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REACTIVITY OF INDOLE DERIVATIVES TOWARDS OXYGENATED RADICALS

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The reactivity of a series of indole derivatives was assessed in the following systems: (i) oxidation of the indole derivatives induced by the thermolysis of 2,2′-azobis-(2-amidinopropane) (ABAP); (ii) oxidation of cumene induced by the thermolysis of 2,2′-azobis-(2-methyl propionitrile) (AIBN); (iii) lysozyme inactivation induced by the thermolysis of ABAP and (iv) brain homogenate autoxidation.

In systems (ii) to (iv), addition of the indole derivatives decreases the rate of the process. The data obtained indicate that common factors (i.e., oxidation potential and presence of N–H bonds) control the reactivity of the indole derivatives in the four systems considered. However, in the brain homogenate autoxidation, hydrophobicity is an additional factor that affects the efficiency of antioxidants, as illustrated by $Q_{1/2}$ values (the concentration of additive required to decrease the autoxidation rate to one half that observed in the absence of additive) of 0.1 mM and $\geqslant$ 8 mM for 3-methylindole and tryptophan, respectively.

KEY WORDS: Lysozyme, inactivation, brain homogenate autoxidation, cumene oxidation, indole derivatives, autoxidation, indole, 1-methylindole, 2-methylindole, 3-methylindole, 4-methylindole, 5-methylindole, 2-methylindoline, tryptophan, indole-3-carbinol, indole acetic acid, 2,3-dimethylindole, oxidation potential.

INTRODUCTION

Trytophan is one of the most reactive amino acids towards active oxygen species[1] and hence it is readily damaged when proteins are exposed to free radicals under aerobic conditions.[2,3] Also, it has been reported that indole-derived compounds possess antioxidant capacities in biological systems.[4,5] An understanding of the role of different indole compounds as antioxidants is precluded by lack of quantitative data regarding the effect of the introduction of different substituent groups upon their reactivity towards alkylperoxyl free radicals. It has been reported that the reaction of *tert.*-butoxyl radicals with substituted indole derivatives in benzene proceeds by hydrogen abstraction which, for compounds unsubstituted at the N-atom, takes place almost exclusively at the N–H bond.[6] The presence of nitrogen-centered radicals was also reported in the interaction of *tert*-butoxyl radicals with indole,[7] as well as in that of the radicals derived from 2,2′-azobis(2-amidinopropane) (ABAP) thermolysis

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under aerobic conditions with tryptophan.[3] The reactivity of substituted indoles with *tert*-butoxyl radicals correlates with their electron donor capacity, pointing to a significant contribution of charge transfer configurations to the stability of the transition state, even in nonpolar solvents.[6] As expected for a process involving hydrogen abstraction from the N–H bond, substitution at the N-atom considerably decreases the reactivity of compounds towards the *tert*-butoxyl radicals. The interaction of trichloromethylperoxyl radicals with tryptophan, using pulse radiolysis, leads to the formation of radicals arising either from abstraction at the N–H bond (a tryptophanyl radical) or by addition at C_2 of the indole ring.[8] Furthermore, the trichloromethylperoxyl radical adds predominantly to the C(2)–C(3) bond of the methyl-substituted indoles, with only a minor fraction reacting through a one-electron transfer path.[9] While N-methylindole and indole react with trichloromethylperoxyl radicals at similar rates, methyl substitution at positions two and/or three significantly increases the overall reaction rate. Merenyi *et al.*[10] have measured the reaction rates between chlorine dioxide and a series of indole derivatives, a process that takes place by one-electron transfer with rates showing a strong correlation with the oxidation potential of the indole-derivative. Tryptophan reacts with hydroxyl radicals at a diffusion controlled rate ($8.5 \times 10^9 M^{-1} s^{-1}$) mainly by addition at the C_2, C_3, C_5 and C_7 positions,[11] while singlet oxygen ($^1O_2$) reacts at a slower rate ($3 \times 10^7 M^{-1} s^{-1}$), producing also a complex series of products.[12] However, tryptophan is almost unreactive towards the superoxide radical anion.[13]

In order to assess the effect of substitution upon their reactivity towards peroxyl radicals, we have evaluated the reactivity of a series of indole derivatives in the following systems: (i) Oxidation of the indole derivatives initiated by ABAP thermolysis, (ii) Cumene oxidation initiated by 2,2′-azobis (2-methyl propionitrile) (AIBN) thermolysis, (iii) Lysozyme inactivation initiated by ABAP thermolysis and (iv) autoxidation of brain homogenates.

