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COMMUNICATION

Amphiphilic antioxidants from "cashew nut shell liquid" (CNSL) waste†

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Hydrogenated cardanol and cardols, contained in industrial grade cardanol oil and obtained by distillation of the raw "cashew nut shell liquid" (CNSL), are easily transformed into efficient 4-thiaflavane antioxidants bearing a long alkyl chain on A ring and a catechol group on B ring.

The manufacture of edible goods from vegetable sources quite often causes the production of large amount of wastes. Their disposal is a serious environmental problem but, at the same time, these materials can be precious resources of organic renewable substrates, which, regrettably, are frequently lost. The recovering of such compounds by transformation into valuable chemicals represents a 'double green' action since recycling a waste goes along with the elimination of an expensive disposal. The shell of the cashew nut (*Anacardium occidentale* L.) contains an alkylphenolic oil internationally named "cashew nut shell liquid" (CNSL), which constitutes nearly 25% of the total weight of the nut, in turn produced in roughly 5×10^5 tons per year.[1,2] This oil, derived from the roasting of the cashew nuts because of the high edible value of the kernels, is composed of anacardic acid, and smaller amounts of cardanol, cardol, and methylcardol, and appears as a dark, partially polymerized tar-like stuff.[3] In all cases, the long alkyl chain may be saturated, mono- (8), di- (8, 11), and tri-olefinic (8, 11, 14). Thermal treatment of cashew nuts and CNSL induces the partial decarboxylation of anacardic acid, which is completed by the subsequent purifying distillation. The result is industrial grade cardanol, in the form of yellow oil containing cardanol **1** (about 90%), with a smaller percentage of cardol **2** and methylcardol **3** (Fig. 1).[2]

On the light of the above concepts, the possibility to use cardanols as a renewable feedstock has been deeply investigated[4] as well as its potential applications in the preparation of functionalized polymers,[5] or in material science, coupled with porphyrines,[6] nanotubes[7] and fullerenes,[8] or in fine chemistry for the preparation of benzo[*b*]furanes.[9] The alkyl phenol skeleton of compounds **1**–**3** suggested their possible activity as lipophilic antioxidants, or antiradicals, for the stabilization of plastics and other materials. However, as expected, the ability of hydrogenated cardanol **1** (3-*n*-pentadecylphenol), or cardols **2** (5-*n*-pentadecylresorcinol) and **3** (2-methyl-5-*n*-pentadecylresorcinol), as radical scavengers was found to be too low in comparison to commercial antioxidants, as BHT (2,6-di-*t*-butyl-4-methyl phenol, *i.e.* Butyl Hydroxy Toluene) or related derivatives.[10] We have recently demonstrated that hydroxy 4-thiaflavanes are efficient radical scavengers able to mimic the mechanism of action of Flavonoids and Tocopherols, the two more important families of natural polyphenolic antioxidants.[11–16] This interesting peculiarity is achieved by assembling the 4-thiaflanic skeleton through an inverse electron demand hetero Diels–Alder reaction between an *ortho*-thioquinone, acting as electron-poor diene, and a styrene used as electron-rich dienophile (Scheme 1).[17] We reasoned that, using derivatives **1**–**3** for the formation of the *ortho*-thioquinone and the 3,4-dihydroxy styrene as electron-rich alkene, respectively, we could build-up some new 4-thiaflavanes bearing a *n*-$C_{15}H_{31}$ aliphatic chain on A ring and a catechol group on B ring. If successful, this strategy should allow the connection of lipophilicity of the long *n*-$C_{15}H_{31}$ alkyl tail with the antioxidant ability of the 1,2-dihydroxy phenyl (catechol) moiety, an advantageous combination in the field of stabilizers as well as in the prevention of lipid peroxidation.[18–22]

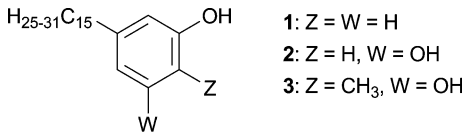
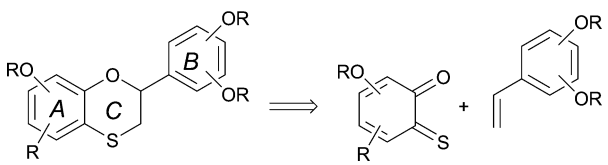


Fig. 1 Components of industrial grade cardanol oil.



