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**An air-stable (amino)amido radical was synthesized by reacting a cyclic (alkyl)(amino)carbene with carbazoyl chloride, followed by one-electron reduction. We show that an adjacent radical center weakens the amide bond. It enables the amino group to act as a strong acceptor under steric constraint, thus enhancing the stabilizing capto-dative effect.**

Glycyl radical enzymes are important biocatalysts that enable a variety of transformations; from the reduction of nucleotides to the breakdown of inactivated hydrocarbons.<sup>1</sup> Their active resting state is generated by H atom abstraction at a glycine residue (Fig. 1a). The resulting C-radical **A** is highly sensitive to oxygen and the enzymatic processes work only under anaerobic conditions. Note that other reactive peptidyl radicals and related (amino)amido C-radicals **B** are rare in nature,<sup>1c,d</sup> but are commonly involved in synthetic radical peptidic chemistry.<sup>2</sup>

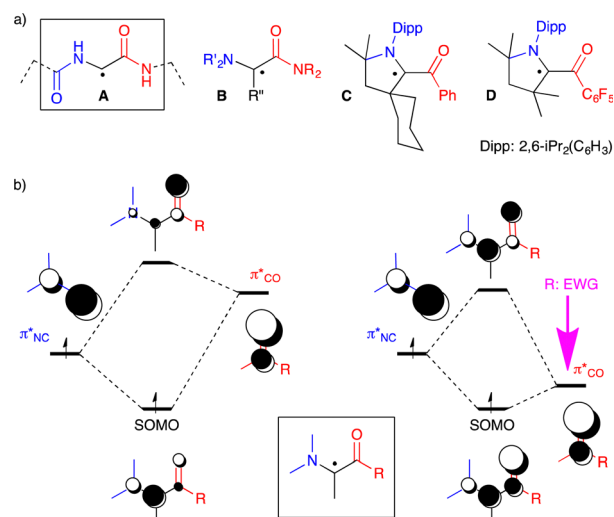
The persistence of the glycyl C-radical pattern in enzymes is usually attributed to the synergic combination of an electron-donating nitrogen (blue on Fig. 1) and an electron-withdrawing carbonyl group (red), a push-pull or captodative effect.<sup>3</sup> The protein environment also precludes the formation of C–C dimers, which are usually obtained with simpler molecular models.<sup>3e–i</sup> In 2013, we took advantage of the bulky pattern of cyclic (alkyl)(amino)carbene (CAAC)<sup>4–6</sup> to synthesize and isolate monomeric (amino)(carboxy) C-radical **C** under inert atmosphere.<sup>5a</sup> In addition, we showed that increasing the electron-withdrawing properties of the carbonyl substituent,

## An air-stable radical with a redox-chameleonic amide†

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such as in compound **D**, resulted in radicals with remarkable air-persistence.<sup>5d,7</sup> A schematic molecular orbital analysis enables the rationalization of this effect. Indeed, the singly occupied molecular orbital (SOMO) is a bonding combination of  $\pi_{\text{CO}}^*$  and  $\pi_{\text{CN}}^*$  (Fig. 1b). An electron-withdrawing substituent on the carbonyl lowers the energy of the  $\pi_{\text{CO}}^*$ , thus increasing the weight of the CO fragment, which has major coefficient on oxygen. Therefore, the formal C-radical shifts to more of an O-centred radical, which is less reactive towards dioxygen.<sup>5d,8</sup>

In this context, as illustrated by the high air-sensitivity of glycyl radical enzymes, amide patterns seem especially unfit for the design of bench-stable radicals; they are among both the poorest available N-donors and the weakest electron-withdrawing carbonyl groups. Herein, we challenge this paradigm and report an air-stable version of an amide-substituted



**Fig. 1** (a) Glycyl radical pattern **A** in Enzymes, (amino)amido C-radical **B**, bottle-able push-pull C-radical **C** (air sensitive) and **D** (highly air-persistent); (b) schematic representations of SOMO of an (amino)(carbonyl) C-radical built from  $\pi_{\text{NC}}^*$  and  $\pi_{\text{CO}}^*$ , left: “classical” case, right: R is an extreme electron-withdrawing group.

