



# Basicity as a Thermodynamic Descriptor of Carbanions Reactivity with Carbon Dioxide: Application to the Carboxylation of $\alpha,\beta$ -Unsaturated Ketones

Pietro Franceschi<sup>1†</sup>, Catia Nicoletti<sup>1†</sup>, Ruggero Bonetto<sup>1</sup>, Marcella Bonchio<sup>1</sup>, Mirco Natali<sup>2</sup>, Luca Dell'Amico<sup>1</sup> and Andrea Sartorel<sup>1\*</sup>

<sup>1</sup>Nano and Molecular Catalysis Laboratory, Department of Chemical Sciences, University of Padova, Padova, Italy, <sup>2</sup>Department of Chemical, Pharmaceutical and Agricultural Sciences (DOCPAS), University of Ferrara, and Centro Interuniversitario per La Conversione Chimica Dell'Energia Solare (SOLARCHEM), Ferrara, Italy

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### \*Correspondence:

Andrea Sartorel  
andrea.sartorel@unipd.it

<sup>†</sup>These authors have contributed  
equally to this work

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The utilization of carbon dioxide as a raw material represents nowadays an appealing strategy in the renewable energy, organic synthesis, and green chemistry fields. Besides reduction strategies, carbon dioxide can be exploited as a single-carbon-atom building block through its fixation into organic scaffolds with the formation of new C-C bonds (carboxylation processes). In this case, activation of the organic substrate is commonly required, upon formation of a carbanion  $C^-$ , being sufficiently reactive toward the addition of  $CO_2$ . However, the prediction of the reactivity of  $C^-$  with  $CO_2$  is often problematic with the process being possibly associated with unfavorable thermodynamics. In this contribution, we present a thermodynamic analysis combined with density functional theory calculations on 50 organic molecules enabling the achievement of a linear correlation of the standard free energy ( $\Delta G^0$ ) of the carboxylation reaction with the basicity of the carbanion  $C^-$ , expressed as the  $pK_a$  of the  $CH/C^-$  couple. The analysis identifies a threshold  $pK_a$  of ca 36 (in  $CH_3CN$ ) for the  $CH/C^-$  couple, above which the  $\Delta G^0$  of the carboxylation reaction is negative and indicative of a favorable process. We then apply the model to a real case involving electrochemical carboxylation of flavone and chalcone as model compounds of  $\alpha,\beta$ -unsaturated ketones. Carboxylation occurs in the  $\beta$ -position from the doubly reduced dianion intermediates of flavone and chalcone (calculated  $\Delta G^0$  of carboxylation in  $\beta = -12.8$  and  $-20.0$   $Kcalmol^{-1}$  for flavone and chalcone, respectively, associated with  $pK_a$  values for the conjugate acids of 50.6 and 51.8, respectively). Conversely, the one-electron reduced radical anions are not reactive toward carboxylation ( $\Delta G^0 > +20$   $Kcalmol^{-1}$  for both substrates, in either  $\alpha$  or  $\beta$  position, consistent with  $pK_a$  of the conjugate acids  $< 18.5$ ). For all the possible intermediates, the plot of calculated  $\Delta G^0$  of carboxylation vs.  $pK_a$  is consistent with the linear correlation model developed. The application of the  $\Delta G^0$  vs.  $pK_a$  correlation is finally discussed for alternative reaction mechanisms and for carboxylation of other C=C and C=O double bonds. These results offer a new mechanistic tool for the interpretation of the reactivity of  $CO_2$  with organic intermediates.

**Keywords:** carbon dioxide fixation, thermodynamic analysis, DFT calculations, reaction intermediates, unsaturated carbonyl

## INTRODUCTION

The activation and transformation of small molecules are pillars of artificial photosynthesis. In particular, carbon dioxide is an appealing target substrate because it is the product of combustion of organic compounds, and its levels in the atmosphere are continuously rising due to anthropogenic emissions while contributing to the greenhouse effect and global warming. Activation of CO<sub>2</sub> can be accomplished through reduction routes (Francke et al., 2018; Melchionna et al., 2021) in which desirable products are carbon monoxide, formic acid, methanol, methane, or > C<sub>2</sub> species (Albero et al., 2020). Alternatively, carbon dioxide can be exploited in cyclic carbonates or heterocycle formation (North et al., 2010; Fiorani et al., 2015; Yu and He, 2015; Guo et al., 2021; Vieira et al., 2018, 2019; Faria et al., 2021) or as a single-carbon-atom building block for its fixation into organic compounds (Liu et al., 2015; Cao et al., 2018; Cherubini-Celli et al., 2018; Tlili and Lakhdar, 2020; Zhang et al., 2020; Sahoo et al., 2021; Yuan et al., 2021; He et al., 2020) upon creation of new C-C or C-heteroatom bonds. Mechanistically, these processes can be accomplished through 1) the reduction of carbon dioxide to its radical anion, followed by its reaction with the organic scaffold (in dimethylformamide, E<sup>0</sup>(CO<sub>2</sub>/CO<sub>2</sub><sup>•-</sup>) = -2.21 V vs. saturated calomel electrode, SCE, corresponding to -1.97 V vs. standard hydrogen electrode) (Lamy et al., 1977; Otero et al., 2006; Berto et al., 2015) or 2) upon the formation of reduced intermediates of the organic substrate accomplished through chemical, electrochemical, or photochemical routes and their subsequent reactivity with CO<sub>2</sub> (Yuan et al., 2021).

This second possibility includes reductive activation of C-LG bonds (LG<sup>-</sup> is a leaving group, often a halide ion) (Meng et al., 2017; Isse et al., 1998; Isse et al., 2002; Isse and Gennaro, 2002; Scialdone et al., 2008; Durante et al., 2013) of C=C or C=N double bonds (Seo et al., 2017; Fan et al., 2018; Chen et al., 2020; Fan et al., 2018; Schmalzbauer et al., 2020) and of C-H bonds (Gui et al., 2017; Seo et al., 2017; He et al., 2020). Recent examples include activation of substituted olefins (Alkayal et al., 2020), of diverse carbonyl compounds (Okumura and Uozumi, 2021) including α-ketoamides and α-ketoesters (Cao et al., 2021), α,β-unsaturated esters (Sheta et al., 2021) and ketones (Chen et al., 2020), and of aldimines generated *in situ* for α-aminoacid synthesis (Naito et al., 2021).

In all cases, a carbanion (hereafter generally indicated as C<sup>-</sup>) is postulated to be the key intermediate that reacts with CO<sub>2</sub> although the nature of the reactive species and the mechanistic comprehension of the reactivity often remain elusive.

As reported by Mayr and coworkers (Li et al., 2020), the prediction of the reactivity of carbon-based nucleophiles with CO<sub>2</sub> is problematic using linear-free energy relationships based on nucleophilicity and electrophilicity parameters (Li et al., 2020; Orlandi et al., 2021); the failure to observe carboxylation products with a variety of nucleophilic carbanions may be caused by unfavorable thermodynamics of the reaction (Li et al., 2020).

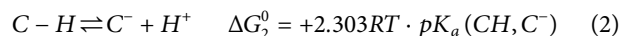
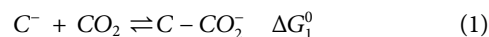
Therefore, we aimed at developing a general tool to predict the thermodynamics of a carboxylation reaction involving a carbon-based anion C<sup>-</sup> by exploiting the basicity of C<sup>-</sup> as a thermodynamic parameter. We propose a thermodynamic analysis supported by

density functional theory calculations on 50 small organic molecules that enable the to correlate the standard free energy of the carboxylation reaction with the basicity of the carbanion C<sup>-</sup>, expressed in terms of the pK<sub>a</sub> of the C-H/C<sup>-</sup> couple. We then apply the model to a real case involving electrochemical carboxylation of α,β-unsaturated carbonyls as the selected model substrates, and finally discuss alternative reaction mechanisms for the carboxylation of C=C and C=O double bonds.

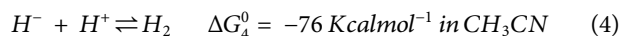
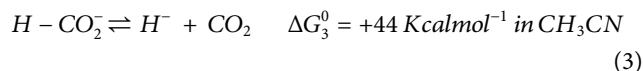
## RESULTS AND DISCUSSION

### Thermodynamic and DFT Analysis of Carbanions Reactivity with CO<sub>2</sub>

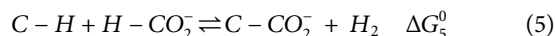
We employed a thermodynamic analysis to correlate the standard free energy of carboxylation of C<sup>-</sup> (ΔG<sub>1</sub><sup>0</sup> in Eq. 1) with the basicity of the carbanion (expressed on the basis of the pK<sub>a</sub> of the conjugate acid C-H, Eq. 2) as a thermodynamic descriptor of its reactivity. This analysis was inspired by a similar one reported by Kubiak and coworkers for correlating the hydricity of metal hydrides with the redox potential of the metal center and for evaluating the standard free energy for the reaction of the metal hydride with CO<sub>2</sub> to produce formate (Waldie et al., 2018).



