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COMMUNICATION

Direct experimental evidence for an enamine radical cation in SOMO catalysis†

Rita Beel, Stefanie Kobialka, Martin L. Schmidt and Marianne Engeser*

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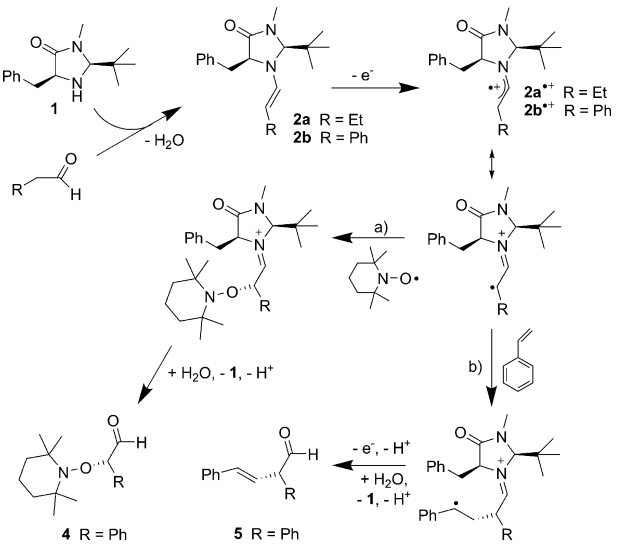
SOMO catalysis has lately obtained large interest as a new and powerful version of enantioselective organocatalysis which includes radical steps initiated by a one-electron oxidation. The intermediate enamine radical cation has been postulated, but has not been observed directly so far. This communication now reports the direct detection of this key intermediate.

Enantioselective organocatalysis has been a major issue in recent years.[1] In 2007, a new version of amine-mediated enantioselective organocatalysis, now termed SOMO catalysis, was introduced by the group of MacMillan.[2] Adding a one-electron oxidant to an enamine compound formed *in situ* from an amine catalyst and an aldehyde should give an enamine radical cation, which reacts with TEMPO, a long-lived organic radical (Scheme 1a).[3j,4] The group of MacMillan has recently shown in a series of publications[2a,3] that the proposed inter mediate enamine radical cation can also undergo a variety of subsequent reactions typical for radical reactivity (Scheme 1b with styrene as a representative example). A second one-electron oxidation followed by anion addition or proton elimination and hydrolytic release of the catalyst terminates the putative catalytic cycle. In this work, we used electrospray (ESI) mass spectrometry to obtain direct experimental evidence for the selective one-electron oxidation of an enamine to the respective enamine radical cation.

ESI mass spectrometry is not only a versatile method for analytical purposes,[5] but can also act as a link between solution and gas-phase chemistry and has been shown to be an excellent tool to investigate reaction mechanisms.[6] Even very reactive radical intermediates have already been observed and characterized experimentally by a sophisticated combination of API-MS/MS with online coupling to a microreactor.[6b,7]

We have used a similar microreactor to study the oxidation of an enamine with a one-electron oxidant. Enamines are formed *in situ* by mixing a solution of a typical MacMillan catalyst **1**·TFA with an aldehyde. Fig. 1a shows a representative



Scheme 1 SOMO catalysis: the proposed intermediate enamine radical cation can be trapped by the stable radical TEMPO (a) or react with *i.e.* styrene (b) followed by a second oxidation and hydrolytic release of the catalyst **1**.

ESI mass spectrum of a solution of **1**·TFA. After addition of butyraldehyde or phenylacetaldehyde, the corresponding enamines are detectable (Fig. 1b and c). The signal for the respective protonated enamine is most intense approximately 1 h after aldehyde addition.

Tris(*p*-bromophenyl)aminiumhexachloroantimonate (**3**) has been successfully used in mechanistic ESI studies.[7b–d] A typical ESI spectrum of **3** is shown in Fig. 2a. The deep blue solution immediately turns colourless upon addition of one of the enamine solutions described above, indicating a fast oxidation. ESI spectra of the colourless reaction mixtures do not show any signal for radical species. In contrast, when mixing solutions of **2b** and **3** in a microreactor directly coupled to the ESI source, very instructive spectra can be recorded (Fig. 2b and c). Thus, a new signal at m/z 348.2 is observed. This signal is due to the enamine radical cation $[\mathbf{2b}]^{\bullet +}$, evidenced by the exact mass difference of $\Delta m = 1.0078$ u to the signal of the protonated enamine $[\mathbf{2b} + H]^{+}$. In contrast, no additional signal is observed one mass below the signal for the protonated catalyst $[\mathbf{1} + H]^{+}$. Therefore, only the enamine is oxidized. This finding is in full accordance with the