MATERIALS AND METHODS

Brain Homogenate Autoxidation

Rats (Division de Ciencias Medicas Occidente, Facultad de Medicina, Universidad de Chile) were anaesthetized with nembutal (50 mg/kg, i.p.) and perfused with cold, 0.15 M KCl through the portal vein to eliminate blood. Brains were removed, washed and stripped of meninges and blood clots using ice-cold phosphate-saline solution containing 140 mM NaCl and 40 mM potassium phosphate buffer pH 7.4.[14] Tissue samples were homogenized in four times their weight of phosphate-saline buffer and centrifuged for 15 min at 1000 × g and 4°C. The supernatants were immediately diluted with three times their volume of phosphate saline buffer. Portions (3 ml) of the diluted brain homogenate were transferred to 15 ml glass vials for luminescence studies.

Chemiluminescence measurements were carried out in a Beckman LS-3150P liquid scintillation counter in the out-of-coincidence mode using the narrow tritium iso-set module at 28°C. Thiobarbituric acid-reactive products of lipid peroxidation (TBAR) were determined in brain homogenates after 1 hour incubation at 37°C, in the absence and presence of additives, according to Fee and Teitelbaum.[15]

Lysozyme Inactivation

Lysozyme Grade I (Sigma) was employed as received. Its activity was measured by following the loss of turbidity when added to suspensions of lyophilized Micrococcus lysodeikticus. Measurements were carried out in a Shimadzu UV-160 spectrophotometer at 436 nm, and the initial values of $-dA/dt$ (A = absorbance) were taken as a measure of the enzyme activity.

Solutions of the enzyme in the presence or absence of additives (added from concentrated stock solutions in methanol) were incubated at 45°C in PBS buffer (0.07 M phosphate, 0.017 M NaCl, pH 6.5) with 10 mM ABAP. Aliquots were withdrawn at different times and analyzed to obtain the remaining enzymatic activity. Control experiments (without additives) and those carried out in the presence of additives were carried out in solutions containing a constant concentration (0.7 M) of methanol.

Cumene Oxidation

Cumene-ethanol mixtures (4 : 1) were incubated at 60°C with 2 mM AIBN in well stirred reactors under initial partial oxygen pressures of c.a. 0.4 atm. A mercury manometer was attached to the reaction vessel, and cumene oxidation rates (arbitrary units) were evaluated from the changes in oxygen pressure over the solution. The measured rates were independent of the initial oxygen pressure.

Free Radical-Induced Indole Derivative Oxidation

Solutions of indolic compounds in distilled water with up to 0.6% methanol, were incubated at 45°C with 10 mM ABAP. Indole derivative oxidation was monitored by measuring the decrease of the solution fluorescence (excitation at 295, emission at 345 nm). No changes in the fluorescence spectral shape were observed, indicating that the indole derivatives are consumed without producing compounds whose fluorescence interferes with that of the parent compounds. Fluorescence measurements were carried out in a Perkin-Elmer 204-S fluorescence spectrophotometer.

Electrochemical Measurements

The electrochemical measurements were carried out at normal temperature (25°C) using a GRC (graphite reinforcement carbon) electrode (0.5 mm nominal diameter; hardness HB) as described by Aoki *et al.*[16] The differential pulse voltammetric study was conducted using a conventional three-compartment electrochemical cell with a platinum wire counter electrode and a saturated calomel reference electrode (sce) in 0.5 M phosphate buffer pH 8.0. A PAR 174A polarographic analyzer and a Houston Omnigraphic 2000 recorder were used. Oxidation potentials were evaluated from voltamograms of indolic solutions (100 μM) that were deaerated by bubbling nitrogen gas prior to the electrochemical measurements.