We then considered Eqs. 3, 4, for which the ΔG<sup>0</sup> in acetonitrile is reported (Waldie et al., 2018), with the goal of expressing the ΔG<sub>1</sub><sup>0</sup> as a function of the pK<sub>a</sub> of the C-H/C<sup>-</sup> couple.



Eq. 5 derives from the sum of Eqs. 1–4:



ΔG<sub>5</sub><sup>0</sup> (in kcalmol<sup>-1</sup>), thus, results in

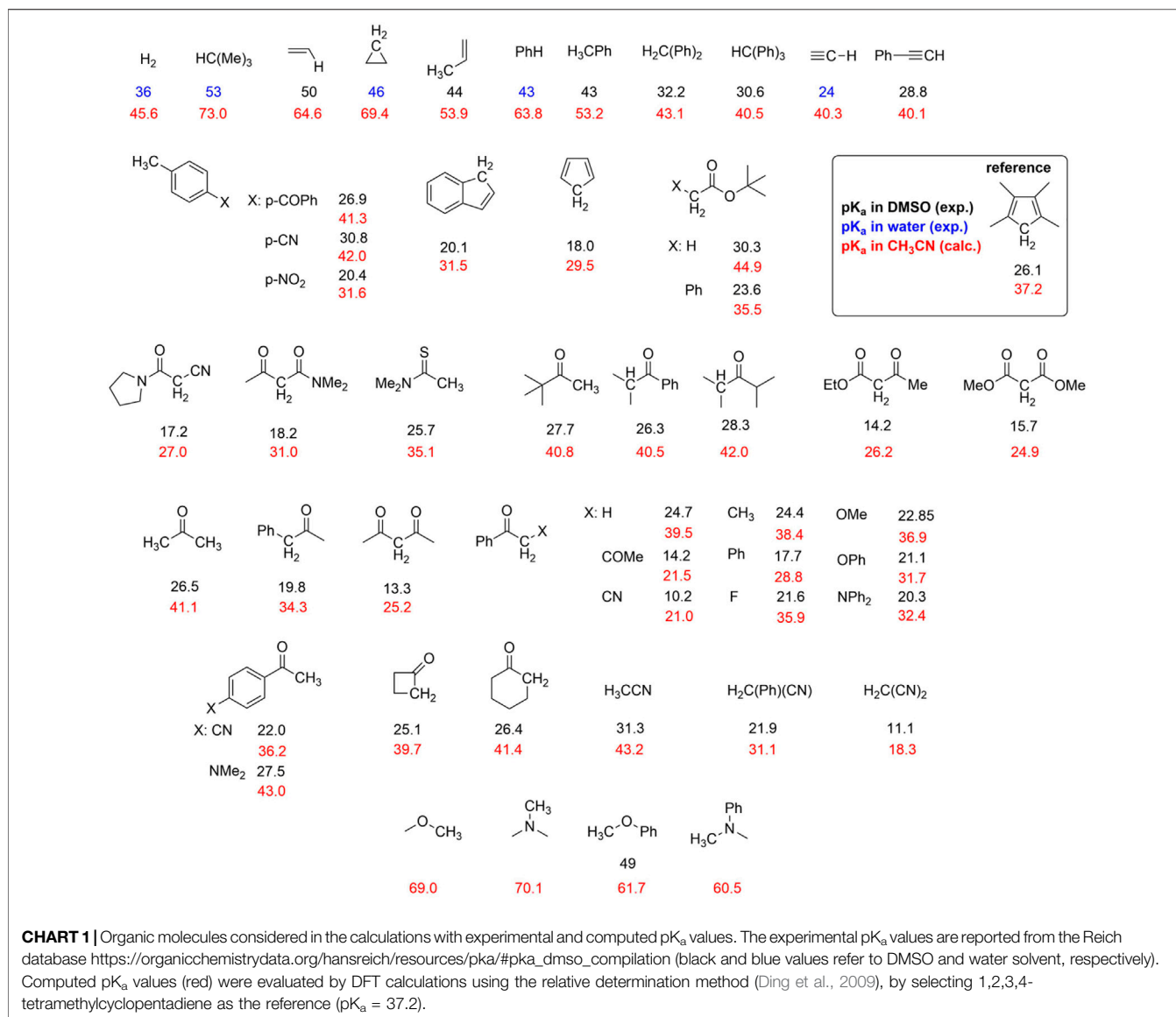
$$\Delta G_5^0 (\text{Kcalmol}^{-1}) = \Delta G_1^0 + 2.303RT \cdot pK_a(CH, C^-) + 44 - 76 \quad (6)$$

and, rearranging,

$$\{\Delta G_1^0 - \Delta G_5^0\} (\text{Kcal mol}^{-1}) = +32 - 2.303RT \cdot pK_a(CH, C^-) \quad (7)$$

Eq. 7, thus, predicts that the difference between ΔG<sub>1</sub><sup>0</sup> and ΔG<sub>5</sub><sup>0</sup> depends linearly on the pK<sub>a</sub> of the C-H/C<sup>-</sup> couple.

In order to evaluate the separate dependence of ΔG<sub>1</sub><sup>0</sup> and ΔG<sub>5</sub><sup>0</sup> on the pK<sub>a</sub> predicted by Eq. 7, we performed DFT calculations on 50 organic molecules containing C-H groups spanning different acidity with experimental pK<sub>a</sub> in the range 9 ÷ 53 reported mainly in dimethylsulfoxide (DMSO), see Chart 1 (experimental pK<sub>a</sub> values are reported from the Reich database: [https://organicchemistrydata.org/hansreich/resources/pka/#pka\\_dmso\\_compilation](https://organicchemistrydata.org/hansreich/resources/pka/#pka_dmso_compilation)). The choice of these 50 molecules was based on the simplicity of the organic scaffold, on the availability of the



experimental pK<sub>a</sub>, and on the possibility of spanning a sufficiently large range of acidity. For these molecules, we calculated the pK<sub>a</sub> of the C-H groups (Eq. 2), the ΔG<sup>0</sup> of carboxylation of the anion C<sup>-</sup> (Eq. 1), and the ΔG<sup>0</sup> referred to Eq. 5, employing a geometry optimization at a b3lyp/6-311g (d,p) level with frequency analysis (Mateos et al., 2020), and including a continuum model for the acetonitrile solvent. Acetonitrile was considered because it provides a high solubility of CO<sub>2</sub> of 0.28 M (Azcarate et al., 2016) and, thus, is widely used in carboxylation reactions. The calculations were done on the parent neutral molecules, on the corresponding carbanions, and on the carboxylated products, i.e., on 150 species.

Several experimental pK<sub>a</sub> values of C-H moieties are reported in DMSO; however, pK<sub>a</sub> is solvent-dependent (Daasbjerg, 1995; Workentin et al., 1995; Izutzu, 1990), and in acetonitrile, it can be rescaled according to pK<sub>a</sub>(CH<sub>3</sub>CN) = 11.6 + 0.98·pK<sub>a</sub>(DMSO); (Ding et al., 2009; Roszak et al., 2019).

When experimental values are not available (as in the case of some intermediates discussed in this work, *vide infra*), pK<sub>a</sub> can be predicted computationally. Thus, the pK<sub>a</sub> values of the C-H groups of the 50 species in **Chart 1** were calculated by DFT, using the *relative* determination method (Ding et al., 2009; Kadiyala et al., 2013; Fu et al., 2005) by employing 1,2,3,4-tetramethylcyclopentadiene reference (pK<sub>a</sub> value in CH<sub>3</sub>CN of 37.2 derived from an experimental pK<sub>a</sub> = 26.1 in DMSO).

As shown in the top panel of **Figure 1**, the plot of calculated vs. experimental (derived values in CH<sub>3</sub>CN) pK<sub>a</sub> values show a linear correlation with a slope of 1.17 ± 0.04, an intercept of -4.7 ± 1.6, and an R-square of 0.95; except for one case, all the points stand within the 95% confidence interval of the linear correlation; the major deviations are observed for species with experimental pK<sub>a</sub> values > 35, for which the available data are more limited and subject to uncertainties.

