Rates of decarboxylation of the radical cations of indol-3-ylacetic acids and comparison with indolizin-1-ylacetic acids

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The radical cations of indol-3-ylacetic acid and derivatives were found to eliminate CO_2 to yield skatolyl radicals with rates in the range *ca.* 10^2 to $>10^5$ s^{-1}, strongly dependent on substitution. For the radical cations substituted at nitrogen, the rate of decarboxylation did not vary with pH 4–7.5, but for those unsubstituted at nitrogen, deprotonation caused the rate of decarboxylation to decrease with increasing pH. The rate of decarboxylation of the radical cations exhibited a strong dependence on the respective reduction potentials, with a 100 mV increase in reduction potential corresponding to a *ca.* tenfold increase in the rate of decarboxylation. Methylation at the side-chain α-position increased the rate of decarboxylation >sixfold, but insertion of a methylene group, as in 3-indol-3-ylpropionic acid or tryptophan, completely inhibited decarboxylation. In contrast, indolizin-1-ylacetic acids, which are isomers of indolylacetic acids in which the heterocyclic nitrogen is the bridgehead, did not decarboxylate on one-electron oxidation.

Introduction

The electrochemical oxidation [eqn. (1)] of carboxylic acids

$$R{-}COO^- - e^- \longrightarrow R^{\bullet} + CO_2 \qquad (1)$$

followed by decarboxylation (the Kolbe reaction) is a well-known process (for a review, see *e.g.* ref. 1). In spite of the frequent use of this reaction to prepare symmetrical R–R compounds, little is known about the kinetics of decarboxylation and the factors affecting it. Madhavan *et al.*[2] found that many aliphatic and aromatic carboxylic acids, including benzoic acid, yield CO_2 in high yield when oxidized by the sulfate radical ($SO_4^{\bullet -}$). However, the oxidation of methoxylated benzoic acids yields radical cations that decay without elimination of CO_2.[3] In contrast, the radical cations from phenylacetic, 4-methoxyphenylacetic, phenylpropionic or phenylbutyric acid decarboxylate with rate constants estimated as $>10^9$ s^{-1}.[4]

The oxidation of indol-3-ylacetic acid by plant peroxidases has been investigated for over two decades.[5] It has been demonstrated that the radical cation undergoes loss of carbon dioxide with formation of a carbon-centred radical.[6,7] Recently, the detailed mechanism of this reaction was elucidated by pulse radiolysis and product analysis studies.[8] In acid solution (pH *ca.* 4), the lifetime of the radical cation was *ca.* 60 μs, a time-scale easily accessible to pulse radiolysis. As part of our studies on the generation of peroxyl radicals, we have recently examined the oxidation of several indolylacetic acid derivatives and were able to determine the reduction potentials of the respective radical cations.[9,10] In the present study, we have compared the structural effects on the rates of decarboxylation of the radical cations of indolyl- and indolizinyl-acetic acid derivatives.

Experimental

Indol-3-ylacetic acid **1**, 5-methoxyindol-3-ylacetic acid **2**, 2-methylindol-3-ylacetic acid **3**, 5-methoxy-2-methylindol-3-ylacetic acid **4**, ethyl indol-3-ylacetate **7**, 3-(indol-3-yl)propionic acid **9** and tryptophan **10** were purchased from Aldrich and used as received. Ethyl 5,6-dimethoxy-2-methylindol-3-ylacetate **5**,[9] 1-methylindol-3-ylacetic acid **6**,[11] 1,2-dimethylindol-3-ylacetic acid **8**,[12] 3-acetyl-2-methylindolizine **19**,[13] 1,2-dimethylindolizine **20**[14] and 3-benzoyl-2-phenylindolizine **21**,[13] were prepared as described. Experimental procedures to obtain melting points, spectroscopic data, elemental analyses and chromatographic separations were as described.[15] All solutions were prepared just before the experiments with water purified by a Millipore Milli-Q system. Solutions of the indolylacetic acids were prepared by gentle warming (*ca.* 40 °C) under nitrogen and protected from the light.

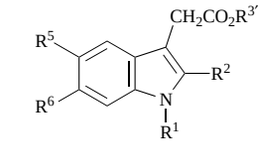
The pulse radiolysis equipment was described previously.[16] Before the experiment, the solutions were saturated with oxygen-free nitrous oxide for *ca.* 30 min and transferred to the anaerobic flow system in air-tight syringes. All experiments were performed at room temperature (22 ± 2 °C). The dibromine radical ($Br_2^{\bullet -}$) was generated by irradiation of solutions containing 0.05 mol dm^{-3} potassium bromide, as described previously.[17–19] In the presence of indol-3-ylacetic acid or its derivatives (typically 0.2 mmol dm^{-3}), $Br_2^{\bullet -}$ oxidized the indole in *ca.* 10 μs.