Chemicals

Indole, 2-methylindole and tryptophan were Fluka products. 1-methylindole, 4-methylindole, 5-methylindole, 2,3-dimethylindole and 2-methylindoline were purchased from Aldrich Chemical Co. Indole acetic acid, indole-3-carbinol and 3-methylindole

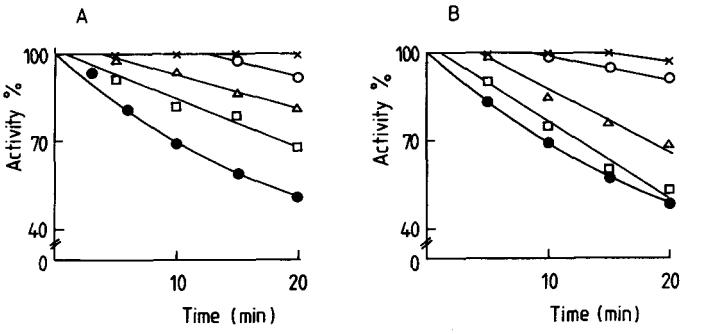

FIGURE 1 Effect of indole (A) and 2-methylindoline (B) addition upon lysozyme inactivation rate. Lysozyme: 3.4 μM; ABAP: 10 mM; temperature: 45°C; under air. (A) (●) control; (□) 0.02 mM; (△) 0.5 mM; (○) 1 mM; (x) 10 mM. (B) (●) control; (□) 2 μM; (△) 5 μM; (○) 25 μM; (x) 50 μM.

were obtained from Sigma (St. Louis, MO). AIBN and ABAP were obtained from Eastman Kodak Co. (Rochester, NY) and Polysciences (Warrington, PA), respectively. Cumene (Hopkin and Williams) was used as received.

RESULTS

Lysozyme Protection

Thermolysis of ABAP, under aerobic conditions, leads to lysozyme inactivation, which is due to modification of a tryptophan group by peroxyl radicals.[3] The inactivation can be prevented or decreased by different compounds able to interfere with the free radical reactions.[3,17] Using the parameter $Q_{1/2}$, i.e., the additive concentration needed to decrease to one half the inactivation rate measured in the absence of the additive, tryptophan was found to exhibit a mild protective capacity ($Q_{1/2}$ = 8 μM).[3]

The effects of indole (Figure 1A) and 2-Methylindoline (Figure 1B) upon the lysozyme inactivation rate indicate that, although an induction time could be defined, different slopes are obtained after the induction times and, in some cases, inactivation rates increase steadily with time. These results are those expected when the additive and the substrate exhibit similar reactivities with peroxyl radicals[17] and make the data analysis more complex due to consumption of the inhibitor. However, an indication

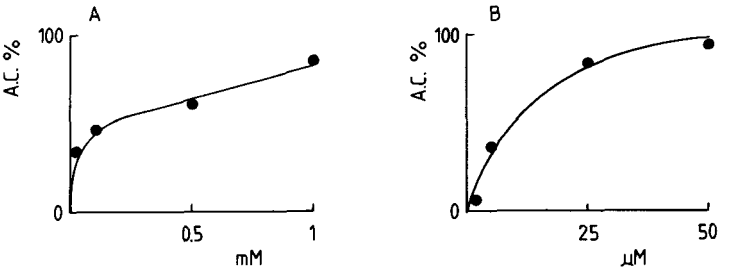

FIGURE 2 Percentage of protection afforded to lysozyme after incubation in the presence of 10 mM ABAP by indole (A) and 2-methylindoline (B). The percentage of protection (A.C.%) is defined by (A.C.%) = 100 [(% activity) − (% activity)^0]/[100 − (% acitivity)^0] where (% activity)^0 and (% activity) are the percentage of remaining activity after 20 min. incubation in absence and in the presence of the additives, respectively.

TABLE I
Experimentally determined $Q_{1/2}$[(a)] values and oxidation potentials

Compound	$(Q_{1/2})_{cumene}$ (mM)	$(Q_{1/2})_{B.H.}$ (mM)	$(Q_{1/2})_{lysozyme}$ (μM)	E^0 (V)
Indole	10.0	0.8	170 (150)	1.24*
1-Methylindole	60.0	1.0 (1.0)	500 (400)	1.23*
2-Methylindole	0.68	0.05	56 (57)	1.10*
3-Methylindole	0.75	0.1 (0.11)	60 (50)	1.07*
4-Methylindole	0.83	0.1	110	1.20*
5-Methylindole	4.20	0.25	80	1.22**
2,3-Dimethylindole	0.10	0.02 (0.024)	45 (40)	0.93*
Indole-3-carbinol	3.80	2.5	400	1.21**
2-Methylindoline	0.023	0.006 (0.007)	9.5 (11)	0.90**
Tryptophan	–	$\geqslant$ 8.0	25	1.24*
				1.08*#