We then determined the ΔG<sup>0</sup> of reactions 1 and 5 (by the difference between the calculated free energy of products and

reactants) for the 50 organic substrates and plotted the calculated  $\Delta G_1^0$  and  $\Delta G_5^0$  values versus the calculated  $pK_a$  of the C-H/C<sup>-</sup> couples (**Figure 1**, bottom panel). Interestingly, the plot of  $\Delta G_1^0$  shows a marked dependence on  $pK_a$  (light gray dots in **Figure 1**, bottom) observing a trend fitted with a linear equation having a slope of  $-1.30 \pm 0.04 \text{ Kcalmol}^{-1}$  and an R-square of 0.96; the slope is close to the value of  $-2.303RT = -1.36 \text{ Kcalmol}^{-1}$  at 298 K (Wiedner et al., 2016) and, thus, indicates that the major dependence of the  $(\Delta G_1^0 - \Delta G_5^0)$  left term in **Eq. 7** on the  $pK_a$  is associated with the contribution of  $\Delta G_1^0$ . Consistently, the plot of  $\Delta G_5^0$  shows a weak  $pK_a$  dependence with a slope of  $0.06 \pm 0.03 \text{ Kcalmol}^{-1}$  resulting from the linear fitting (dark gray dots in **Figure 1**, bottom panel); this weak dependence can be explained by considering that  $\Delta G_5^0$  can be approximated as in **Eq. 8** (i.e., by considering negligible entropic effects and expressing the  $\Delta G_5^0$  as the difference/sum of bond enthalpies  $DH$  of the bonds being formed/broken in **Eq. 5**):

$$\Delta G_5^0 \approx -DH_{H-H} - DH_{C-C(OO)} + DH_{H-C(OO)} + DH_{C-H} \quad (8)$$

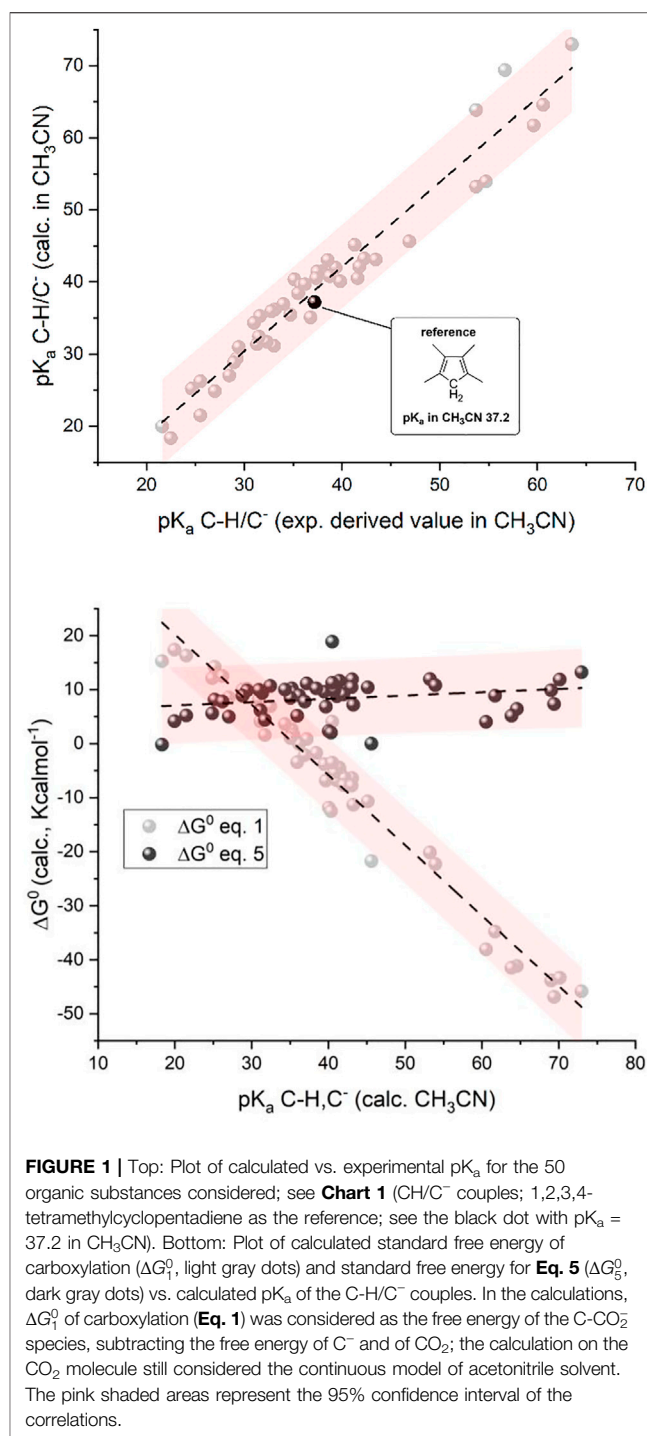
considering  $DH_{H-H} = +104 \text{ kcalmol}^{-1}$  and  $DH_{H-C(OO)} = +96 \text{ kcalmol}^{-1}$ , (Blanksby and Ellison, 2003), the weak dependence of  $\Delta G_5^0$  on  $pK_a$  is, thus, associated with the variation of  $DH$  of C-C(OO) and C-H bonds (**Eq. 5**).

In short, the presented analysis supports a linear correlation of the standard free energy of carboxylation of C<sup>-</sup> ( $\Delta G_1^0$  in **Eq. 1**) with the  $pK_a$  of the C-H/C<sup>-</sup> couples (**Eq. 2**) with a slope close to the theoretical value of  $-2.303RT = -1.36 \text{ Kcalmol}^{-1}$  at 298 K; interestingly, the calculations predict a threshold  $pK_a$  value of ca 36 (in CH<sub>3</sub>CN, corresponding to ca 25 in DMSO) for the C-H/C<sup>-</sup> couple that delimits positive/negative values of  $\Delta G_1^0$  of the carboxylation reaction.

Clearly, the  $\Delta G_1^0$  is associated with the equilibrium constant of **Eq. 1**, implying that, under suitable conditions (high CO<sub>2</sub> concentration or pressure), the carboxylation of the carbanion can be observed also in the case of a slightly positive  $\Delta G_1^0$ . Indeed, carboxylation of indene and phenylacetonitrile (calc.  $pK_a$  31.5 and 31.1, respectively; calc.  $\Delta G_1^0$  +7 and +4  $\text{Kcalmol}^{-1}$ , respectively) was observed in DMSO in the presence of carbon dioxide, 18-crown-6 and K<sub>2</sub>CO<sub>3</sub> as a base (Chiba et al., 1992; Chiba et al., 1994). The occurrence of an equilibrium in **Eq. 1** is also associated with microscopic reversibility, by which backward decarboxylation can occur (Destro et al., 2020; Kong et al., 2020; Zhou et al., 2021): carboxylation and decarboxylation processes are typically associated with a low energy barrier in aprotic solvents (Zhou et al., 2021).

## Evaluation of the Model for Electrochemical Carboxylation of $\alpha,\beta$ -Unsaturated Carbonyls

We then examined the consistency of the predictive model with the experimental electrochemical carboxylation of flavone and chalcone as representatives of  $\alpha,\beta$ -unsaturated carbonyl scaffolds retaining significant biological interest (Zhuang et al., 2017; Pietta, 2000). Moreover, under cathodic conditions, these substrates lead to the formation of multiple reduced



intermediates, thus providing an ideal platform to assess their reactivity with carbon dioxide: the electrochemical methodology is indeed suitable to selectively generate the desired intermediate by tuning the operating potential.

## Carboxylation of Flavone

Cyclic voltammetry of flavone **F** under cathodic scan shows a first, quasi-reversible wave at  $E_{1/2} = -2.09 \text{ V}$  vs  $Fc^+/Fc$  ( $\Delta E = 120 \text{ mV}$ )

due to the one-electron reduction of **F** to the flavone radical anion, **F(RA)** (see **Figure 2**); scanning the CV analysis toward more negative potentials, a second, irreversible wave is observed peaking at  $E = -2.71$  V vs  $Fc^+/Fc$ , associated with the formation of the dianion **F(DA)** and its further reduction (see **Figure 2**); previous polarographic evidence suggests the occurrence of a two-electron process for this second wave due to a further irreversible reduction of **F(DA)** at this potential (Vakulskaya et al., 2011). Under  $CO_2$  saturation, the first wave becomes completely irreversible, and the cathodic peak shifts toward less negative potentials by 50 mV (**Figure 2**). A major change is instead associated with the second wave, suggesting reactivity of **F(DA)** with  $CO_2$ ; the decrease of the current suggests that the presence of  $CO_2$  inhibits the further reduction of the **F(DA)** with the latter likely involved in a different reaction pathway with  $CO_2$ .