Scheme 1 Inverse electron demand hetero Diels–Alder disconnection approach to 4-thiaflavanes.

Thus, following our original procedure, hydrogenated cardanol **1** was reacted with phthalimidesulfenyl chloride **4** (PhtNSCl, Pht = Phthaloyl) in dry chloroform to obtain the corresponding less

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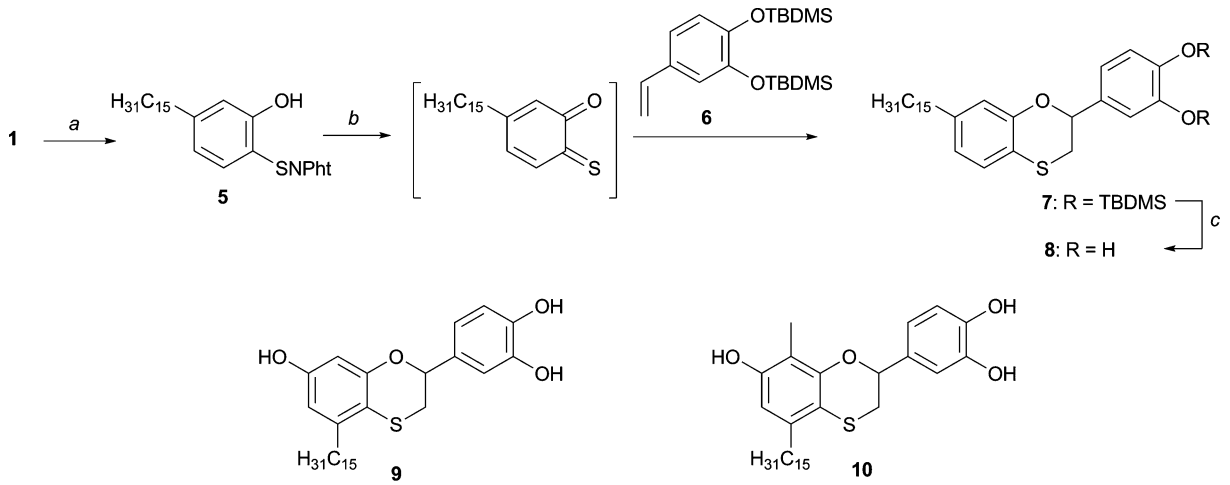
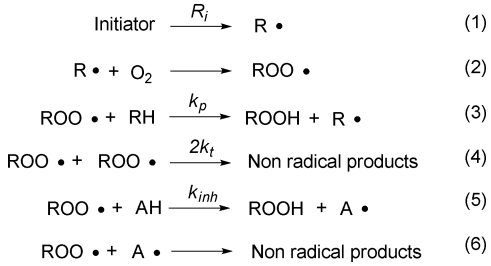
† Electronic supplementary information (ESI) available: Experimetal details for the preparation of derivatives **8–10** and their precursors, equations used to obtain k_{inh} and additional oxygen consumption traces are available. See DOI: 10.1039/c0ob01040e



Scheme 2 Reagents and condition: *a*) PhtNSCl (**4**) 1 equiv, dry $CHCl_3$, rt, 24h, 82%; *b*) Et_3N 1 equiv, **6** 1.5 equiv, dry $CHCl_3$, 60 °C, 24h, 64%; *c*) TBAF·$3H_2O$ 2 equiv, dry THF, –10 °C, 1h, 98%.

hindered[23] 2-hydroxy-4-pentadecyl-*N*-thiophenyl phthalimide **5** in 82% yield. Reacting **5** with 1 equiv of Et_3N in dry $CHCl_3$ at 60 °C causes the formation of the corresponding *ortho*-thioquinone which reacts with the *bis*-dimethyl-*t*-butyl-silylether of 3,4-dihydroxystyrene **6** to give cycloadduct **7** isolated in 64% yield. Desilylation of benzoxathiine **7** with 2 equiv of tetrabutylamonium fluoride hydrate (TBAF·$3H_2O$) in dry THF at –10 °C[24] gave amphiphilic hydroxy thiaflavane **8** in nearly quantitative yield as reported in Scheme 2. The reaction sequence was validated transforming also the minor components **2** and **3** into the catechol containing thiaflavanes **9** and **10** (Scheme 2).[25]

As it is reported below, we evaluated the antioxidant activity of derivatives **8–10** by studying their ability to inhibit the autoxidation of an oxidizable organic substrate (reactions 1–6). Data obtained were compared with those of cardanol **1**, pentamethyl chromanol **11**, 4-methyl catechol **12** and 4-thiaflavane **13**[11,12] (Fig. 2).