[(a)]Values in parentheses were evaluated from the decrease in TBARS accumulation (brain homogenate autoxidation) or in oxygen saturated solutions (lysozyme inactivation). $Q_{1/2}$ values were obtained by interpolation in plots like those given in Figure 2 for the lysozyme system. Estimated uncertainty of the data: $\pm$ 20%.

(*)Values from Ref. 10.

(**)Values obtained in the present work normalized to a value of 1.24 V for indole.

(#)pH below 7.

of the relative inhibitor efficiencies can be obtained from the changes in inactivation extent measured at a fixed time, as a function of the additive concentration. This type of plot is shown in Figure 2 for indole and 2-methylindoline, and the respective ($Q_{1/2}$) values, evaluated after 20 min. incubation, are summarized in Table I. Similar $Q_{1/2}$ values were obtained when the enzyme inactivation was carried out in oxygen saturated solutions. This result indicates that the effect of the added indole derivatives in unlikely to be due to trapping of the initially produced C-centered alkyl radicals.

The behaviour observed in the present work, as well as the $Q_{1/2}$ values obtained for tryptophan, are rather different to those reported in previous works,[3,17] and can be attributed to the presence of c.a. 0.7 M methanol. Although this compound can be considered as unreactive towards the free radicals produced under our experimental conditions, the presence of this additive decreases the inactivation rate of lysozyme, suggesting changes in the enzyme activity that lead to the appearance of induction times.

Indole Derivative Oxidation Induced by Free Radicals

Lissi and Clavero have shown that the free radicals produced by ABAP thermolysis are able to induce tryptophan oxidation,[3] which can be followed by the decrease in fluorescence intensity of the indole moiety. Similar processes are observed for all the indole derivatives considered in the present work, whose initial consumption rates increase with the substrate concentration (Table II), according to

$$-\mathrm{d}\,[\mathrm{Indole}]/\mathrm{d}t = k\,[\mathrm{Indole}]^a \qquad (1)$$

with

$$0 < a \leqslant 1$$

The value of a depends both on the compound considered and its concentration. This type of behaviour has been explained previously in terms of competitive processes of the ABAP derived radicals plus short chains involving the substrate-derived radicals.[3]

TABLE II
Oxidation of indole derivatives induced by the thermolysis of ABAP[a]

Compound	Concentration (μM)	Consumption rate $10^{-9}M^{-1}s^{-1}$	n
Indole	40	4.0	0.1
	120	9.0 (10)	0.22
1-Methylindole	40	4.8	0.12
	120	7.9 (9.0)	0.19
2-Methylindole	40	12.0	0.3
	120	21.0 (23)	0.52
3-Methylindole	40	19.3	0.47
	120	24.0 (29)	0.58
4-Methylindole	40	5.8	0.14
	120	12.0 (13)	0.30
5-Methylindole	40	5.8	0.14
	120	14.4 (16)	0.35
2,3-Dimethylindole	40	38.0	0.94
	120	60.0 (75)	1.45
Indole-3-carbinol	40	7.7	0.19
	120	23.0	0.56
	240	51 (51)	1.2
3-Indolebutyric acid	40	15.0	0.36
	120	24.0 (25)	0.58
Tryptophan	20	17 (17)	0.4
	40	34.0	0.8
	120	28.0	0.7
	240	41 (51)	1.0

Estimated uncertainty of the initial consumption rates and n values are $\pm$ 10%. Values in parentheses were measured under oxygen.

In agreement with an oxidation mechanism involving as rate limiting step the interaction between the substrate and a peroxyl radical, the rate of the process remains almost unchanged when the dissolved oxygen concentration increases by a factor of c.a. 5 in oxygen saturated solutions (Table II).