General methylation methods

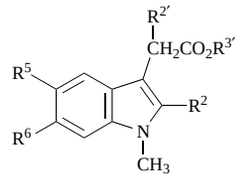
Two methods were employed using methyl iodide: (*a*) the procedure reported by Heaney and Ley[20] and (*b*) a more recent method.[9]

Ethyl 2-(1-methylindol-3-yl)propionate 11. Method (*a*) yielded an oil which was purified by column chromatography (silica gel, ethyl acetate–light petroleum, 2:3) to yield the *propionate* as a yellow oil (70%), ν_{max}/cm^{-1} 1730 (CO); $\delta_H(CDCl_3)$ (*J* values in Hz throughout) 1.20 (3H, t, *J* 7.2, CH_2CH_3), 1.57 (3H, d, *J* 6.6, $CHCH_3$), 3.63 (3H, s, NCH_3), 3.95 (1H, q, *J* 6.6, $CHCH_3$), 4.04 (2H, q, *J* 7.2, CH_2CH_3), 6.92 (1H, s, ArH) and 7.17–7.60 (4H, m, ArH); *m*/*z* 231 (M^+, 28%) and 158 (100) (Found: C, 72.59; H, 7.45; N, 5.98. $C_{14}H_{17}NO_2$ requires C, 72.73; H, 7.36; N, 6.06%).

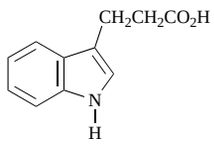
Methyl 1,2-dimethyl-5-methoxyindol-3-ylacetate 13. Method (*a*) gave the off-white microcrystalline *ester* (73%), mp 94–95 °C; ν_{max}/cm^{-1} 1715 (CO); $\delta_H(CDCl_3)$ 2.35 (3H, s, 2-CH_3), 3.59 (2H, s, CH_2), 3.63 (3H, s, OCH_3), 3.65 (3H, s, NCH_3), 3.83 (3H, s, OCH_3) and 6.69–7.14 (3H, m, ArH); *m*/*z* 247 (M^+, 85%)



	R^1	R^2	R^5	R^6	$R^{3'}$
1	H	H	H	H	H
2	H	H	CH_3O	H	H
3	H	CH_3	H	H	H
4	H	CH_3	CH_3O	H	H
5	H	CH_3	CH_3O	CH_3O	CH_3CH_2
6	CH_3	H	H	H	H
7	H	H	H	H	CH_3CH_2
8	CH_3	CH_3	H	H	H



	R^2	R^5	R^6	$R^{2'}$	$R^{3'}$
11	H	H	H	CH_3	CH_3CH_2
12	H	H	H	CH_3	H
13	CH_3	CH_3O	H	H	CH_3
14	CH_3	CH_3O	H	H	H
15	CH_3	CH_3O	CH_3O	CH_3	CH_3CH_2
16	CH_3	CH_3O	CH_3O	CH_3	H
17	H	CH_3O	H	H	CH_3
18	H	CH_3O	H	H	H



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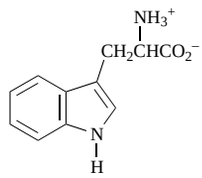

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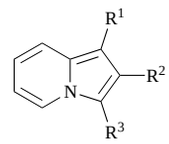


	R^1	R^2	R^3
19	H	CH_3	$COCH_3$
20	CH_3	CH_3	H
21	H	C_6H_5	COC_6H_5
22	$CH_2CO_2CH_2CH_3$	CH_3	$COCH_3$
23	CH_3	CH_3	$CH_2CO_2CH_2CH_3$
24	$CH_2CO_2CH_2CH_3$	C_6H_5	COC_6H_5
25	CH_2CO_2H	CH_3	$COCH_3$
26	CH_2CO_2H	C_6H_5	COC_6H_5
27	CH_2CO_2H	C_6H_5	H
28	CH_3	CH_3	CH_2CO_2H

and 232 (100) (Found: C, 67.72; H, 6.89; N, 5.59. $C_{14}H_{17}NO_2$ requires C, 68.08; H, 6.93; N, 5.66%).