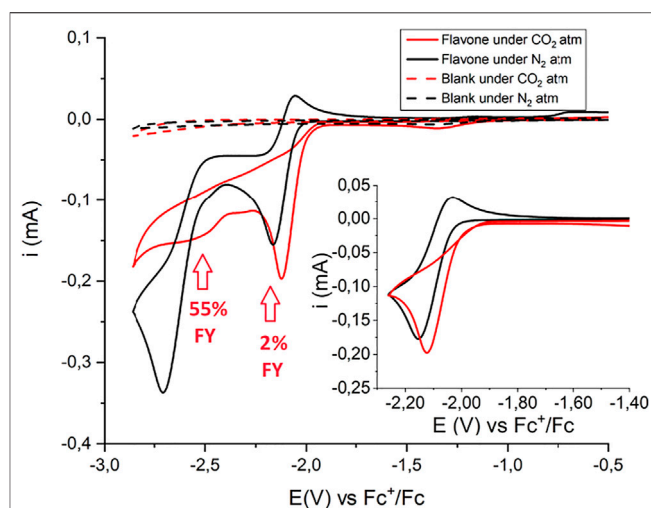
Controlled potential electrolysis (CPE) experiments were then performed to assess the reactivity of both the **F(RA)** and **F(DA)** species by applying a suitable operating potential to a glassy carbon rod working electrode. Electrolysis was conducted in a cell with two compartments separated by a ceramic frit. To evaluate the Faradaic yield of formation of the carboxylation product(s), an esterification procedure was performed involving treatment of the electrolyzed solution with  $H_2SO_4$  in methanol for 1 h under microwave heating at  $80^\circ C$  (**Scheme 1**).

**Reactivity of flavone radical anion, F(RA):** In the presence of  $CO_2$ , a CPE held at  $-2.21$  V (a potential associated with the electrogeneration of **F(RA)**), led to the production of flavanone-2-carboxylic acid methyl ester in a 2% Faradaic yield (**Scheme 1**, see also the red arrow in **Figure 2**; in CPE, a 20 mM concentration of flavone was used, fourfold higher with respect to CV conditions), and the electrolysis led mainly to the formation of 2,2-biflavanone (racemate and meso forms) dimerization by-products (see **Supporting Information**) (Sisa et al., 2010). This result suggests that **F(RA)** is not an intermediate favorably reacting with  $CO_2$  along a carboxylation reaction.

The unfavorable reactivity of **F(RA)** with  $CO_2$  is supported by DFT analysis. **F(RA)** was optimized as a doublet, displaying spin density mainly at the carbon in  $\beta$  to the carbonyl group (0.28 spin density) at the ortho and para positions of the phenyl ring in  $\beta$  (0.16–0.22 spin density) and at the carbonyl group (0.12 and 0.13 spin density at the carbon and oxygen atoms, respectively); no significant spin density is observed at the carbon in  $\alpha$  to the carbonyl (see **Supporting Figure S1**).

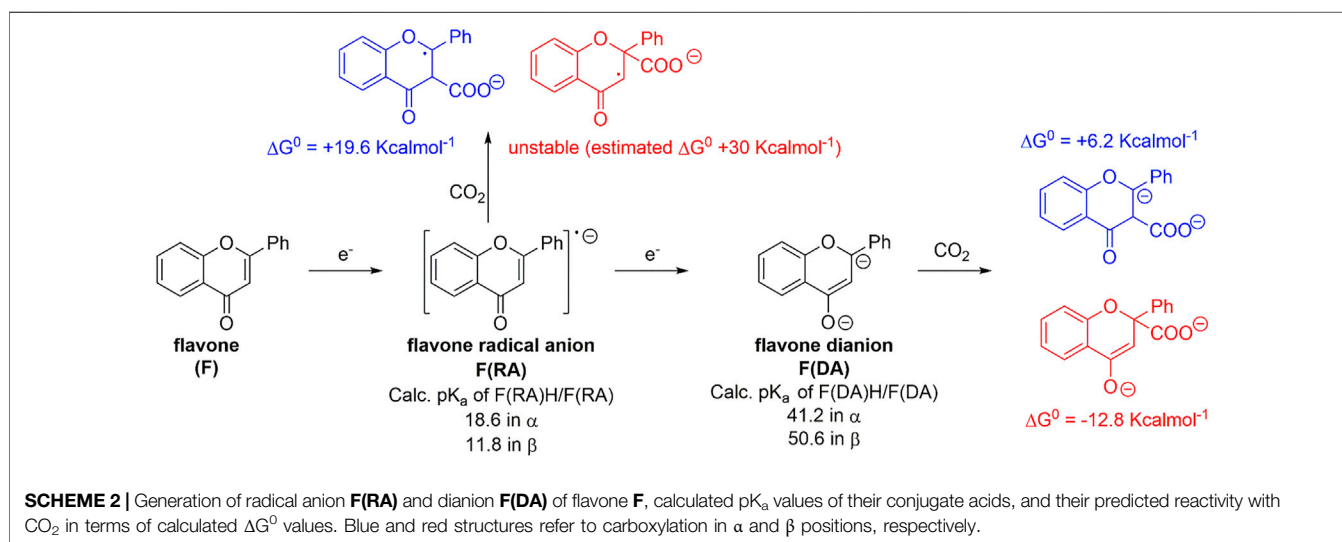
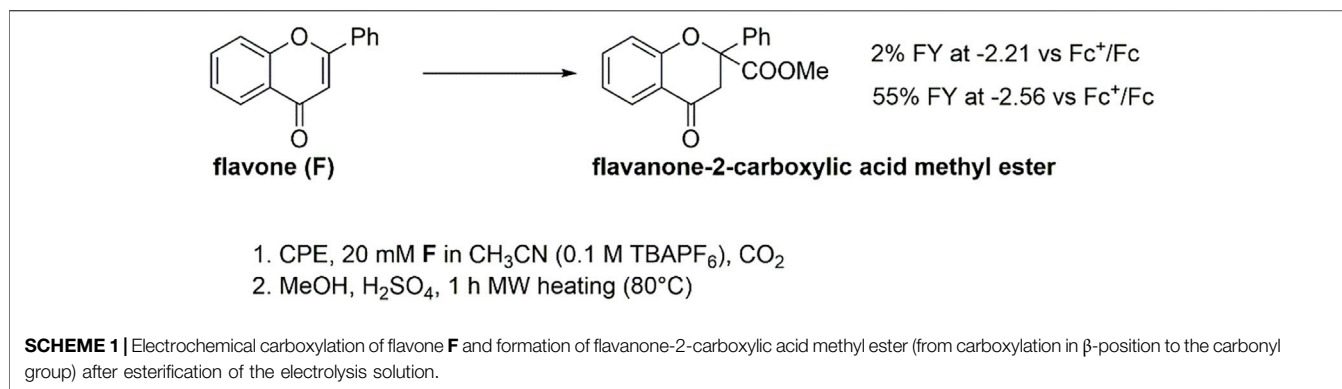
Calculations on the conjugate acids of **F(RA)** were performed by considering protonation of **F(RA)** in  $\alpha$  or  $\beta$  positions; the computed free energies allowed to determine the calculated  $pK_a$  of the C-H/ $C^-$  couples according to the abovementioned procedure, resulting in  $pK_a$  values of 18.6 and 11.8 for the  $\alpha$  and  $\beta$  positions, respectively. Both these values fall above the previously discussed threshold to reach a favorable carboxylation process. Consistently, a calculated  $\Delta G^0$  of  $+19.6$  kcalmol $^{-1}$  was found for the carboxylation of **F(RA)** in  $\alpha$  position, and the carboxylation product of **F(RA)** in the  $\beta$  position was unstable during the optimization process, decomposing into  $CO_2$  and **F(RA)**; see **Scheme 2** and **Figure 3**.

**Reactivity of flavone dianion, F(DA):** CPE at  $-2.56$  V vs  $Fc^+/Fc$  (**Scheme 1**, see also the red arrow in **Figure 2**) leads to the



**FIGURE 2** | CV of 5 mM Flavone in  $CH_3CN$  with 0.1 M tetrabutylammonium hexafluorophosphate supporting electrolyte under  $N_2$  (black traces) and  $CO_2$  (red traces). The inset shows the scan conducted in a narrow potential range and limited to the first reduction process. Glassy carbon working electrode (GC, 0.3 cm diameter,  $0.07$  cm $^2$  geometric area), Pt counter electrode, Ag/AgCl reference electrode, scan rate  $0.1$  V s $^{-1}$ . Potentials were then converted to  $Fc^+/Fc$  registering a CV scan of a ferrocene solution under the same conditions. The red arrows and the corresponding FY values refer to the carboxylation process and to the production of flavanone-2-carboxylic acid methyl ester. In principle, the operating potentials could be compatible with the production of the carbon dioxide radical anion,  $CO_2^{\bullet -}$ : the  $E^0(CO_2/CO_2^{\bullet -}) = -2.21$  V vs SCE corresponding to  $-2.63$  V vs.  $Fc^+/Fc$  (Lamy et al., 1977; Berto et al., 2015; Christensen et al., 1990). However, only a slight increase of the CV traces below  $-2.7$  V is observed passing from  $N_2$  to  $CO_2$  in the control experiments in the absence of flavone (dashed black and red traces, respectively). With GC electrodes, reduction of  $CO_2$  suffers indeed of an additional overpotential, and gives CO with almost quantitative Faradaic yield, accompanied by formation of  $CO_3^{2-}$  (Berto et al., 2015; Christensen et al., 1990). Considering the ca 15-fold larger current observed in the presence of flavone (5 mM) and the higher concentrations of flavone used in CPE experiments (20 mM), the reduction of flavone is envisaged as the predominant route under these conditions.