From the indole derivative consumption rate and the rate of radical input,[3,17] the number of indole derivative molecules consumed by each radical introduced into the system (n) can be obtained from Eq. (2),

$$n = \{-\mathrm{d}\,[\mathrm{Indole}]/\mathrm{d}t\}/Ri \qquad (2)$$

where Ri is the rate of ABAP-derived radical input. The values of n obtained are given in Table II. These values must reflect both the reactivity of the compounds towards the primary radicals and the length of the oxidation chains. At low substrate concentrations (and for substrates of low reactivity) the values of n will be determined by the former factor, while at high substrate concentrations the increase in n mostly reflects the oxidation chain. The results of Table II also show that similar indole derivate consumption rates, and hence n values, are measured both in air and in oxygen saturated solutions, indicating that processes involving indole derived radicals and oxygen are not rate limiting. Actually, the small increase in oxidation rates observed for some indole derivatives in the oxygen saturated solutions can be explained in terms of a more efficient trapping of the indole derived free radicals.

Inhibition of Cumene Oxidation

Cumene oxidation can be induced by free radicals.[18] The oxidation of this substrate takes place by a simple mechanism (at least at low percentages of cumene oxidation) involving a chain reaction that can be depicted by

$$R\cdot + O_2 \rightarrow ROO\cdot \quad (3)$$

$$ROO\cdot + RH \rightarrow ROOH + R\cdot \quad (4)$$

where R· stands for the cumyl radical. This chain leads to the overall oxidation process

$$RH + O_2 \rightarrow ROOH \quad (5)$$

that can be monitored by the rate of oxygen consumption. The process can be initiated by any free radical source (e.g. AIBN) and inhibited by substrates able to trap the cumylperoxyl (ROO·) radicals. Figure 3 shows the effect of 3-methylindole upon the rate of oxygen uptake. The decrease observed can be understood in terms of a competition between process (4) and

$$ROO\cdot + \text{Indole} \rightarrow \text{termination} \quad (6)$$

and hence the relative efficiency of differents compounds can be considered as a measure of their relative reactivity towards peroxyl radicals.[17] This reactivity can be related to the $Q_{1/2}$ value, defined as the additive concentration required to decrease the oxygen consumption rate to one half the value measured in absence of additives. These values are collected in Table I. Tryptophan reactivity was not determined since the low polarity of the reaction mixture employed precludes its solubilization at the required concentrations.

Brain Homogenate Autoxidation

The autoxidation of brain homogenates can be employed as a model system to evaluate the capacity of different additives to affect lipid-peroxidation in biological samples.[14] The process is iron-ion-dependent but is almost insensitive to the addition of hydroxyl radical scavengers.[14,21] The antioxidant capacity of an additive will then be determined by its capacity to chelate metal ions and/or its ability to interfere with the chain propagating steps of the lipid peroxidation process.

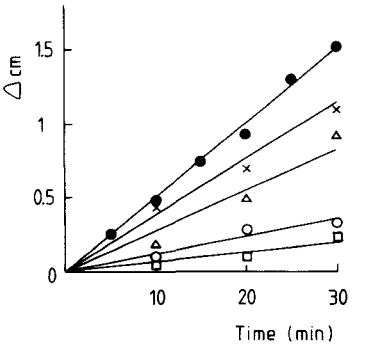

FIGURE 3 Effect of 2-methylindole addition upon the rate of oxygen uptake (arbitrary units). (●) control (no 3-methylindole added); (×) 0.5 mM; (△) 0.75 mM; (○) 1 mM; (□) 2 mM.

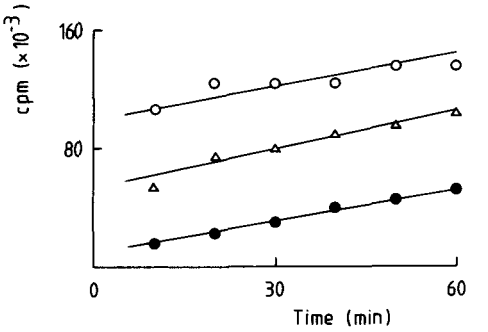

FIGURE 4 Effect of indole acetic acid upon the visible luminescence emitted in the brain homogenate autoxidation. (●) control (no indole acetic acid added); (△) 2.5 mM; (○) 5 mM.

Most of the indole derivatives considered in the present work decreased the lipid peroxidation rate, as evaluated from the emitted luminescence. Furthermore at sufficiently high concentrations the light emission is totally suppressed. For these compounds $Q_{1/2}$ values can be obtained, and they are collected in Table I. The $Q_{1/2}$ values obtained by this procedure are very close to those derived by the decrease in TBARS accumulation (Table I).