Ethyl 2-(5,6-dimethoxy-1,2-dimethylindol-3-yl)propionate 15. Method (*b*) gave the *propionate* as an off-white solid (53%), mp 119–121 °C; ν_{max}/cm^{-1} 1725 (CO); $\delta_H(CDCl_3)$ 1.19 (3H, t, *J* 6.9, CH_2CH_3), 1.55 (3H, d, *J* 6.6, $CHCH_3$), 2.23 (3H, s, 2-CH_3), 3.61 (3H, s, NCH_3), 3.90 (6H, s, 5- and 6-OCH_3), 3.96 (1H, q, *J* 7.6, $CHCH_3$), 4.08 (2H, q, *J* 6.9, CH_2CH_3), 6.70 (1H, s, ArH) and 6.92 (1H, s, ArH); *m*/*z* 305 (M^+, 96%) and 232 (100) (Found: C, 66.59; H, 7.57; N, 4.54. $C_{17}H_{23}NO_4$ requires C, 66.88; H, 7.54; N, 4.59%).

Methyl 5-methoxy-1-methylindol-3-ylacetate 17. The crude product from method (*b*) was purified by column chromatography (silica gel, ethyl acetate–light petroleum, 2:8) to give a yellow oil (52%), ν_{max}/cm^{-1} 1720 (CO); $\delta_H(CDCl_3)$ 1.25 (3H, s, CO_2CH_3), 3.69 (2H, s, CH_2), 3.71 (3H, s, NCH_3), 3.85 (3H, s, OCH_3) and 6.90–7.18 (4H, m, ArH); *m*/*z* 233 (M^+, 60%) and 218 (100).

Hydrolysis of esters to give the acetic acids 12, 14, 16 and 18

The procedure was that described[9] for the formation of **6** from its ethyl ester.

2-(1-Methylindol-3-yl)propionic acid 12. The acid **12** was obtained by hydrolysis of ester **11** and crystallized from ethanol–water to give the *propionic acid* as a colourless solid (50%), mp 117–119 °C; ν_{max}/cm^{-1} 3435 (OH) and 1720 (CO); $\delta_H(CDCl_3)$ 1.58 (3H, d, *J* 7, $CHCH_3$), 3.68 (3H, s, NCH_3), 3.99 (1H, q, *J* 7, $CHCH_3$), 6.93 (1H, s, 2-H), 7.35 (4H, m, ArH) and 10.31 (1H, br s, exchanged with D_2O, OH); *m*/*z* 203 (M^+, 22%), 158 (100) and 143 (24) (Found: C, 70.93; H, 6.49; N, 6.87. $C_{12}H_{13}NO_2$ requires C, 70.92; H, 6.45; N, 6.87%).

5-Methoxy-1,2-dimethylindol-3-ylacetic acid 14. The acid **14**, obtained from **13**, was crystallized from ethyl acetate–light petroleum as prisms (51%), mp 170–172 °C (lit.,[14] 169–171 °C); $\delta_H[(CD_3)_2SO]$ 2.28 (3H, s, 2-CH_3), 3.54 (2H, s, CH_2), 3.58 (3H, s, NCH_3), 3.71 (3H, s, OCH_3) and 6.69–7.25 (3H, m, ArH); *m*/*z* 233 (M^+, 94%) and 188 (100).

2-(5,6-Dimethoxy-1,2-dimethylindol-3-yl)propionic acid 16. The hydrolysis of **15** yielded the *acid* as an off-white powder (60%), mp 98–100 °C; ν_{max}/cm^{-1} 3440 (OH) and 1715 (CO); $\delta_H[(CD_3)_2SO]$ 1.38 (3H, d, *J* 7.4, $CHCH_3$), 2.12 (3H, s, 2-CH_3), 3.58 (3H, s, NCH_3), 3.73 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.04 (1H, q, *J* 7.4, $CHCH_3$), 6.88 (1H, s, ArH), 6.89 (1H, s, ArH) and 12.3 (1H, br s, exchanged with D_2O, OH); *m*/*z* 277 (M^+, 33%), 247 (39) and 233 (100) (Found: C, 60.78; H, 8.1; N, 4.82. $C_{15}H_{19}NO_4 \cdot H_2O$ requires C, 61.02; H, 7.12; N, 4.75%).

5-Methoxy-1-methylindol-3-ylacetic acid 18. The acid **18** was obtained from **17** as a yellow powder (55%), mp 139–141 °C (lit.,[21] mp 139–140 °C); $\delta_H[(CD_3)_2SO]$ 3.56 (2H, s, CH_2), 3.68 (3H, s, NCH_3), 3.72 (3H, s, OCH_3) and 6.77–7.29 (4H, m, ArH); *m*/*z* 219 (M^+, 75%) and 174 (100).