$\beta$ -C carboxylation of flavone with 55% Faradaic yield upon isolation of the flavanone-2-carboxylic acid methyl ester. This evidence indicates a reaction of **F(DA)** with  $CO_2$  in the  $\beta$ -position (Senboku et al., 2011; Senboku et al., 2012). The reactivity of **F(DA)** with  $CO_2$  was supported by DFT calculations. **F(DA)** was optimized as a singlet state (**Supporting Figure S2**), and similarly to the case of **F(RA)** previously discussed, calculations on the conjugate acids of the **F(DA)** were performed by considering protonation of **F(DA)** in the  $\alpha$  and  $\beta$  positions to determine the calculated  $pK_a$  of the C-H/ $C^-$  couples:  $pK_a$  values of 41.2 and 50.6 were obtained for the conjugate acids of **F(DA)** in the  $\alpha$  and  $\beta$  positions, respectively (**Scheme 2** and **Figure 3**). Concerning the carboxylation upon reaction of **F(DA)** with  $CO_2$ , calculated  $\Delta G^0$  of  $+6.2$  kcalmol $^{-1}$  and of  $-12.8$  kcalmol $^{-1}$  were found for the carboxylation of **F(DA)** in the  $\alpha$  and  $\beta$  positions, respectively (**Scheme 2** and **Figure 3**), thus supporting the preferred carboxylation in  $\beta$ -position (Senboku et al., 2011; Senboku et al., 2012).



Importantly, the calculated  $\Delta G^0$  vs  $\text{pK}_a$  values for **F(RA)** (in the  $\alpha$  position) and **F(DA)** (in both  $\alpha$  and  $\beta$  positions) were observed to be consistent with the trend predicted in **Figure 1** right for the 50 organic substrates (**Scheme 2** and **Figure 3**).

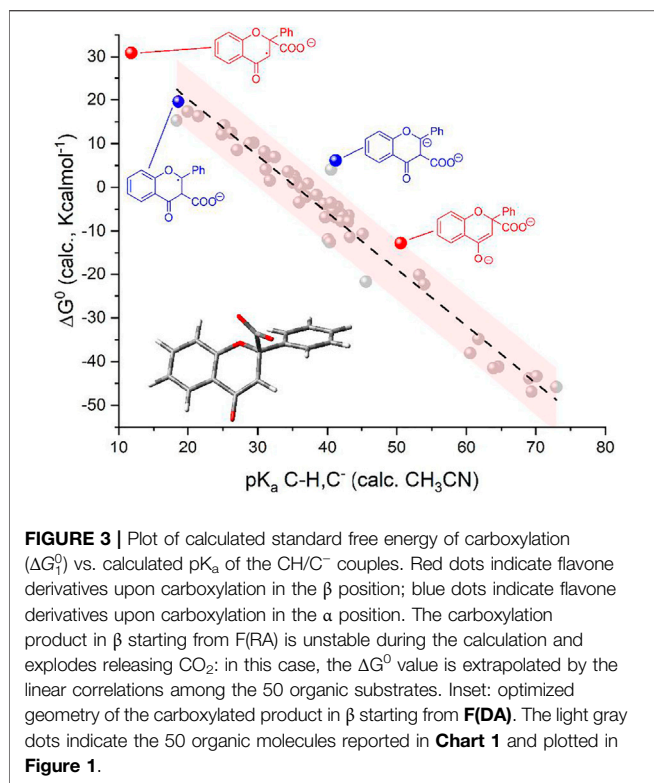
### Carboxylation of *Trans*-Chalcone

An analogous scenario was reached exploring the carboxylation of *trans*-chalcone (**C**). The CV analysis under cathodic scan and  $\text{N}_2$  atmosphere shows the presence of a first irreversible wave peaking at  $-1.9 \text{ V}$  vs  $\text{Fc}^+/\text{Fc}$ , attributed to the formation of the chalcone radical anion **C(RA)**, **Supplementary Figure S3**. This is followed by a second wave, composed of two contributions at  $E_{1/2} = -2.3 \text{ V}$  vs  $\text{Fc}^+/\text{Fc}$  and  $E_{1/2} = -2.45 \text{ V}$  vs  $\text{Fc}^+/\text{Fc}$ , likely associated with the formation of the chalcone dianion **C(DA)** (Chen et al., 2020); the splitting of the wave into two contributions with a halved intensity with respect to the first one could be ascribed to the rotation of the C-C bond in **C(RA)**, leading to two *cis/trans* isomeric forms that are further reduced to **C(DA)** at slightly different potentials. Upon addition of  $\text{CO}_2$ , the first wave is almost unaffected, and the second one shows marked changes with the formation of a single irreversible wave peaking at  $E_{\text{pc}} = -2.5 \text{ V}$  vs.  $\text{Fc}^+/\text{Fc}$  and, thus, suggesting reactivity of **C(DA)** with  $\text{CO}_2$ . This is confirmed by CPE experiments, that allowed the

isolation of methyl-4-oxo-2,4-diphenylbutanoate with 41% FY upon electrolysis at  $-2.7 \text{ V}$  vs  $\text{Fc}^+/\text{Fc}$  followed by esterification of the carboxylate product, consistent with effective carboxylation in the  $\beta$  position to the carbonyl group (**Scheme 3**).

Similar to what previously discussed in the case of flavone, the reactivity trend of chalcone reduced species **C(RA)** and **C(DA)** toward  $\text{CO}_2$  was supported by DFT calculations (**Scheme 4** and **Figure 4**). **C(RA)**, optimized as a doublet, shows a planar structure and a spin density localized mainly on the carbon in  $\beta$  to the carbonyl (0.33 spin density) and on the carbonyl group (0.18 and 0.19 spin density for C and O, respectively); see **Supplementary Figure S4**. Calculations on the conjugate acids of **C(RA)** by considering a protonation in the  $\alpha$  and  $\beta$  positions to the carbonyl, lead to the determination of  $\text{pK}_a$  values of 18.5 and 18.2 in the  $\alpha$  and  $\beta$  positions, respectively; these  $\text{pK}_a$  values are below the predicted threshold of reactivity with  $\text{CO}_2$ , and consistently, positive  $\Delta G^0$  of  $+22.0$  and of  $+20.2 \text{ kcalmol}^{-1}$  were obtained for the carboxylation of **C(RA)** in the  $\alpha$  and  $\beta$  positions, respectively, see **Scheme 4** and **Figure 4**.

Optimization of **C(DA)** as a singlet led to a planar structure (**Supplementary Figure S5**); calculations on the conjugate acids of **C(DA)** by inserting a proton in the  $\alpha$  and  $\beta$  positions, led to the determination of  $\text{pK}_a$  of 43.1 and 51.8 for C-H groups in the  $\alpha$  and



$\beta$  positions, respectively. Consistently, negative  $\Delta G^0$  for the carboxylation reaction involving  $C(DA)$  were determined of  $-3.9$  and  $-20.0$   $Kcalmol^{-1}$  for the  $\alpha$  and  $\beta$  positions, respectively (**Scheme 4** and **Figure 4**).

Again, the calculated  $\Delta G^0$  vs.  $pK_a$  values for  $C(RA)$  and  $C(DA)$  in both  $\alpha$  and  $\beta$  positions were observed to be consistent with the linear trend predicted in **Figure 1** for the 50 organic substrates (**Figure 4**) with all the points standing within the 95% confidence interval, supporting the need to generate the dianion of chalcone to achieve the carboxylation in the  $\beta$ -position as experimentally observed.