Indole acetic acid, when added to the brain homogenate, showed a completely different behaviour (see Figure 4). Addition of this compound to the samples increases the observed luminescence in a concentration dependent fashion. However, the shape of the light profiles is not that expected from an increase in lipid peroxidation rates and would indicate an extra luminescence that might be due to oxidation process involving the substrate.[22] In agreement with this, addition of up to 5 mM indole acetic acid to brain homogenate samples did not produce any significant change in the TBARS accumulated after 60 min incubation (data not shown).

DISCUSSION

The results obtained in homogeneous systems show that while 1-methyl substitution decreases or barely modifies the reactivity of indole derivatives towards oxygenated radicals, substitution at other positions, particularly at the C-3 and C-2 carbons, increases it. Similar reactivity patterns have been previously reported for trichloromethylperoxyl[9] and *tert*-butoxyl[6] radicals. For the latter radical, the main reaction path involves hydrogen abstraction and the reported trend was considered to be indicative of hydrogen abstraction from the N–H group.[6] In the present system involving peroxyl radicals, while hydrogen abstraction is an attractive hypothesis, the data could be also explained in terms of processes dominated by one electron transfer.[10] In this regard, it is interesting to note that the one electron oxidation potentials reported in Table I follow a rather similar trend with substitution and that they are of the same order of magnitude as those reported for alkylperoxyl radicals.[23] The relationship between oxidation potentials and the rate parameters measured in the different systems is stressed by the plot given in Figure 5 and the data reported in Table III for the compounds unsubstituted at the nitrogen atom. However, it has to be noticed that the dependence of the rate on the oxidation potential observed in the present work (as measured from the slope of the log (reactivity) vs oxidation potential

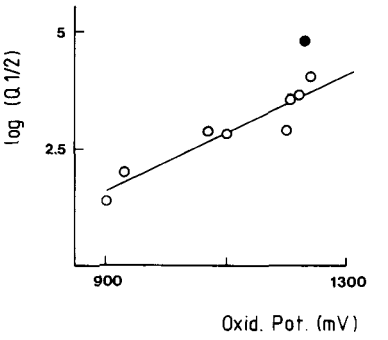

FIGURE 5 Relationship between log $Q_{1/2}$ values in the cumene oxidation and the additives oxidation potentials. (●) 1-methylindole.

plots) is considerably smaller than that measured for endothermic processes involving total electron transfer (see Table III). This fact, together with the low reactivity values obtained in the present systems for N-methylindole, would suggest that in the present systems the process can be represented by

$$ROO\cdot + InH \leftrightarrow [ROO^{\delta-}\text{–}H\text{–}In^{\delta+}] \rightarrow ROOH + In\cdot$$

with significant charge transfer contributions to the energy of the critical intermediate. The relevance of these configurations can be inferred from the slopes of the Log (reactivity) vs (Oxidation Potential) plots. The values obtained range from 6.0 (cumene oxidation) to $3.5\,V^{-1}$ (lysozyme protection) and are considerably smaller than that obtained for the reaction of chlorine dioxide[10] or the theoretical value expected for an endothermic single electron transfer process.

If all systems considered in the present work involve an interaction of peroxyl radicals with the indole derivatives, one would expect a close relationship between the relative efficiences observed in the different systems. Figure 6A shows that there exists a good correlationship between log ($Q_{1/2}$) values in cumene and brain homogenate autoxidation for lipid soluble compounds. Indole-3-carbinol departs from the correlationship, a result that can be explained in terms of its lower hydrophobicity. The relevance of the solute hydrophobicity in the brain homogenate system is particularly stressed by the lack of protection afforded by tryptophan when added in concentrations up to 8 mM.

TABLE III
Slopes of the log (reactivity) vs E^0 plots

System	Slope (V^{-1})	Correlation coefficient
Theoretical electron transfer	16.7	
ClOO· + InH	13.0	
Cumene oxidation	6.0	0.95* $p < 0.0002$
Autoxidation	4.3	0.91* $p < 0.0005$
Brain homogenate	5.0	0.92** $p < 0.002$
Lysozyme protection	3.5	0.80* $p < 0.006$
t-BuO· + InH	≈2.0	

(*) without considering the data for 1-methylindole.
(**) without considering the data for 1-methylindole and indole-3-carbinol.