General method for the indolizinylacetates 22–24

Substitution by ethoxycarbonylcarbene was used to obtain the ethyl acetates. A solution of ethyl diazoacetate (0.069 mol dm^{-3}) in benzene (100 ml) was added dropwise to a boiling solution of indolizine **19**,[13] **20**[22] or **21**[13] (0.018 mol dm^{-3}) in benzene (100 ml) containing a catalytic quantity of copper(I) chloride. After cooling, the solid was removed, the solvent evaporated and the residue purified by column chromatography (silica gel, ethyl acetate–light petroleum).

Ethyl 3-acetyl-2-methylindolizin-1-ylacetate 22. The acetate **22** (30%) had mp 35–37 °C; $\delta_H(CDCl_3)$ 1.24 (3H, t, CH_3), 2.57 (3H, s, CH_3), 2.59 (3H, s, $COCH_3$), 3.72 (2H, s, CH_2), 4.13 (2H, q, CH_2), 6.80 (1H, m, 6-H), 7.13 (1H, m, 7-H), 7.47 (1H, m, 8-H), 10.0 (1H, d, *J* 7, 5-H); *m*/*z* 259 (M^+, 77%), 244 (10) and 186 (100) (Found: M^+, 259.1208. $C_{15}H_{17}NO_3$ requires M^+, 259.1207).

Ethyl 1,2-dimethylindolizin-3-ylacetate 23. The acetate **23** was obtained as an oil (20%); $\delta_H[(CD_3)_2SO]$ 1.16 (3H, t, CH_3), 2.13 (3H, s, CH_3), 2.18 (3H, s, CH_3), 3.93 (2H, s, CH_2), 4.08 (2H, q, CH_2), 6.49 (2H, m, 6- and 7-H), 7.29 (1H, dd, *J* 2 and 7, 8-H), 7.86 (1H, d, *J* 8, 5-H); *m*/*z* 231 (M^+, 77%), 158 (100), 146 (17) and 127 (11) (Found: M^+, 231.1259. $C_{14}H_{17}NO_2$ requires M^+, 231.1258). This ester was unstable and rapidly became green.

Ethyl 3-benzoyl-2-phenylindolizin-1-ylacetate 24. The acetate

24 was isolated as an oil (49%); δ_H[$(CD_3)_2SO$] 1.08 (3H, t, CH_3), 3.68 (2H, s, CH_2), 3.98 (2H, q, CH_2), 6.96–7.37 (12H, m, 2 × Ph, 6- and 7-H), 7.80 (1H, d, *J* 8, 8-H) and 9.68 (1H, d, *J* 7, 5-H); *m*/*z* 383 (M^+, 67%), 368 (20), 310 (58), 105 (52) and 83 (100) (Found: M^+, 383.1521. $C_{25}H_{21}NO_3$ requires 383.1520).

General method for the indolizinylacetic acids 25 and 26

The appropriate ester (2.3 mmol dm^{-3}) was dissolved in aqueous ethanol (4:1) (20 ml), sodium hydroxide solution (25%, 20 ml) was added and the mixture refluxed for 3 h. The concentrated solution was acidified with hydrochloric acid and the precipitated acid collected. The instability of ester **23** prevented us from obtaining the acid **28**.

3-Acetyl-2-methylindolizin-1-ylacetic acid 25. The acid **25** crystallized from a mixture of chloroform and light petroleum as a colourless solid (68%), mp 197–198 °C; ν_{max}/cm^{-1} 3100–2922 (OH), 1722 (CO); δ_H[$(CD_3)_2SO$] 2.48 (3H, s, CH_3), 2.53 (3H, s, $COCH_3$), 3.74 (2H, s, CH_2), 6.93 (1H, m, 6-H), 7.22 (1H, m, 7-H), 7.66 (1H, d, *J* 8, 8-H), 9.86 (1H, d, *J* 7, 5-H), 12.33 (1H, br s, exchanged with D_2O, OH); *m*/*z* 231 (M^+, 74%), 186 (100), 149 (22), 85 (10) (Found: C, 67.38; H, 5.71; N, 5.99. $C_{13}H_{13}NO_3$ requires C, 67.52; H, 5.67; N, 6.05%).

3-Benzoyl-2-phenylindolizin-1-ylacetic acid 26. The acid **26** (54%), from aqueous methanol, had mp 203–205 °C; ν_{max}/cm^{-1} 3100–2950 (OH), 1730 (CO); δ_H[$(CD_3)_2SO$] 3.56 (2H, s, CH_2), 6.94–7.36 (12H, m, 2 × Ph, 6- and 7-H), 7.76 (1H, d, *J* 9, 8-H), 9.67 (1H, d, *J* 7, 5-H), 12.04 (1H, br s, exchanged with D_2O, OH); *m*/*z* 355 (M^+, 70%), 310 (74), 105 (36), 83 (100) (Found: C, 77.55; H, 4.90; N, 3.87. $C_{23}H_{17}NO_3$ requires C, 77.73; H, 4.82; N, 3.94%).