The rate constants for the reaction with peroxyl radicals (k_{inh}, reaction 5) were measured by studying the autoxidation of styrene at 30 °C, inhibited by small amounts (5–50 μM) of compounds **1** and **8–13** (see Fig. 3).[26] Autoxidations, initiated by the thermal decomposition of 2,2′-azobisisobutyronitrile (AIBN), were followed by measuring the oxygen uptake by a gas-recording apparatus built in our laboratory which has been previously described.[10] The experiments were performed either in homogeneous solutions, using chlorobenzene as solvent, or in a two-phases system,[27] consisting of a mixture of water and styrene in 1 : 1 vol/vol ratio. The oxygen consumption rate observed during the non-inhibited autoxidation of styrene was not influenced by the presence of water, indicating that reactions 1–6 take place in

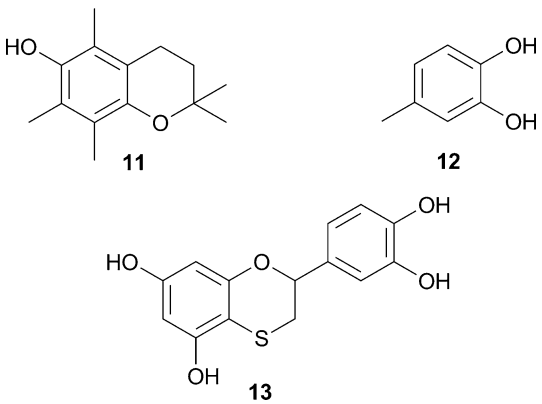


Fig. 2 Hydrophilic and hydrophobic model radical scavengers used in this study.

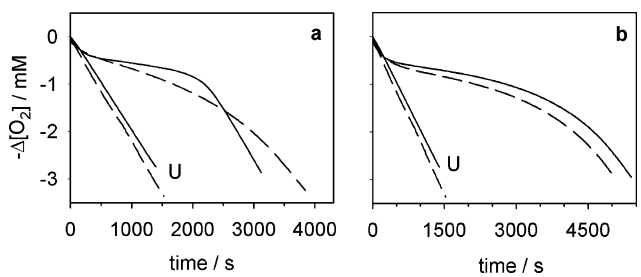


Fig. 3 Plot of oxygen consumption observed during the autoxidation of styrene (4.3 M) initiated by AIBN (0.05 M) at 30 °C without inhibitor (U), inhibited by **12** (panel **a**, [**12**] = 6.3 μM), and inhibited by **10** (panel **b**, [**10**] = 8.2 μM) in homogeneous solution (solid lines) and in the two-phases system (dashed lines).

the lipophilic phase (see ESI†). Therefore, the rate constants of propagation (k_p) and termination ($2k_t$) of the styrene autoxidation in the two-phases system were assumed to be equal to those measured in homogeneous solution (41 $M^{-1}s^{-1}$ and 4.2×10^7 $M^{-1}s^{-1}$ respectively).[26,28]

The values of k_{inh} were obtained from the slope of the oxygen consumption during the inhibited period (see ESI†), while the

Table 1 Inhibition rate constants (k_{inh}) obtained by studying the AIBN initiated autoxidation of styrene at 303 K in homogeneous solution using chlorobenzene (PhCl) as a solvent, or in the two-phases water/styrene system

	$k_{inh}/10^5$ $M^{-1}s^{-1}$		
	Styrene/PhCl	Styrene/H_2O[a]	k_{inh} (H_2O/PhCl)
1	≈0.1	≈0.1	1
8	4.8 ± 0.4	3.9 ± 0.4	0.8
9	7.0 ± 0.5	5.2 ± 0.5	0.7
10	7 ± 1	5.3 ± 0.5	0.9
11	32[b]	35 ± 3	1
12	9.4 ± 0.5	0.7 ± 0.1	0.07
13	6.8[c]	<0.1	<0.01

[a] Concentrations of the reacting species are referred to the total volume of the sample (styrene and H_2O). [b] From ref. 26 [c] From ref. 14.