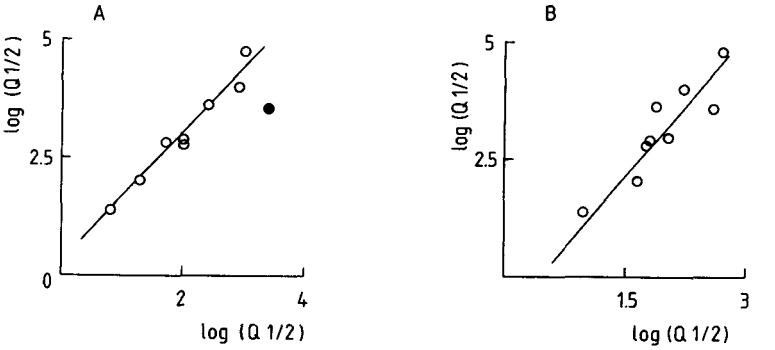

FIGURE 6 (A) Relationship between log $Q_{1/2}$ values in the cumene oxidation (ordinate) and log $Q_{1/2}$ values for the brain homogenate autoxidation (abscissa) (●) indole-3-carbinol. (B) Relationship between log $Q_{1/2}$ values in the cumene oxidation (ordinate) and log $Q_{1/2}$ values for lysozyme protection (abscissa).

Figure 6B shows also a fairly good correlation between $Q_{1/2}$ values in cumene and $Q_{1/2}$ values in the lysozyme protection experiments. Similar correlations were observed among the four systems considered, the correlation coefficients being given in Table IV. These data indicate that common factors (i.e., oxidation potential and presence of N–H bonds) are controlling the reactivity of the indole derivatives in the four systems considered, the only additional factor being the hydrophobicity in the brain homogenate system. This suggests that relative reactivities obtained in simple systems (such as cumene oxidation) can be employed as a guide to predict antioxidant capacities in more complex systems.

The present data suggest that indolic compounds, and particularly indoline derivatives, are able to interfere with free radical processes. The role of indolic compounds in biological systems is open to discussion. While it is widely recognized that tryptophan is one of the early targets of free radical mediated damage[1-3] and that the radical derived from it can be repaired by α-tocopherol,[24] the role of other indolic compounds is less straight forward. In fact, indole acetic acid has been shown to be a source of free radicals through peroxidase-mediated processes[25] and indole-3-carboxaldehyde has been shown to produce excited species able to initiate free radical processes,[26] Bray and Kubow have provided evidence suggesting an involvement of free radicals in the mechanism of 3-methylindole-induced pulmonary toxicity,[27] a process also mediated by metabolic activation. On the other hand, Hoekstra *et al.*[4] and Adams *et al.*[28] concluded that 3-methylindole can act as an antioxidant, and Shertzer *et al.*[5] have

TABLE IV
Correlation coefficient between the reactivity in the different systems

Systems	Correlation coefficient
lysozyme–brain homogenate	0.93(*)
lysozyme–autoxidation	0.76
lysozyme–cumene oxidation	0.90
brain homogenate–autoxidation	0.86(*)
brain homogenate–cumene oxidation	0.98(*)
cumene oxidation–autoxidation	0.83

(*) Data obtained for tryptophan and indole-3-carbinol not included.

reported data indicating that indole-3-carbinol can decrease free radical mediated hepatotoxicity and lipid peroxidation in homogeneous systems, homogenates, vesicles and mouse liver microsomes, suggesting that this compound could be a natural antioxidant in the human diet. Similarly, Cadenas *et al.*[29] have reported antioxidant activity for 5-hydroxytryptophan and 5-hydroxyindole in the Fe-induced lipid peroxidation of microsomes, probably due to a one electron-transfer reduction of α-tocopherol derived radicals. The data obtained in the present work show that the studied indole derivatives are able to prevent, or significantly decrease, both the free radical mediated inactivation of lysozyme and the lipid peroxidation of brain homogenates, and that their relative efficiency is determined by their capacity to interact with alkylperoxyl radicals and, in the brain homogenate system, by their hydrophobicity.

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