### Alternative Mechanisms and Perspectives in the Carboxylation of C=C and C=O Bonds

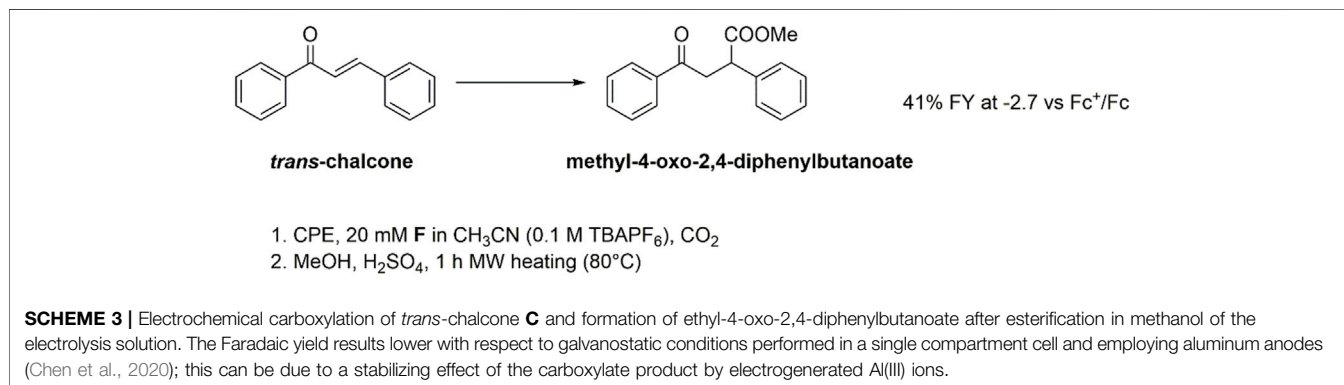
Based on the above discussion, some considerations of general relevance can be finally addressed and focused in particular on 1)

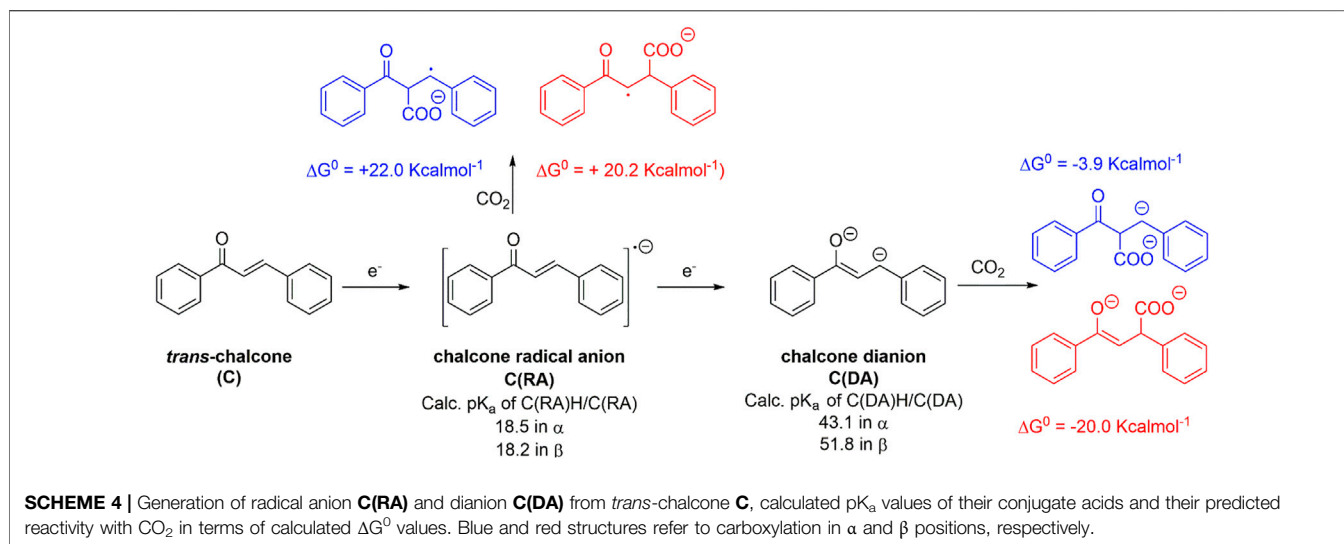
the reactivity of radical anions, generated from a one-electron reduction of the parent C=C bond; this type of intermediate is often envisaged in photochemical carboxylation processes (Nikolaitchik et al., 1996; Seo et al., 2017); 2) the reactivity of carbanions generated from an activation of C=O bonds, via an umpolung strategy (Juhl and Lee, 2018; Juhl et al., 2019; Cao et al., 2021).

In the case of  $\alpha,\beta$ -unsaturated carbonyl compounds, a positive, unfavorable  $\Delta G^0$  in the reactivity of the radical anion toward  $CO_2$  seems to be a general feature as predicted by the DFT calculations on other  $\alpha,\beta$ -unsaturated carbonyl scaffolds summarized in **Supplementary Table S1**. However, other reaction pathways that are alternative to the generation of a further reduced dianion intermediate can be envisaged to achieve carboxylation of this class of substrates. One possibility exploits hydrogen atom transfer (HAT) from a suitable HAT donor (Capaldo and Ravelli, 2017; Costas and Bietti, 2018). Still considering the representative case of flavone and chalcone, a HAT to  $F(RA)$  and  $C(RA)$  occurs preferentially in  $\beta$  positions to generate the corresponding flavone and chalcone anions,  $F(A)$  and  $C(A)$  (**Scheme 5**; these are  $12.8$  and  $11.9$   $Kcalmol^{-1}$  more stable with respect to the isomeric species generated by a HAT in the  $\alpha$  position to flavone and chalcone, respectively). Because the HAT is more favorable in the  $\beta$  position, the possible reactivity of  $F(A)$  and of  $C(A)$  with  $CO_2$  should occur in the  $\alpha$  position.

Calculations predict  $pK_a$  values of  $35.9$  and  $43.1$  for the conjugate acids of  $F(A)$  and  $C(A)$ , respectively, and the  $\Delta G^0$  for the carboxylation are  $+2.1$  and  $-3.9$   $Kcalmol^{-1}$  starting from  $F(A)$  and  $C(A)$ , respectively (**Scheme 5**); the  $pK_a$  and  $\Delta G^0$  values fit well with the model previously developed, standing within the 95% confidence interval (**Figure 5**). Therefore, the basicity of  $F(A)$  and  $C(A)$  is greatly enhanced with respect to the corresponding radical anions  $F(RA)$  and  $C(RA)$  with differences in the  $pK_a$  values of  $17.3$  and  $24.6$ , respectively; the enhancement of basicity leads to a favorable gain in the  $\Delta G^0$  of carboxylation in the  $\alpha$  position of  $17.5$  and  $25.9$   $Kcalmol^{-1}$  for flavone and chalcone, respectively, when passing from the radical anions to the anions. The use of a HAT donor additive can, thus, be considered in the carboxylation processes although the regioselectivity should be properly evaluated.

Although unfavorable in the case of  $\alpha,\beta$ -unsaturated carbonyls, the negligible reactivity of radical anion intermediates toward carboxylation should not be considered as a general feature of

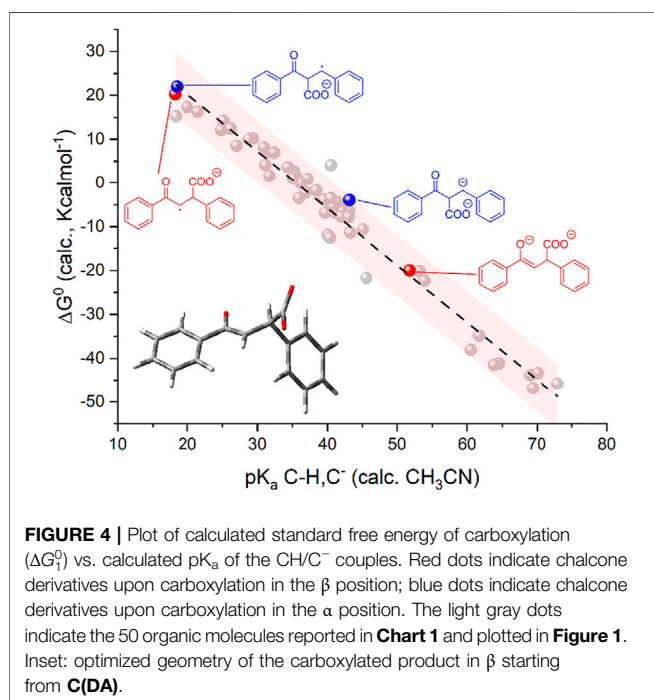




C=C double bonds. We performed DFT calculations on the radical anions of selected alkenes, such as ethylene, 2-butene, and diphenylethylene isomers as well as of phenanthrene as representative of a fully aromatic scaffold to calculate the corresponding basicity and the  $\Delta G^0$  of the carboxylation reaction involving these radical anions. The results are summarized in **Supplementary Table S1** and plotted in the  $\Delta G^0$  vs.  $pK_a$  graph of **Figure 6**. A nice match is observed between these data and those of the 50 organic substrates previously employed in the construction of the linear trend. Interestingly, these calculations predict that 1) radical anions of alkenes can be sufficiently basic to achieve a favorable  $\Delta G^0$  for carboxylation when hydrogen or alkyl groups

are bound to the C=C double bond; 2) phenyl groups bound to the carbon atoms of the C=C bond reduce the basicity of the radical anion and tend to disfavor the carboxylation (differences of ca 30  $pK_a$  units and of 40  $Kcalmol^{-1}$  in  $\Delta G^0$  of carboxylation are observed by comparing *trans*-2-butene and *trans*-1,2-diphenylethylene); 3) when phenyl groups are present, reactivity is expected to be favorable if one of the carbon atoms of the C=C bond does not bear phenyl substituents as in the case of 1,1-diphenylethylene; and 4) radical anions of C=C bonds in aromatic scaffolds show unfavorable basicity and carboxylation reactivity as in the case of phenanthrene. Further investigations on structure-reactivity analysis on this kind of substrate are ongoing.