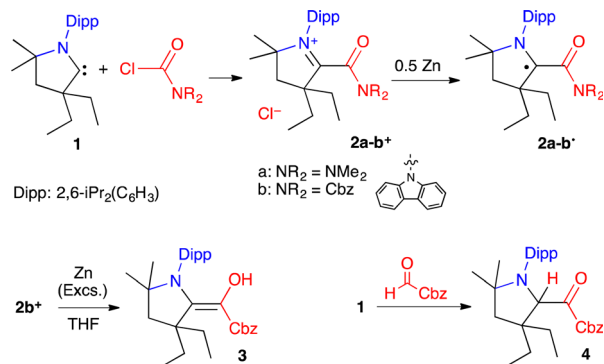
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Scheme 1 Synthesis of radicals **2a-b•** and their derivatives.

captodative radical. We show that the adjacent radical centre weakens the amide bond and enables the N-group to act as a strong acceptor.

We initially considered a simple  $N,N'$ -dimethylamido group. The chloride salt of acylium **2a<sup>+</sup>** was synthesized by the addition of CAAC **1** to dimethylcarbamoyl chloride (Scheme 1). Cyclic voltammetry indicated two reversible reductions at  $-1.34$  and  $-2.00$  V (versus  $\text{Fc}/\text{Fc}^+$ ), corresponding to the formation of **2a•** and the enolate **2a<sup>-</sup>**, respectively (Fig. 2a). Radical **2a•** was generated *in situ* by bulk electrolysis at  $-1.43$  V. This highly air-sensitive radical was also synthesized by chemical reduction of acylium **2a<sup>+</sup>** with 0.5 equivalent of  $\text{Zn}(0)$  and isolated as a yellow solid in 88% yield. A single crystal X-ray diffraction study (Fig. 2b) revealed a dimethyl amino group with pronounced pyramidalization (sum of angles around  $\text{N}2$ :  $331.6^\circ$ ). The lone pair of the amide nitrogen is not conjugated, but perpendicular to the carbonyl. As a result, the long  $\text{C}2\text{-N}2$  distance (143.7 pm) is typical for a single bond and sharply contrasts with the usual bond length in planar acyclic amides (132–134 pm).<sup>9</sup>

Acyclic twisted amide patterns usually require the deactivation of the nitrogen with an ancillary electron-withdrawing substituent or the incorporation into an aromatic ring.<sup>10,11</sup> The local environment of  $\text{N}2$  is more reminiscent of “anti-Bredt” amides or ureas, which feature a polycyclic saturated backbone with a bridgehead nitrogen.<sup>12,13</sup> These compounds are not stable when there is a significant twisting around the  $(\text{OC})\text{-N}$  bond, as they feature both an activated electrophilic carbonyl and a nucleophilic nitrogen centre. In radical **2a•**, the twist of the  $N,N'$ -di(methyl)amino group is maximal; however the amine acts as a strong electron-withdrawing group, which is a favourable electronic situation for a push-pull radical.<sup>5</sup>

We turned to a carbazole substituent to increase the electron-withdrawing capability of the carbonyl moiety. We synthesized acylium **2b<sup>+</sup>** (Scheme 1). Cyclic voltammetry featured two reversible processes at  $-0.63$  and  $-1.59$  V, which are significantly more positive values than in the case of **2a<sup>+</sup>** (Fig. 2). Radical **2b•** was generated *in situ* by bulk electrolysis at  $-0.78$  V. The radical was also synthesized by chemical reduction of acylium **2b<sup>+</sup>** with 0.5 equivalent of  $\text{Zn}(0)$  and isolated as a colourless solid in 84% yield. Of note, attempts to further reduce the radical with one equivalent of  $\text{Zn}(0)$  lead

