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An insight into the mechanism of the aerobic oxidation of aldehydes catalyzed by N-heterocyclic carbenes

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N-Heterocyclic carbene catalysis for the aerobic oxidation and esterification of aromatic aldehydes was monitored by ESI-MS (MS/MS) and the key intermediates were intercepted and characterized using the charge-tag strategy.

The electron richness and structure of the N-heterocyclic carbene (NHCs) provide a unique class of d-donor species, which have found widespread applications in organocatalysis. The most successful uses of these azolylidene catalysts involve the polarity reversal of aldehydes, in which the NHC promotes the formation of an acyl anion equivalent commonly referred as the Breslow intermediate (II of Figure 1). This NHC-catalysis has been recently enriched with oxidative protocols to access a wide range of organic compounds, especially acids and esters. The key oxidation event characterizing these transformations takes place on the Breslow intermediate II, which may be converted by air as the terminal oxidant into an electrophilic acyl azolium ion III (stoichiometric external oxidants as MnO₂, azobenzene, riboflavin, phenazine, TEMPO, and quinones can also be employed) and/or into an azolium peroxidic species V. In the former case III is prone to transfer the acyl group to an alcohol forming the corresponding ester (oxidative pattern) in the latter case V is supposed to intercept a second molecule of aldehyde or II to generate the carboxylic acid via formation of the corresponding peracid and/or the anionic intermediate VI (oxygenative pattern). Eventually, the acid is converted into the ester by O-alkylating reagents and base (Figure 1). A number of mechanistic studies have been performed on the NHC-catalyzed aerobic oxidation of aldehydes, nevertheless, key questions concerning the Breslow intermediate fate are still unanswered, including a precise characterization of the postulated intermediates and a rationalization of the proposed mechanistic dichotomy.

In the attempt to provide responses to these issues and as part of our ongoing interest on the chemistry of NHCs, we envisaged the use of charge-tagged N-heterocyclic carbenes as mass spectrometric probes to identify the species involved in the different oxidation steps and their dynamic equilibria. The charge-tag strategy entails the use of reagents, catalysts or ligands bearing a cationic or anionic unit installed remotely from the reaction site. It is noteworthy, also, that mass spectrometry (MS) has gained great benefit from the advent of electrospray ionization (ESI), since molecules of high polarity and complexity can be gently transferred directly from solution to gas-phase, thus permitting the detection of elusive and highly reactive intermediates.

In the present study, the 3,3'-dimethyl-1,1'-hexane-1,6-diyl) diimidazolium glutarate I has served as the precursor of carbene catalysts 2, which displays the second imidazolium ring as positive label for MS detection (Scheme 1). By this approach, we provide evidence of the key intermediates III, V, and VI as well as justification of preferential oxidative or oxygenative patterns in dependence of aldehyde stereoelectronic features.
Our investigation began with the ESI-MS monitoring of the reaction between pre-catalyst 1 and the model 2-bromo benzaldehyde 3a using acetonitrile-MeOH (5:1) as the eluent. Firstly, it was observed that significant amounts of 2 could be produced without the need of an external base, being the relative intensity of 2 (m/z 247) about 70% in the absence of base. Upon addition of 3a the intensity of 2 quickly decreased in parallel with an increase (up to 100%) of the signal at m/z 447 (11Br isotope) unequivocally assigned, by accurate mass analysis, to the Breslow intermediate 4a containing an additional oxygen atom [4a+O] (Figure 2 and Scheme 2). Noteworthy, when this ionic species was mass selected and submitted to collision induced fragmentation (MS/MS), the release of the neutral carboxylic acid 7a and formation of the NH2 2 was observed. Significantly, this decomposition perfectly fits with the reactivity found in solution (Table 1), thus corroborating the structure proposed in Figure 2 for the [4a+O]$^+$ ion.

![Figure 2](image-url)

**Figure 2.** MS/MS of the Breslow intermediate 4a containing an additional oxygen atom (m/z 447) formed by the 1/3a reaction. In addition, the full scan acquisition highlighted the presence, although in much lower relative intensity (ca. 2%), of a second important ion cluster (m/z 463), identified as the Breslow intermediate formally containing two oxygen atoms [4a+2O]$^+$. The MS/MS analysis of this ionic species disclosed even more important information consisting in the release of O$_2$ with formation of the genuine Breslow intermediate 4a (m/z 431), species otherwise not detectable in the full mass spectrum. The detailed snapshots of the involved intermediates and their preferential decomposition substantiate the mechanism described in path A of Scheme 2. Accordingly, molecular oxygen adds to the Breslow intermediate 4 with formation of the zwitterionic peroxyide 5 (heretofore named [4a+2O]$^+$); reasonably, 5 then attacks a second molecule of aldehyde by a mechanism reminiscent of the Baeyer-Villiger oxidation to yield a first molecule of acid 7. The final event consists in the release of an additional molecule of 7 from the intermediate 8 (heretofore named [4a+O]$^+$) with regeneration of catalyst 2. Remarkably, in our MS experiments we had no evidence of the formation of free deprotonated peracids (Figure 1), species that survive the (--)ESI MS conditions, as proved by control experiments with genuine samples.