Kekulé-Institut für Organische Chemie und Biochemie, Universität Bonn, Gerhard-Domagk-Str. 1, 53121 Bonn, Germany. E-mail: Marianne.Engeser@uni-bonn.de; Fax: +49 228 73 5683; Tel: +49 228 73 2849

† Electronic supplementary information (ESI) available: Experimental details and spectra of double microreactor experiments with TEMPO and styrene, respectively. See DOI: 10.1039/c0cc05347c

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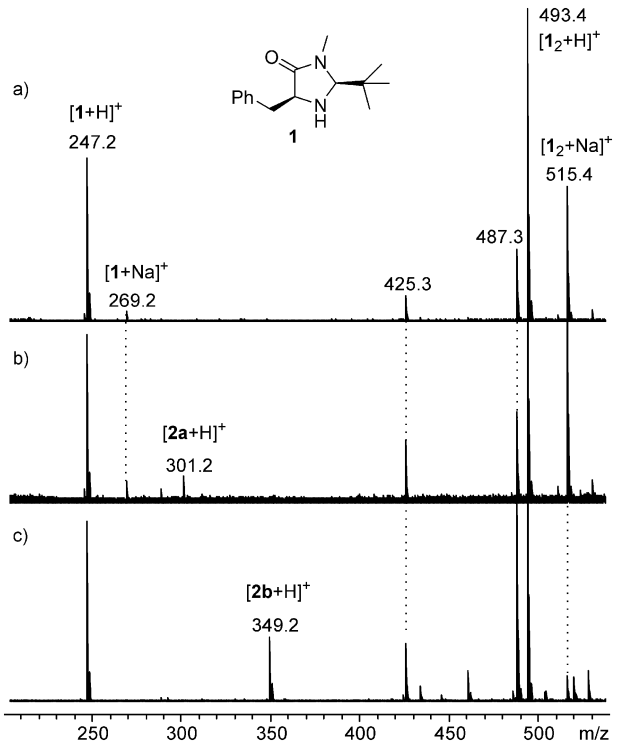

Fig. 1 ESI mass spectra of acetonitrile solutions of **1**·TFA before (a) and 1 h after adding butyraldehyde (b) or phenylacetaldehyde (c). The signals at *m*/*z* 487.3 and 425.3 correspond to [$\mathbf{1}_2$–3 H_2 + H^+] and [$\mathbf{1}_2$–C_5H_8 + H^+], respectively. These ions are formed by hydrolytic condensation of **1** in acidic solution.

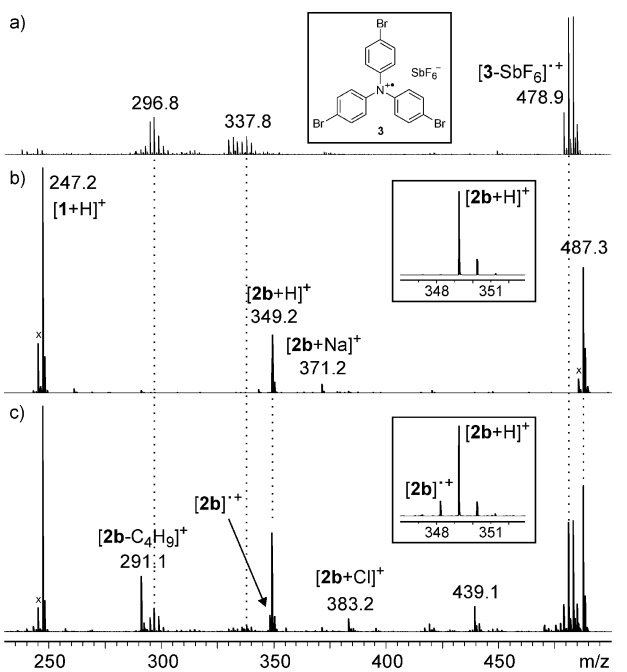

Fig. 2 ESI mass spectra of the one-electron oxidant **3** (a), enamine **2b** generated *in situ* (b), and after mixing the two solutions in a microreactor coupled directly to the ESI source (c). A new signal for the enamine radical cation [**2b**]$^{\bullet+}$ appears at *m*/*z* 348.2. Capillary length and flow rate correspond to a reaction time of approximately 8 s. Signals marked with x correspond to loss of H_2 due to collision induced fragmentation in the ESI source.