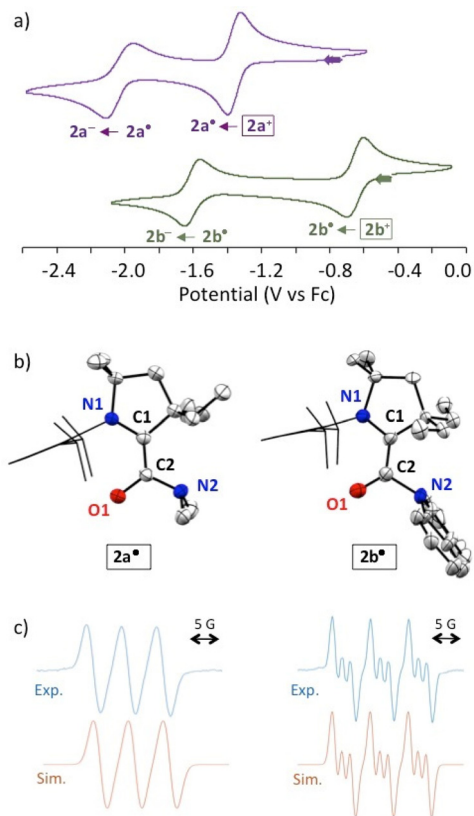


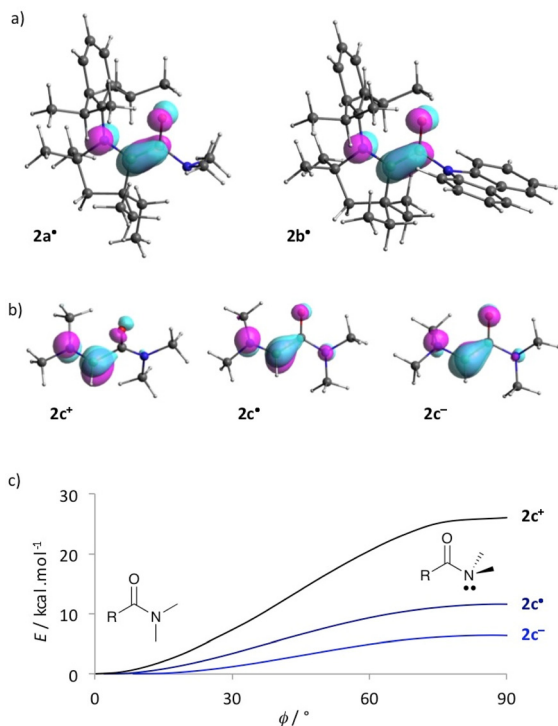
Fig. 2 (a) Cyclic voltammograms of a 1 mM solution for both the chloride salt of **2a<sup>+</sup>** (top) and **2b<sup>+</sup>** (below) in 0.1 M  $n\text{Bu}_4\text{NPF}_6$  acetonitrile solution at  $100\text{ mV s}^{-1}$  rates. (b) Solid state structures of radicals **2a•** and **2b•**. Thermal ellipsoids are set to 50% probability. Molecules of solvent, hydrogen atoms and ellipsoids on 2,6-diisopropylphenyl groups are omitted for clarity. (c) top: X-band EPR spectra of **2a•** (left) and **2b•** (right) in acetonitrile at room temperature; below: corresponding simulated spectra with the following set of parameters: **2a•**, Lorentzian line-broadening parameter  $L_w = 0.264$  and hyperfine coupling constant  $a(^{14}\text{N}) = 15.8$  MHz (1 nucleus); **2b•**,  $L_w = 0.143$ ,  $a(^{14}\text{N}) = 18.3$  MHz (1 nucleus) and 4.0 MHz (1 nucleus).

after work-up to the isolation of few crystals of the corresponding enaminal **3** (Scheme 1), which was characterized by X-ray diffraction (see ESI<sup>†</sup>). As in **2b•**, the carbazole is orthogonal to the carbonyl. This is in line with a previous study by Berkessel *et al.*, which shows that strong electron-withdrawing groups stabilize Breslow-type enols.<sup>14</sup> Interestingly, we were also able to isolate the corresponding keto tautomer **4** from the reaction of CAAC with  $N$ -formyl carbazole.<sup>15</sup>

As for **2a•**, a single crystal X-ray diffraction study of **2b•** revealed a pyramidalized  $\text{N}2$  centre (sum of angles around  $\text{N}2$ :  $330.7^\circ$ ), a formal lone pair perpendicular to the carbonyl and a long  $\text{C}2\text{-N}2$  distance (143.3 pm).<sup>16</sup> Importantly, in marked contrast with sensitive radical **2a•**, **2b•** is remarkably robust towards air in the solid state and in toluene. The observation of a fast decay by EPR monitoring required heating an aerated solution in ethanol at  $60^\circ\text{C}$ .

DFT<sup>17</sup> optimized structures of **2a-b•** at the b3lyp/6-311g(d,p) level of theory matched the experimental solid-state geometries, as well as the EPR isotropic hyperfine coupling constants,<sup>18</sup>





**Fig. 3** (a) Optimized DFT geometry of **2a-b•** with representations of corresponding SOMO. (b) Optimized DFT geometry of model **2c+**, **2c•** and **2c-** with representation of corresponding LUMO, SOMO and HOMO, respectively. (c) Energy in relaxed scan optimization of **2c+**, **2c•** and **2c-** as a function of  $\phi$ , the torsion angle between the formal N lone pair and the  $\pi_{\text{CO}}$  molecular orbital.