2-Phenylindolizin-1-ylacetic acid hydrochloride 27. A mixture of 3-benzoyl-2-phenylindolizin-1-ylacetic acid **26** (0.18 g, 0.05 mmol dm^{-3}) and hydrochloric acid (4 mol dm^{-3}, 10 ml) was refluxed for 40 min, cooled, filtered and evaporated to dryness *in vacuo*. The residue was crystallized from methanol–ethyl acetate to give the *title compound* (53%), mp 121–123 °C; ν_{max}/cm^{-1} 3320 (OH), 1750 (CO); δ_H[$(CD_3)_2SO$] 3.71 (2H, s, CH_2CO), 4.78 (2H, br s, exchanged with D_2O, 3-CH_2), 6.54 (1H, m, 6-H), 6.70 (1H, m, 7-H), 7.26–7.66 (7H, m, Ph and 8-H), 8.22 (1H, d, *J* 6, 5-H); *m*/*z* 251 (M^+ − HCl, 21%), 206 (M − HCO_2, 58), 83 (63), 31 (100) [Found: (FAB, nitrobenzyl alcohol) M − Cl, 252.1018. $C_{16}H_{14}NO_2$ requires 252.1023].

Results

Synthesis

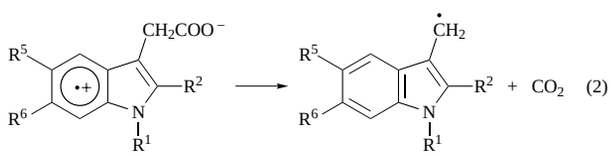
Our intention was to obtain the *N*-substituted indoles from the *N*-unsubstituted compounds by *N*-methylation. A procedure[20] for the *N*-alkylation of indoles using methyl iodide in dry dimethyl sulfoxide (DMSO) in the presence of potassium hydroxide gave the *N*-methylindolylpropionate **11** from **7** by both *N*- and *C*-methylation and afforded the *N*-methylated acetate **13** from the acid **4**. The conversion of the acid **2** to the *N*-methyl ester **17** was achieved using methyl iodide in dry acetone in the presence of the base modified by the addition of potassium carbonate.[9] This procedure gave both *N*- and *C*-methylation of the ester **5** to provide the **15**. Hydrolysis of the esters **11**, **13**, **15** and **17**, yielded the corresponding acids **12**, **14**, **16** and **18**.

Indolizine and some alkylindolizines are easily oxidized[23] and are unstable to light and air.[24] However, certain substituents, *e.g.* acyl and aryl groups on the five-membered ring, do confer stability on the heterocycle. With this in mind, we decided to prepare one indolizinylacetic acid carrying an acetyl group, one having methyl substituents only and one with a phenyl nucleus. The literature records the formation of ethyl 3-benzoylindolizin-1-ylacetate by ethoxycarbonylcarbene insertion into the C(1)−H bond of 3-benzoylindolizine[25] and we adopted this approach to the required acetates. The known 3-acetyl-2-methylindolizine **19**,[13] 1,2-dimethylindolizine[22] **20** and 3-benzoyl-2-phenylindolizine[13] **21** were prepared and treated with ethyl diazoacetate in boiling benzene in the presence of copper(I) chloride. The products obtained showed mass and NMR spectra expected for indolizinylacetates. The structures were deduced by comparison of ^{1}H NMR spectra of the acetates and the corresponding indolizines. The singlets due to H-1 at δ 6.47 and 6.54 and H-3 at δ 7.07 in the spectra of **19**, **21** and **20**, respectively, were absent from the spectra of the corresponding acetates, **22**, **24** and **23**. Hydrolysis of the esters **22** and **24** afforded the stable acids **25** and **26**, and the latter was further modified by debenzoylation under acidic conditions to give the acid, isolated as its hydrochloride, **27**. As expected the dimethylindolizinylacetic acid **28**, was unstable and could not be isolated.

Free-radical chemistry

In agreement with previous studies,[8,26] we observed that the reaction of the dibromine radical anion ($Br_2^{\bullet -}$) with indol-3-ylacetic acid and derivatives in aqueous solution at pH *ca.* 4 yields transients with absorption spectra characterized by two maxima, one in the UV (λ_{max} *ca.* 310 nm), and one in the visible (λ_{max} *ca.* 580 nm). These transients have been identified as the radical cations of the indolylacetic acids, in which the spin is distributed over the indole moiety.

