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

 Jesse L. Peltier,^a Melinda R. Serrato,^a Valentin Thery,^b Jacques Pecaut,^c Eder Tomás-Mendivil,^b Guy Bertrand,^a Rodolphe Jassar^a and David Martin^{a,b}

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.¹ 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,^{1c,d} but are commonly involved in synthetic radical peptidic chemistry.²

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.³ The protein environment also precludes the formation of C–C dimers, which are usually obtained with simpler molecular models.^{3e–i} In 2013, we took advantage of the bulky pattern of cyclic (alkyl)(amino)carbene (CAAC)^{4–6} to synthesize and isolate monomeric (amino)(carboxy) C-radical **C** under inert atmosphere.^{5a} In addition, we showed that increasing the electron-withdrawing properties of the carbonyl substituent,

such as in compound **D**, resulted in radicals with remarkable air-persistence.^{5d,7} A schematic molecular orbital analysis enables the rationalization of this effect. Indeed, the singly occupied molecular orbital (SOMO) is a bonding combination of π_{CO}^* and π_{CN}^* (Fig. 1b). An electron-withdrawing substituent on the carbonyl lowers the energy of the π_{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.^{5d,8}

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

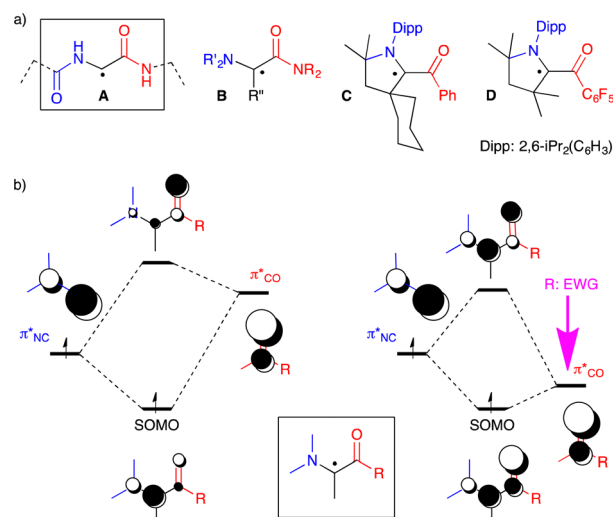


Fig. 1 (a) Glycyl radical pattern **A** in Enzymes, (amino)(amido) C-radical **B**, bottle-able push-pull C-radical **C** (air sensitive) and **D** (highly air-persistent); (b) schematic representations of SOMO of an (amino)(carbonyl) C-radical built from π_{NC}^* and π_{CO}^* , left: “classical” case,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

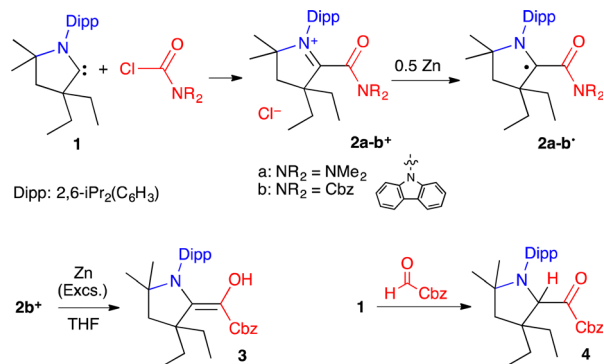
^a UCSD-CNRS Joint Research Chemistry Laboratory (IRL 3555), Department of Chemistry and Biochemistry, University of California San Diego, La Jolla, California 92093-0358, USA

^b University Grenoble Alpes, CNRS, DCM, Grenoble 38000, France.
 E-mail: david.martin@univ-grenoble-alpes.fr

^c University Grenoble Alpes, CEA, CNRS, INAC-SyMMES, UMR 5819, Grenoble 38000, France

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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⁺** 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* Fc/Fc⁺), corresponding to the formation of **2a•** and the enolate **2a⁻**, 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⁺** with 0.5 equivalent of 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 N2: 331.6°). The lone pair of the amide nitrogen is not conjugated, but perpendicular to the carbonyl. As a result, the long C2–N2 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).⁹

Acyclic twisted amide patterns usually require the deactivation of the nitrogen with an ancillary electron-withdrawing substituent or the incorporation into an aromatic ring.^{10,11} The local environment of N2 is more reminiscent of “anti-Bredt” amides or ureas, which feature a polycyclic saturated backbone with a bridgehead nitrogen.^{12,13} These compounds are not stable when there is a significant twisting around the (OC)–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.⁵

We turned to a carbazole substituent to increase the electron-withdrawing capability of the carbonyl moiety. We synthesized acylium **2b⁺** (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⁺** (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⁺** with 0.5 equivalent of Zn(0) and isolated as a colourless solid in 84% yield. Of note, attempts to further reduce the radical with one equivalent of Zn(0) lead