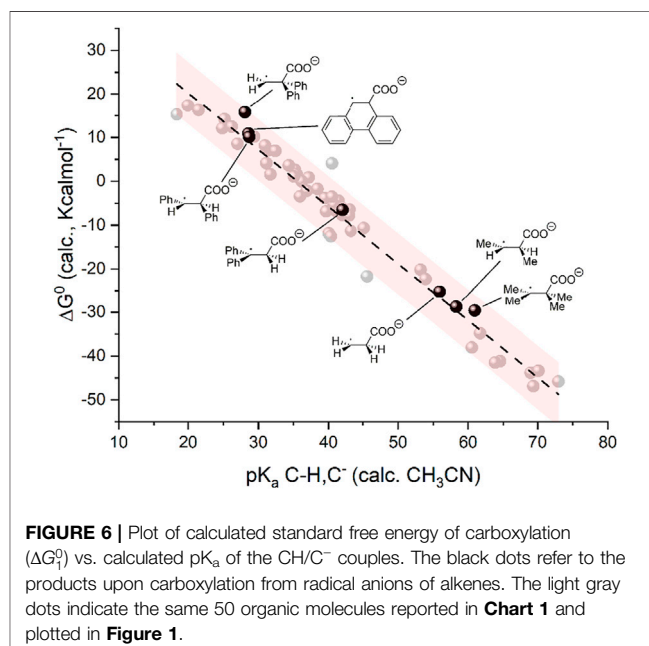
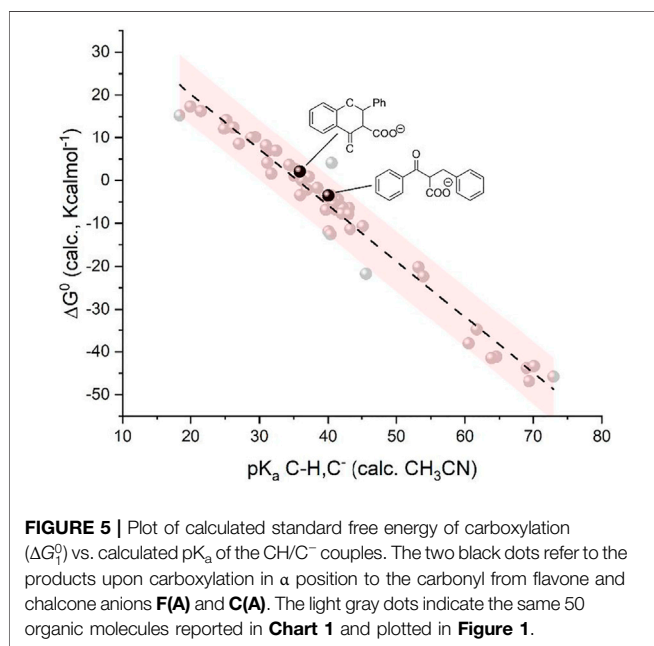
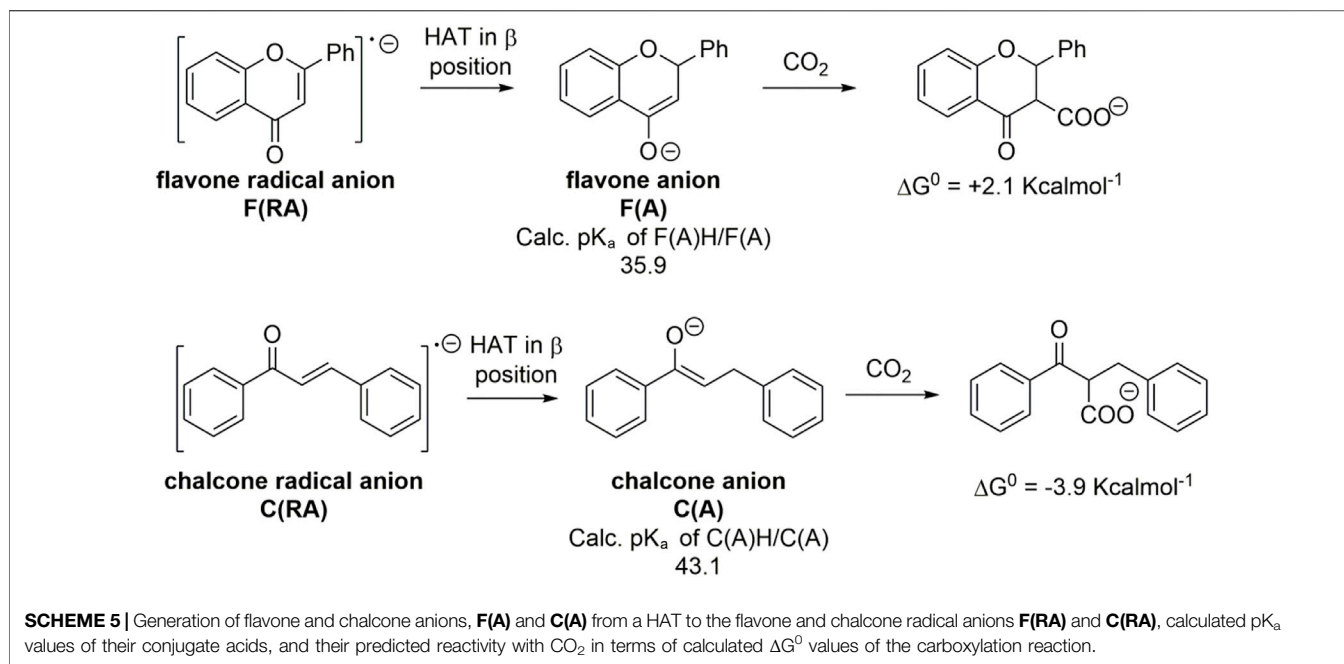
We finally verified if the model is suitable for the prediction of carboxylation of carbanions generated by activation of C=O groups through an umpolung strategy. In particular, we considered a carbanion of 4-fluorobenzaldehyde activated via a cyanohydrin intermediate (Juhl and Lee, 2018) and the carbanions of alkyl aryl ketones,  $\alpha$ -ketoesters, and aryl aldehydes generated through a photochemical process combining a trimethylsilyl (in the case of the alkyl aryl ketones and of  $\alpha$ -ketoesters) or triphenylsilyl (in the case of aryl aldehydes) activating/protecting group, see **Scheme 6** (Cao et al., 2021). Gratifyingly, the calculations predict a negative  $\Delta G^0$  for the carboxylation of such intermediates (Juhl et al., 2019), thus supporting the experimental outcome (see the yields of carboxylation in **Scheme 6**) (Juhl and Lee, 2018; Cao et al., 2021). In addition, the  $pK_a$  and  $\Delta G^0$  values fit well with the model previously developed (**Figure 7**).



## CONCLUSION AND PERSPECTIVES

We present a thermodynamic analysis combined with density functional theory calculations that enable linearly correlating the standard free energy  $\Delta G^0$  of the carboxylation reaction of a carbanion  $C^-$  with its basicity expressed as the  $pK_a$  of the  $CH/C^-$  couple. This offers a new mechanistic tool for the interpretation of the

