.* 1971, 49, 3483–3488.
[8] a) R. B. Cundall, A. W. Locke, *J. Chem. Soc. B-Phys. Org.* 1968, 98–103; b) F. Huo, Y. Lu, *React. Chem. Eng.* 2020, 5, 387–394; c) C. Fehling, G. Friedrichs, *J. Am. Chem. Soc.* 2011, 133, 17912–17922.
[9] W. Beck, K. Feldl, Angew. Chem. Int. Ed. 1966, 5, 722–723; Angew. Chem. 1966, 78, 746–746.
[10] W. P. Jencks, *J. Am. Chem. Soc.* 1958, 80, 4581–4584.
[11] K. Kaur, S. Srivastava, New J. Chem. 2020, 44, 18530–18572.
[12] TURBOMOLE V7.3, 2018, a development of University of Karlsruhe and Forschungszentrum Karlsruhe GmbH, 1989–2007, TURBOMOLE GmbH, since 2007; available from http://www.turbomole.com.
[13] J. Tao, J. P. Perdew, V. N. Staroverov, G. E. Scuseria, *Phys. Rev. Lett.* 2003, 91, 146401–146404.
[14] a) S. Grimme, J. Antony, S. Ehrlich, H. Krieg, *J. Chem. Phys.* 2010, 132, 154104–154119; b) S. Grimme, S. Ehrlich, L. Goerigk, *J. Comput. Chem.* 2011, 32, 1456–1465.
[15] F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* 2005, 7, 3297–3305.
[16] A. Klamt, G. Schüürmann, J. Chem. Soc., *Perkin Trans. 2* 1993, 799–805.
[17] F. Weigend, *Phys. Chem. Chem. Phys.* 2006, 8, 1057–1065.
[18] S. Grimme, *Chem. Eur. J.* 2012, 18, 9955–9964.
[19] F. Eckert, A. Klamt, AIChE J. 2002, 48, 369–385.
[20] F. Eckert, A. Klamt, 2015, COSMOtherm, Version C3.0, Release 16.01; COSMOlogic GmbH & Co. KG, Leverkusen, Germany.
[21] Y. Zhao, D. G. Truhlar, *J. Phys. Chem. A* 2005, 109, 5656–5667.
[22] a) Z. W. Qu, H. Zhu, S. Grimme, *ChemCatChem* 2020, 12, 3656–3660; b) H. Zhu, Z. W. Qu, S. Grimme, *Chem. Eur. J.* 2019, 25, 4670–4672; c) H. Zhu, Z. W. Qu, S. Grimme, *Eur. J. Org. Chem.* 2019, 4609–4612; d) Z. W. Qu, H. Zhu, S. Grimme, *ChemistryOpen* 2019, 8, 807–810; e) Z. W. Qu, H. Zhu, S. Grimme, ChemCatChem 2021, 13, 207–211.
[23] L. Goerigk, A. Hansen, C. Bauer, S. Ehrlich, A. Najibi, S. Grimme, *Phys. Chem. Chem. Phys.* 2017, 19, 32184–32215.

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