The radical cations were unstable, as shown by the decay of the absorption at 560 nm in timescales varying from *ca.* 10 μs [in the case of 2-(1-methylindol-3-yl)propionic acid **12**] to >50 ms (in the case of 5,6-dimethoxy-2-methylindol-3-ylacetic acid). The decay was first order and independent of the indolylacetic acid concentration (in the range 0.1–1 mmol dm^{-3}). For some of the indolylacetic acids, spin-trapping[7] and product analysis experiments, including the detection of carbon dioxide,[11] have led to the conclusion that the radical cations decay by fragmentation of the side-chain carbon–carbon bond, yielding CO_2 and carbon-centred radicals (skatolyl radicals) [eqn. (2)]. The rate of decay of the radical cations of compounds **1**–**4** and **6** has been previously reported.[11] As in our previous studies, and in order to minimize the decay of the radical cations by second-order reaction (reaction between two radicals), the doses used were such that the initial radical concentration was *ca.* 1 μmol dm^{-3}. The radical cation of 5,6-dimethoxy-2-methylindol-3-ylacetic acid **5** was found to decay so slowly that the contribution from second-order reactions was noticeable, even under these conditions. To determine the rate of the first-order decay, an exponential function was fitted to the absorbance decay measured during the initial 10 ms following the electron pulse. The observed rates of decay were found to vary with the radiation dose in the range 0.3–0.8 Gy, *i.e.* with the initial concentration of radicals in the range 0.2–0.6 μmol dm^{-3}. The rate of first-order decay was obtained from the linear extrapolation to zero dose.



The eventual reaction of the indolyl radical cations with bromide was investigated by pulse radiolysis experiments with 5,6-dimethoxy-2-methylindol-3-ylacetic acid **5** at pH 4.2. The concentration of potassium bromide was varied and the rate of decay of the radical cation was monitored, at a constant dose per pulse of 0.4 Gy. A moderate increase (*ca.* 20%) in the rate of decay was detected on increasing the concentration of KBr from 0.05 to 0.25 mol dm^{-3}, but it remained constant on further increase up to 1 mol dm^{-3}. This result excludes a bimolecular reaction between the indolyl radical cation and bromide; the small variation of the rate of decay of the radical cation may be attributed to the effect of the increasing ionic strength.

Table 1 Rates of decarboxylation of the radical cations of indolylacetic acid and related compounds in aqueous solution at room temperature

Compound	$k_{dec}/10^3$ s^{-1}
1 Indol-3-ylacetic acid[a]	15.7 ± 0.5
2 5-Methoxyindol-3-ylacetic acid[a]	8.5 ± 0.1
3 2-Methylindol-3-ylacetic acid[a]	1.7 ± 0.3
4 2-Methyl-5-methoxyindol-3-ylacetic acid[a]	2.6 ± 0.3
5 2-Methyl-5,6-dimethoxyindol-3-ylacetic acid	0.14 ± 0.03
6 *N*-Methylindol-3-ylacetic acid[a]	15.4 ± 0.4
7 *N*-Methyl-5-methoxyindol-3-ylacetic acid	9.9 ± 0.2
8 *N*,2-Dimethylindol-3-ylacetic acid	2.4 ± 0.1
9 *N*,2-Dimethyl-5-methoxyindol-3-ylacetic acid	2.2 ± 0.1
10 3-(Indol-3-yl)propionic acid[a]	<0.1
11 Tryptophan	<0.1
12 2-(1-Methylindol-3-yl)propionic acid	>100

[a] Value from L. P. Candeias, L. K. Folkes, M. Porssa, J. Parrick and P. Wardman, *Free Radical Res.*, 1995, **23**, 403.

In neutral solution, the species formed on one-electron oxidation of indolylacetic acids unsubstituted at nitrogen have absorption spectra distinct from those of the respective radical cations, whereas the *N*-substituted compounds yield the same spectrum at pH 4 or 7.4. This has been interpreted,[8,11,26] by the deprotonation of the radical cations with pK_a values in the range 5–8. Similarly, changing the pH from 4 to 7.4 caused a decrease of the rate of first-order decay of the radical cations of the compounds unsubstituted at nitrogen (**1**–**5**), but the *N*-substituted radical cations exhibited a rate of first-order decay independent of the pH in the range 4–7.4. These rates are listed in Table 1.

Previously,[11] the radical cation of 3-(indol-3-yl)propionic acid **9** was found not to decarboxylate, unlike the several examples of indolylacetic acid radical cations. We have now investigated the formation of carbon dioxide on oxidation of tryptophan [2-amino-3-(indol-3-yl)propionic acid **10**] by $Br_2^{\bullet -}$ at pH 7.4 by steady-state radiolysis followed by addition of sodium hydroxide and analysis for carbonate, as described previously.[11] We could not detect the formation of carbon dioxide, from which we conclude that the radical cation of tryptophan does not decarboxylate.