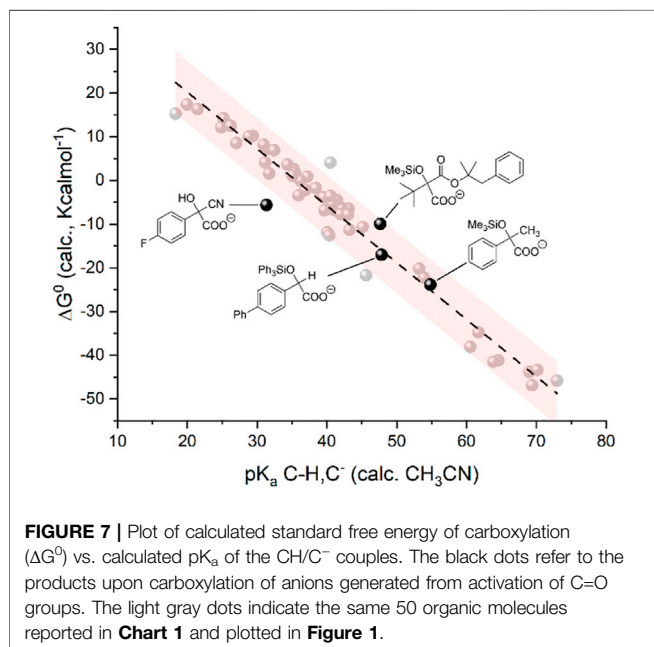
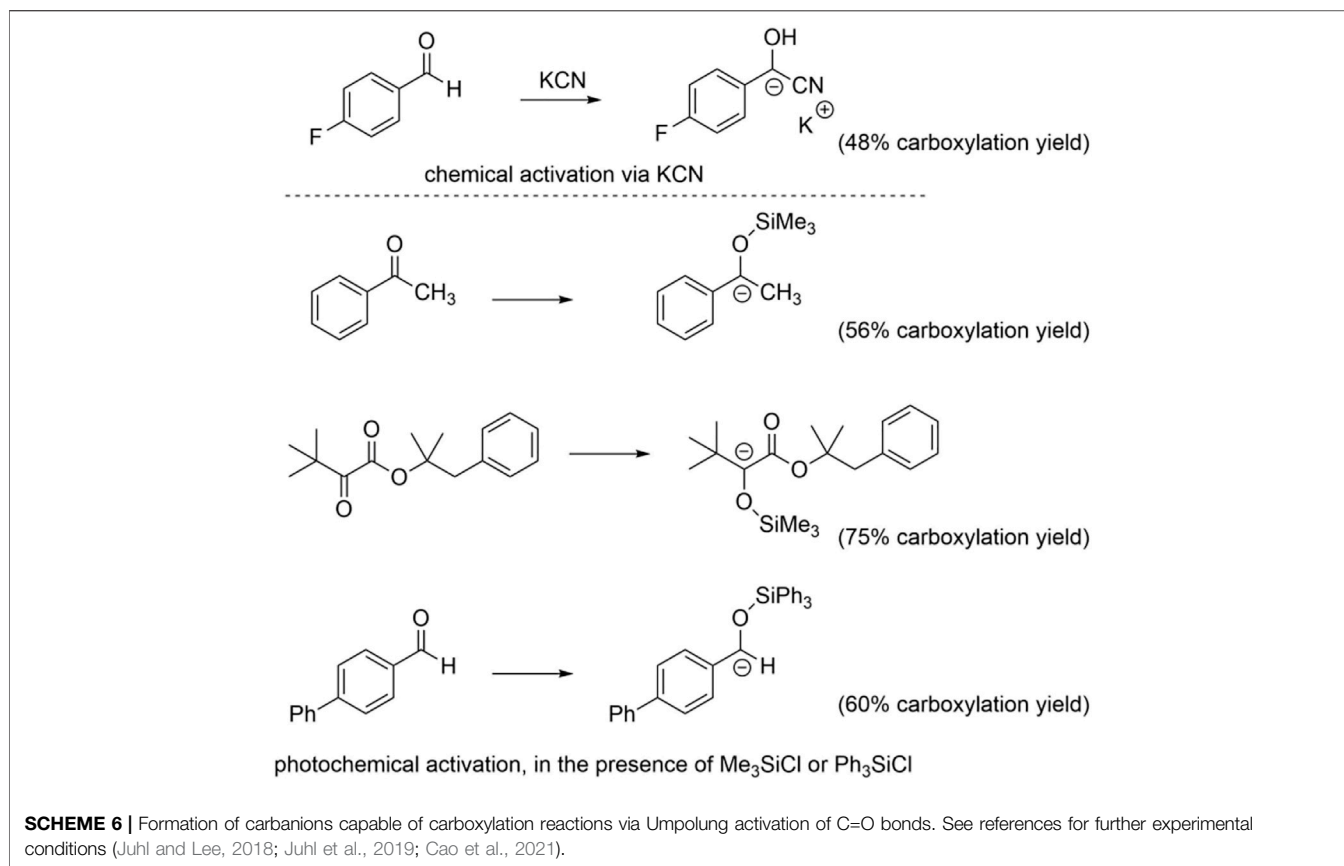




reactivity of  $\text{CO}_2$  with organic intermediates. The analysis identifies a threshold  $\text{pK}_a$  of ca 36 (in  $\text{CH}_3\text{CN}$ ) for the  $\text{CH}/\text{C}^-$  couple, above which the  $\Delta G^0$  of the carboxylation reaction is negative and, thus, indicative of a thermodynamically favorable process. Because fast tools are nowadays available for the estimation of  $\text{pK}_a$  of C-H groups (Roszak et al., 2019), the  $\text{pK}_a$  vs  $\Delta G^0$  correlation enables a fast analysis and prediction of the thermodynamics of the carboxylation reaction.

Application of the model to the electrochemical carboxylation of flavone and chalcone as representative compounds of  $\alpha,\beta$ -unsaturated ketones allows the prediction of the carboxylation occurring in the

$\beta$ -position from the doubly reduced dianion intermediates of the starting compounds ( $\Delta G^0$  of carboxylation in  $\beta = -12.8$  and  $-20.0 \text{ Kcalmol}^{-1}$  for flavone and chalcone, respectively, associated to  $\text{pK}_a$  values for the conjugate acid of 50.6 and 51.8, respectively). The one-electron reduced radical anions are instead not reactive toward carboxylation ( $\Delta G^0 > +20 \text{ Kcalmol}^{-1}$  for both substrates in either  $\alpha$  or  $\beta$  position, consistent with  $\text{pK}_a$  of the conjugate acid  $< 18.5$ ). In all cases, the calculated  $\text{pK}_a$  and  $\Delta G^0$  of carboxylation are consistent with the linear correlation model developed, thus supporting its application also to more complex organic scaffolds.



The analysis was extended to alternative carboxylation mechanisms and to other organic substrates that were already employed in carboxylation reactions in previous literature studies.

Further tuning of the model could consider possible specific stabilization of the species involved and, in particular, of the charged ones by the nature of the solvent or by the presence of additives. As discussed by (Pletcher and Slevin, 1996),  $Mg^{2+}$  ions are known to stabilize reduced intermediates and carboxylate species (Corbin et al., 2021) and are proposed to play a key role in the electrochemical carboxylation of benzalacetone ( $Mg^{2+}$  are typically generated under electrochemical conditions, when employing Mg sacrificial anodes) (Wang et al., 2017; Bhasha Sayyed and Sakaki, 2014).

## EXPERIMENTAL

The cyclic voltammetry (CV) characterizations were carried out with a three-electrode system controlled by a BASi EC Epsilon potentiostat-galvanostat. The working electrode was a glassy carbon disk electrode (BioLogic, nominal diameter 3 mm), the auxiliary electrode was a platinum electrode (BASi), and the reference electrode was an Ag/AgCl (NaCl 3 M) electrode; potentials were then referenced to the ferrocenium/ferrocene ( $Fc^+/Fc$ ) couple upon addition, at the end of each experiment session, of ferrocene to the analyte solutions as internal standard; 0.1 M tetrabutylammonium hexafluorophosphate ( $Bu_4NPF_6$ ) was used as a supporting electrolyte.

Constant potential electrolysis experiments were performed with a Metrohm Autolab PGSTAT204 potentiostat-galvanostat in combination with the NOVA 2.1.4 software (<https://www.metrohm-autolab.com/Products/Echem/Software/Nova.html>).

The cell generally employed for preparative electrolysis was a custom-made, six-necked, two-compartment glass cell with the two compartments being separated by a porous glass frit.

Quantitative gas chromatographic (GC) analysis were performed on a Shimadzu GC-2010 Pro gas chromatograph equipped with a flame ionization detector (FID). Every measurement was performed by automatic injection of 1  $\mu$ L of the sample solution. Quantification of the starting material and ester products was achieved by internal calibration of the instrument upon the construction of a calibration curve by the injection of known volumes of reagents and mesitylene as a standard. The response factor of the initial substrate was used also to quantify the ester product because the presence of one -COOCH<sub>3</sub> additional group with respect to the initial substrate is expected to have a minor effect in the FID response.

<sup>1</sup>H NMR spectra were recorded on a Bruker 300 Advance spectrometer equipped with BBO probe head 5 mm. NMR spectra were processed using MestReNova software.

EI-MS spectra were registered using an Agilent 6,850 Network GC system equipped with a 5975 Series MSD detector. ESI-MS spectra were acquired with an Agilent Technology LC/MSD Trap SL, interfaced to an Agilent 1100 binary pump.

Esterification procedures were done by a CEM Discover microwave reactor (300 W maximum power) setting the bulk temperature at 80°C for 1 h.

For all species, geometry optimizations and frequency calculations were done to give the best suited Gibbs energies by DFT calculations performed at the b3lyp/6-311 + g(d,p) level of theory with Gaussian16 and GaussView 6 software packages (Frisch et al., 2016). The self-consistent reaction field was used with DFT energies, optimizations, and frequency calculations to model systems in acetonitrile solution. The convergence criteria for interatomic force minimization (geometry optimization) were the standard ones of the Gaussian16 software.

Further details are reported in **Supplementary Information**.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**; further inquiries can be directed to the corresponding author.

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## AUTHOR CONTRIBUTIONS

The laboratory work was carried out by PF, CN, and RB. PF, CN, RB, MB, MN, LD'A, and AS (all authors) contributed to the analysis, review and interpretation of data. LD'A and AS supervised the work. AS designed the study and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fchem.2021.783993/full#supplementary-material>

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