significantly lower ionization potential expected for the enamine with respect to the reactants **1** and the aldehyde.[2a] The signal at *m*/*z* 383.2 shows an isotope pattern for a monochlorinated species and can be assigned to [**2b** + Cl]$^+$. Although the aggregation with chloride anions is a common phenomenon in ESI mass spectra, the signal is highly remarkable in this case because the enamine radical cation [**2b**]$^{\bullet+}$ must have experienced a second one-electron oxidation to form [**2b** + Cl]$^+$ with a chloride anion. This is an indication that two subsequent one-electron oxidation steps can occur in the course of the reaction even in the absence of other reactants like styrene. Further, an interesting signal is found at *m*/*z* 291.1. It can be assigned to a loss of a butyl radical from the enamine radical cation [**2b**]$^{\bullet+}$ which probably happens due to collisions in the ESI process.

Reasonable intensities for the enamine radical cation are obtained by tuning the ESI parameters, so that the ion could be mass-selected and fragmented in the FT-ICR cell using an infrared laser (IRMPD). The resulting spectrum is shown in Fig. 3a. The only visible fragmentation pathway for [**2b**]$^{\bullet+}$ is indeed the loss of a butyl radical. A stable iminium ion with a delocalized π-system can be assigned to the resulting ion at *m*/*z* 291.2; this fragmentation is in full accordance with typical signals observed in ESI mass spectra of enamines.[8] For comparison, the protonated enamine [**2b** + H]$^+$ at *m*/*z* 349.2 was fragmented as well. As anticipated by the even-electron rule, no radical elimination pathway is observed for this closed-shell ion (Fig. 3b).

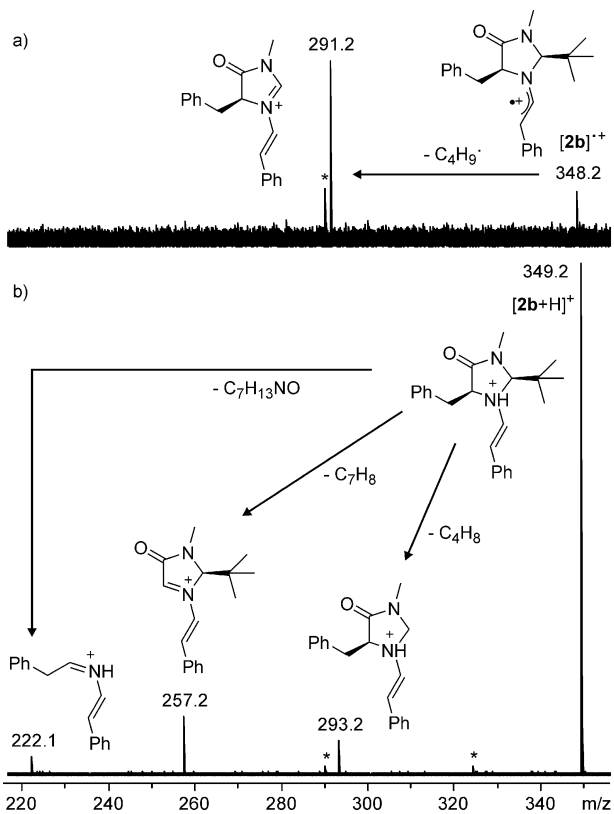

Fig. 3 Infrared multiphoton dissociation (IRMPD) MS/MS spectrum of mass-selected [**2b**]$^{\bullet+}$ (a) and [**2b** + H]$^+$ (b) with laser power 95% and irradiation time 2 s (* electronic noise).

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In a first attempt to sample the reactivity of the enamine radical cation $[\mathbf{2b}]^{\bullet +}$, a second microreactor was inserted between the ESI needle and the first microreactor in which $[\mathbf{2b}]^{\bullet +}$ was generated as described above (Fig. S1, ESI†). In the second microreactor, the solution of $[\mathbf{2b}]^{\bullet +}$ was mixed with a solution of TEMPO (Scheme 1a). The ESI spectra indeed show the presence of the expected hydrolyzed trapping product $[\mathbf{4} + H]^+$ at m/z 276.2 (Fig. S2, ESI†). Similarly, the final reaction product $[\mathbf{5} + H]^+$ at m/z 223.1 was observed when a solution of styrene (Scheme 1b) was added in the second microreactor (Fig. S3, ESI†). We are currently optimizing the conditions of the setup to further study these and other typical reactions[2,3] of enamine radical cations in detail to obtain more insight into the nature and order of the reaction steps following the formation of the enamine radical cation in SOMO catalysis.

We present direct experimental evidence for the selective oxidation of an enamine to an enamine radical cation with a one-electron oxidant under conditions of SOMO catalysis.

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