The behaviour of the radical cation of 2-(1-methylindol-3-yl)propionic acid **12** was investigated by pulse radiolysis. The transient species resulting from the oxidation by $Br_2^{\bullet -}$ exhibited no absorbance in the visible, and only a weak absorbance in the UV, similar to the absorption spectrum of the skatolyl radical obtained on decarboxylation of the indol-3-ylacetic acid radical cation. This suggests that the decarboxylation of the radical cation of 2-(1-methylindol-3-yl)propionic acid is so fast that the reaction of the parent compound with $Br_2^{\bullet -}$ is rate-limiting. A lower limit for the rate of decarboxylation can therefore be obtained from the observed rate of decay of absorbance at 580 nm.

Like the indolylacetic acids, the indolizin-1-ylacetic acids **25**–**27** were found to react rapidly with $Br_2^{\bullet -}$ at pH 7. Pulse radiolysis experiments with 2-phenylindolizin-1-ylacetic acid (**27**) showed the decay of $Br_2^{\bullet -}$ and formation of a transient with an absorbance maximum at 380 nm ($\varepsilon = 2200$ dm^3 mol^{-1} cm^{-1}, based on a yield of 0.7 μmol J^{-1}). The indolizinylacetic acids **25** and **26** have absorption in the visible. On reaction with $Br_2^{\bullet -}$ the depletion of this absorbance is observed; the resulting transient has a weaker absorbance that tails off to longer wavelengths (Fig. 1). From the observed rate of decay of $Br_2^{\bullet -}$ or build-up of products, the rate of reaction is estimated as *ca.* 10^9 dm^3 mol^{-1} s^{-1}, for the three indolizinylacetic acids. By analogy with the oxidation of indolylacetic acids and other reactions of $Br_2^{\bullet -}$, we assign this reaction to the one-electron oxidation of the indolizine moieties, eqn. (3). The species formed in this reaction had lifetimes that depended on the initial concentration (dose per pulse), showing that they decay by radical–

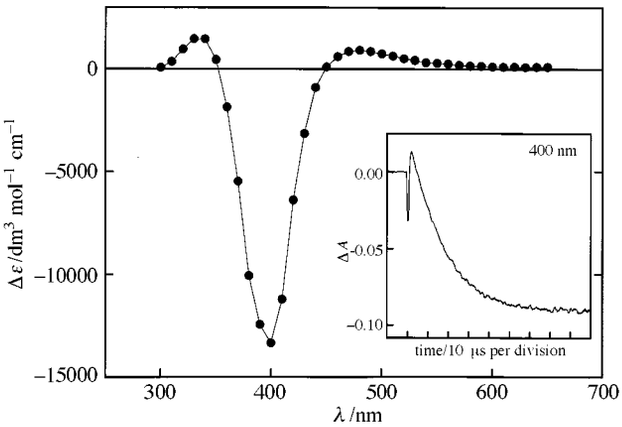
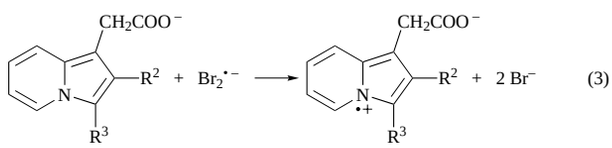


Fig. 1 Absorbance changes observed on oxidation of 3-benzoyl-2-phenylindolizin-1-ylacetic acid **26** by $Br_2^{\bullet -}$, measured by pulse radiolysis of a N_2O-saturated solution of **26** (0.1 mmol dm^{-3}) in aqueous KBr (0.05 mol dm^{-3}) and phosphate (2.5 mmol dm^{-3}) at pH 7. The absorbance change relative to the pre-pulse value was measured 75 μs after the pulse and the extinction coefficient was calculated assuming radiation chemical yield 0.7 μmol J^{-1}. The insert shows the transient absorbance change at 400 nm after a pulse of 9.6 Gy.



(3)

radical reactions. No evidence was found for first-order reactions of the indolizinylacetic acid radicals. Steady-state irradiation experiments showed no formation of carbon dioxide on oxidation of the indolizinylacetic acids by $Br_2^{\bullet -}$ at pH 7.