To corroborate the above findings, the reaction of 2-bromo benzaldehyde 3a with pre-catalyst 1 (1 equiv.) was investigated in solution (anhydrous THF, molecular sieves, 55 °C) using DBU (1.1 equiv.) as the base. As hinted in the mechanistic proposal (path A), aldehyde 3a was converted into the corresponding acid 7a in 51% yield. However, when this reaction was performed in THF-MeOH (2:1), a low amount (5%) of methyl ester 11a was detected together with the acid 7a (45%; Table 1, entry 1). Extension of these conditions to aldehydes 3b-k possessing ortho-, meta- or para-groups with either electron-withdrawing or electron-donating properties, confirmed the concurring partial or almost complete esterification of the substrates (Table 1). Although the activity of pre-catalyst 1 in solution was limited, its utilization represented the gateway for accessing key intermediates by ESI-MS. Replacement of the cationic imidazolium tag of 1 with an uncharged alkyl chain as in 1-buty1-3-methylimidazolium trifluoromethanesulfonate [bmm(OtS)] produced similar results in terms of isolated yields of acids 7 and esters 11 (entries 1 and 5).

**Scheme 2.** Proposed mechanism for the aerobic oxidation of aldehydes: path A, oxidative, path B, oxidative.

This divergent reactivity was deeply examined by the ESI-MS monitoring of the reaction between 1 and a model aldehyde that predominantly affords the ester rather than the acid, i.e. the 4-bromo benzaldehyde 3e.

**Table 1.** Oxidation/esterification of aldehydes 3a-k.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>X</th>
<th>8</th>
<th>10$^+$ (ab. %)$^*$</th>
<th>7/11</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>2-Br</td>
<td>100</td>
<td>N</td>
<td>45/5 (37/8)$^d$</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>2-Cl</td>
<td>80</td>
<td>N</td>
<td>32/8</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>2-NO$_2$</td>
<td>[5]$^c$</td>
<td>N</td>
<td>40/0</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>2-OMe</td>
<td>60</td>
<td>N</td>
<td>24/0</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>4-Br</td>
<td>&lt;1</td>
<td>Y</td>
<td>11/78 (19/72)$^d$</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>4-Cl</td>
<td>8</td>
<td>Y</td>
<td>10/76</td>
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<tr>
<td>7</td>
<td>3g</td>
<td>4-NO$_2$</td>
<td>&lt;1</td>
<td>Y</td>
<td>5/84</td>
</tr>
<tr>
<td>8</td>
<td>3h</td>
<td>4-OMe</td>
<td>10</td>
<td>Y</td>
<td>6/32</td>
</tr>
<tr>
<td>9</td>
<td>3i</td>
<td>3-Br</td>
<td>8</td>
<td>Y</td>
<td>10/72</td>
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<tr>
<td>10</td>
<td>3j</td>
<td>2,6-C$<em>6$H$</em>$_4Cl$_2$</td>
<td>80</td>
<td>N</td>
<td>25/5</td>
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<tr>
<td>11</td>
<td>3k</td>
<td>2,4,6-Me$_3$C$_6$H$_2$</td>
<td>100</td>
<td>N</td>
<td>28/0</td>
</tr>
</tbody>
</table>

$^*$Relative abundance as determined by ESI-MS (see Electronic Supplementary Information). $^d$N = not detected; Y = detected and characterized. $^c$Isolated yield. $^d$Reaction performed with bmm(OtS). $^e$Very unstable species that spontaneously undergoes fragmentation.

The most resounding evidence in the (--)ESI full spectrum was the absence of the oxidized Breslow intermediate 8e. Detectable, on the contrary, remained the peroxodic Breslow intermediate 5e, whose MS/MS spectrum showed the release of O$_2$, thus confirming oxygen insertion on 4 still effective. Pleasantly, it was also possible to detect...
and characterize the crucial intermediate 10e of the oxygenative mechanism (path B), which was intercepted as a doubly charged ion at m/z 215. The MS/MS spectrum of 10e enlightened us about its structure since the observed fragments were the acyl cation (m/z 183) and the singly charged catalyst 2 (m/z 247; Figure S16, Supporting Information). It is worth to emphasize that all aldehydes having preference for exer over acid formation showed the presence of the related acyl intermediate 10 and traces of the oxidized Breslow species 8, while distinctive for preferential acid production was the detection of 8 in high relative abundance (Table 1, columns 4 and 5). Few mechanistic considerations would be appropriate in light of these results. Nucleophilic addition of carbene by O2 to give the radical cation [4+] and the superoxide radical anion [O2•−]. Accordingly, we calculated at the DFT level the structure of the complex between [4+] and [O2•−]. The optimized structures are reported along with spin densities in Figure 3 for 4a and 4e. We found that a fraction of the [O2•−] spin density spreads on [4+], mainly on the C-atom next to the OH group. This result fully conforms with those reported for triazolium-based systems.3c

![Complexes between [4+] and [O2•−]](image)

**Notes and references**


9. Since O2 and CH3OH are isobaric, addition of methanol on 4a was excluded by using acetamide-CD3OD or DMSO as ESI eluting solvent (Supporting Information).

10. C. Lehtinen, V. Nevalainen, and G. Brunow, *Tetrahedron*, 2000, **56**, 9375. Attempts to intercept and characterize intermediate 6 were unsuccessful; the possibility of reaction between 4 and 5 as suggested in Ref. 2b cannot be ruled out.

11. Reaction of 3e with catalytic 1 (20 mol%; 24 h): 7e (24%), 11e (65%). Reaction of 3e with equimolar 1 at 25 °C (72 h): 7e (28%), 11e (45%). Background oxygen oxidation of 3a-1 under optimized conditions are reported in Table S1 (Supporting Information).