(Fig. 2c; **2a•**, computed  $a(^{14}\text{N})$ : 14 MHz, experimental: 15.8 MHz; **2b•**, computed  $a(^{14}\text{N})$ : 16 and 3 MHz, experimental: 18.3 and 4.0 MHz). The distribution of the Mulliken spin density (see also the representation of SOMO in Fig. 3a) is similar for both radicals (**2a•**: N1: 25%, C1: 41%, C2: 7%, O1: 26%; **2b•**: N1: 25%, C1: 37%, C2: 7%, O1: 30%). These values are reminiscent of the spin distribution of highly air persistent radical **D**, featuring a perfluorophenyl in place of the twisted amino groups. This suggests that the O-centred character of **2a-b•** was sufficient to disfavour triplet oxygen addition at the C1 atom.<sup>5d,8</sup> Accordingly, this reaction is predicted to be endergonic for **2a-b•** by  $\Delta G = +10.2$  and  $+21.2 \text{ kcal mol}^{-1}$ , respectively. Thus, we considered that a single electron transfer to dioxygen was a more plausible initiation step for the pathway of decay of **2a•** in the presence of air. Indeed, radical **2a•** stands out with a very low oxidation potential ( $-1.34 \text{ V}$ ) when compared to previously reported CAAC-based (amino)(carboxy)radicals (from  $-0.2 \text{ V}$  to  $-0.9 \text{ V}$ ).<sup>5</sup> Note that the computed ionization potential fits well with values for parented radicals (**2a•**: 5.1, **2b•**: 5.4, **C**: 5.1 and **D**: 5.5 eV). However, the conformational relaxation of **2a•**, which follows the vertical ionization of **2a•**, is especially exothermic (**2a**:  $-28$ , **2b**:  $-19$ , **C**:  $-19$  and **D**:  $-15 \text{ kcal mol}^{-1}$ ). Therefore, we concluded that the low oxidation potential of **2a•** was also due to the singular stability of **2a•** compared to other acyliums of the series. Indeed, the di(methyl)amino group has a chameleonic behaviour: it is twisted and acts as a  $-I$  attractor in

radical **2a•**, but it is a fully conjugated strong  $+M$  donor (stronger than the aromatic carbazole of **2b•**) in acylium **2a+**.

To get further insights, we considered simplified acylium, radical and enolate, **2c+**, **2c•** and **2c-** respectively, which feature a dimethylaminocarbene in place of the bulky CAAC pattern. Note that in acyliums **2a-c+** the iminium moieties are perpendicular to the carbonyl, whereas the N-C-CO pattern is fully conjugated in radicals **2a-c•** and enolates **2a-c-**. Interestingly, the small model compound **2c•** differs from CAAC-based radicals **2a-b•** with a fully conjugated amide moiety and only a slight pyramidalization at the nitrogen is found in **2c-**; the conformations of **2c+**, **2c•** and **2c-** with formal N2 nitrogen lone pair perpendicular to the carbonyl are transition states (Fig. 3b). However, introducing a radical or an anion in  $\alpha$  position of the carbonyl significantly weakens the amide bond. Indeed, the formal one electron reduction to afford **2c•** (respectively **2c-**) consists in populating the LUMO of **2c+** (SOMO of **2c•**, respectively) with anti-bonding character between C2 and N2. Accordingly, the energy barrier for full twisting dramatically decreases from **2c+** ( $\Delta G^\ddagger = +26.2 \text{ kcal mol}^{-1}$ ) to **2c•** ( $+7.1 \text{ kcal mol}^{-1}$ ) and **2c-** ( $+6.7 \text{ kcal mol}^{-1}$ ).

Amido groups have been classified as latent rotational stereoelectronic chameleons by Alabugin *et al.*<sup>19</sup> Misalignment of the nitrogen lone pair with the carbonyl usually requires polycyclic structures or high steric strain; however, the enhanced flexibility of an amide bond that results from an adjacent radical centre has gone unnoticed to date. Beyond implications for the design of bench-stable organic radicals, it is likely that natural evolution has already taken advantage of such redox-chameleonic behaviour.<sup>20</sup> This effect should not be overlooked in future studies on glycol enzymes or peptidyl radical chemistry.

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## Conflicts of interest

There are no conflicts to declare.

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