Discussion

The rates of decarboxylation of the radical cations and indol-3-ylacetic acid and derivatives were found to vary over three orders of magnitude. Previous studies[11,26] have shown that electron-donating substituents decrease the rate of decarboxylation. However, quantitative dependencies on Hammett (σ) or Brown–Okamoto (σ^+) substituent parameters have not been satisfactory. Recently, we have been able to determine the reduction potentials of the indolylacetic acid radical cations ($E°$) and found an approximate relation with substituent parameters.[9] The $E°$ values used here have been recalculated to consider the recent reevaluation of the reduction potential of the promethazine radical dication, used as a standard.[10] Fig. 2 reveals a steep logarithmic relation between the rate of decarboxylation of an indolylacetic acid radical cation and the respective reduction potential. The slope of this line (10.4 ± 1.9 V^{-1}) indicates that an increase of 100 mV in reduction potential is associated with a *ca.* tenfold increase of the rate of decarboxylation. Unfortunately, the reduction potentials of the *N*-substituted radical cations could not be measured due to their instability in both acidic and neutral solution, but for all compounds studied, the methylation at nitrogen did not significantly affect the rate of decarboxylation. This observation is consistent with the usually small effect of *N*-methylation on the properties of heterocyclic radical cations (see for example ref. 27).

The energetic driving force for the decarboxylation of the indolylacetic acid radical cations is proportional to the energy difference between the skatolyl radical and the parent radical cation. The latter term is in turn proportional to the reduction potential of the radical cation, thus explaining the observed relation between rate of decarboxylation and reduction potential. However, the radical cations of tryptophan **10** and 3-(indol-3-yl)propionic acid **9** did not decarboxylate, despite the fact that the insertion of a methylene group in the side chain is

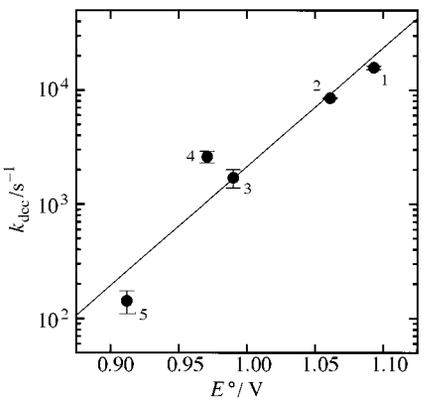


Fig. 2 Rate of decarboxylation of the radical cations of indol-3-ylacetic acid radical and derivatives plotted against the respective reduction potentials

not likely to have a large effect on the reduction potential of the radical cation. The reduction potential of the tryptophan radical cation has been reported as $E°(Trp^{\bullet+}/Trp) = 1.21$ V,[28] fairly close to that of the indol-3-ylacetic acid radical cation, $E°(IAA^{\bullet+}/IAA) = 1.09$ V.[10] Likewise, the additional methylene group cannot affect the rate of charge transfer from the heterocyclic core to the side-chain. In fact, the additional carbon bond is expected to decrease the rate of electron transfer not more than fourfold. Therefore, the different behaviour of the radical cations of the indolylacetic acids and of the indolylpropionic acids must be due to the lower energy of the former, suggesting that the skatolyl radical is stabilized by resonance with the heterocyclic π-electrons.

The behaviour of the radical cations of indolylcarboxylic acids is markedly different to those of phenylcarboxylic acids. In the latter case, it was concluded from the analysis of EPR spectra that fast decarboxylation takes place when the carboxylate group is separated from the aromatic ring by one, two or three methylene groups.[4,29] A plausible explanation of this fact is the predictably much higher reduction potentials of the radical cations of phenylcarboxylic acids, which may enable the oxidation of the side-chain to take place without requiring the stabilization of the carbon-centred radical.

Further confirmation of the effect of the stability of the carbon-centred radical on the rate of decarboxylation is offered by the radical cation of 2-(1-methylindol-3-yl)propionic acid **12**. The decarboxylation of this radical is at least three orders of magnitude faster than that of the 3-(indol-3-yl)propionic acid radical cation. As discussed above, this large difference cannot be attributed to the effect of *N*-methylation. The results suggest a pronounced effect of the methyl group in the α position on the rate of decarboxylation. The greater than three orders of magnitude increase in rate indicates a steep Taft relation with $\rho^* < -6$.

In the indolizinylacetic acids the nitrogen is at the bridgehead. The one-electron oxidation yields radical cations which cannot deprotonate and would therefore be expected to undergo decarboxylation, even in neutral solution. Surprisingly, no evidence for decarboxylation could be found.

In conclusion, the rate of decarboxylation of indol-3-ylacetic acid radical cations is strongly dependent on their stability, measured by the respective reduction potentials. In addition, the stabilization of the skatolyl radical by resonance with the heterocyclic π-electrons is required for the decarboxylation to occur. Stabilization of the skatolyl radical by a methyl substituent at the α position drastically increases the rate of decarboxylation. The radical cations of the isomeric indolizinylacetic acids did not decarboxylate.

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