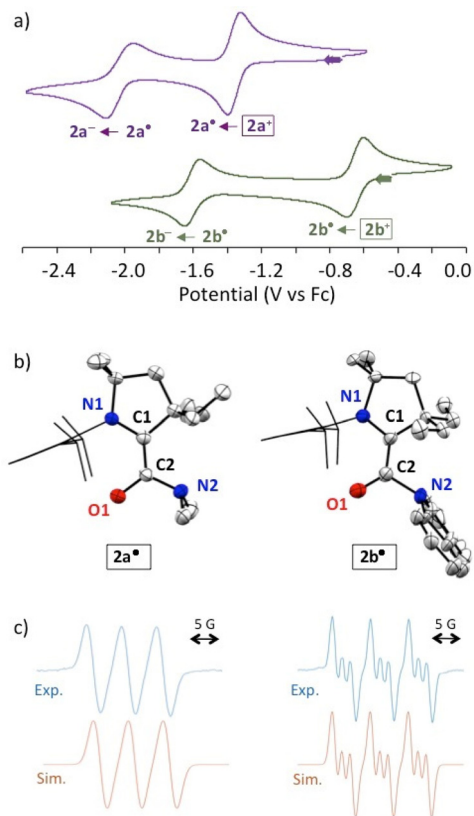


Fig. 2 (a) Cyclic voltammograms of a 1 mM solution for both the chloride salt of **2a⁺** (top) and **2b⁺** (below) in 0.1 M *n*Bu₄NPF₆ acetonitrile solution at 100 mV s⁻¹ rates. (b) Solid state structures of radicals **2a•** and **2b•**. Thermal ellipsoids are set to 50% probability. Molecules of solvent, 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[†]). 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.¹⁴ Interestingly, we were also able to isolate the corresponding keto tautomer **4** from the reaction of CAAC with *N*-formyl carbazole.¹⁵

As for **2a•**, a single crystal X-ray diffraction study of **2b•** revealed a pyramidalized N2 centre (sum of angles around N2: 330.7°), a formal lone pair perpendicular to the carbonyl and a long C2–N2 distance (143.3 pm).¹⁶ 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 °C.

DFT¹⁷ 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,¹⁸



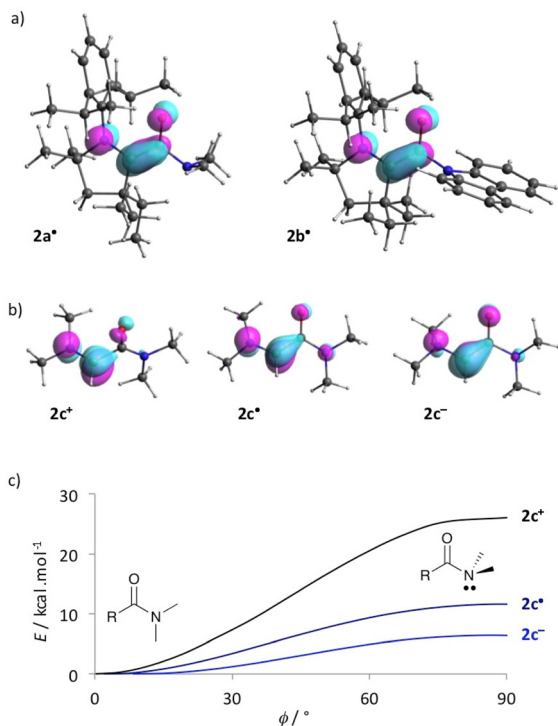


Fig. 3 (a) Optimized DFT geometry of **2a-b•** with representations of corresponding SOMO. (b) Optimized DFT geometry of model **2c⁺**, **2c•** and **2c⁻** with representation of corresponding LUMO, SOMO and HOMO, respectively. (c) Energy in relaxed scan optimization of **2c⁺**, **2c•** and **2c⁻** as a function of ϕ , the torsion angle between the formal N lone pair and the π_{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.^{5d,8} Accordingly, this reaction is predicted to be endergonic for **2a-b•** by $\Delta G = +10.2$ and $+21.2$ 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 V) when compared to previously reported CAAC-based (amino)(carboxy)radicals (from -0.2 V to -0.9 V).⁵ 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 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 α 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⁺** ($\Delta G^\ddagger = +26.2$ kcal mol⁻¹) to **2c•** ($+7.1$ kcal mol⁻¹) and **2c⁻** ($+6.7$ kcal mol⁻¹).

Amido groups have been classified as latent rotational stereoelectronic chameleons by Alabugin *et al.*¹⁹ 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.²⁰ 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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