number of radicals trapped by each antioxidant (n) was determined from the length of the inhibited period (τ) by equation 7.

$$n = \frac{R_i \tau}{[AH]} \quad (7)$$

The n coefficients showed no differences among the two experimental settings, and were determined as 2.0 ± 0.2 for compounds **8**, **11** and **12**, and 3.6 ± 0.3 for compounds **9** and **10**. As each phenolic or catecholic moiety traps two ROO$^\bullet$ radicals,[26] this indicates that in **9** and **10** the A and B rings act independently (catechin-like plus tocopherol-like behaviour).[11–15] In the case of weak antioxidants, capable only to retard the oxygen consumption ($k_{inh} \leq 10^5$ $M^{-1}s^{-1}$, see Table 1), n could not be determined.

From the k_{inh} values collected in Table 1, it can be inferred that in homogeneous solution all the synthesized compounds show good antioxidant activity, and are much better antioxidants than unmodified hydrogenated cardanol (**1**). This is due to the presence of the catechol moiety, which efficiently donates H atoms to ROO$^\bullet$ radicals in apolar solvents.[29] Their reactivity is smaller than that of 4-methylcatechol (**12**), probably because of the inductive effect of the oxathiin endocyclic oxygen which reduces the electron donating ability of the methyl group. The presence of additional hydroxyl groups in **9** and **10** respect to **8** gives an additional inhibiting activity, which can be seen at the end of the strong induction period due to the catechol moiety (see Fig. 3B). From the slopes of this retarded oxygen consumption, the k_{inh} of the OH groups on the ring A were estimated as about 1–2 × 10^5 $M^{-1}s^{-1}$, with no detectable differences between **9** and **10**. If considering the results obtained in the two-phases water/styrene system, the synthesized compounds **8**, **9** and **10** were found to possess a stronger antioxidant activity compared to the reference phenols **12** and **13**.

In Table 1 it is shown that this observation is due to a dramatic reactivity decrease of **12** and **13** in the biphasic system, while the reactivity of **8–10** remains almost unaffected. In the biphasic system, inhibition constants calculated from the slopes of the oxygen consumption traces actually depend on the molar fraction of the antioxidant that is located in the lipophilic phase (X_{lipo}) as shown by the equation: $k_{inh} = X_{lipo}\, k_{inh}'$. The value of k_{inh}', the inhibition constant in the lipophilic phase, is expected to be very similar to that measured in styrene/chlorobenzene (see Fig. 4). The relevance of antioxidant partitioning between styrene and

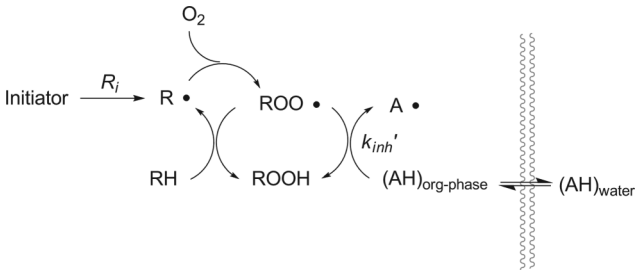


Fig. 4 Autoxidation scheme in the two-phase system.

H_2O was checked by measuring the UV-Vis absorbance of aqueous solutions of **12** and **13** before and after the addition of an equal amount of styrene, that is, under conditions similar to those used in the autoxidation experiments. The molar fractions of **12** and **13** in the organic phase are 0.4 ± 0.1 and 0.20 ± 0.06 respectively, indicating that these phenols are mainly in the H_2O layer, while their concentration in the lipophilic phase, where the autoxidation takes place, is reduced.

The presence of the long alkyl chain in the cardanol or cardol derivatives **8**, **9** and **10** ensures their partitioning in the organic phase, so that their k_{inh} are more or less the same under the two experimental settings. Although this model explains qualitatively the experimental results, it may be noticed that the reactivity decrease of **12** and **13** is larger than that expected on the basis of their percentages in the organic phase, indicating that other processes contribute in determining the k_{inh} values.[30] Further work will be devoted to fully clarify these aspects, for instance by using water-soluble initiators. The two-phases system used in the present work can be considered a simplified model to study antioxidants in biphasic or emulsified systems, as for instance in cosmetics or foods. It is known that, in these cases, apolar antioxidants are more active than their polar counterparts (the so called "polar paradox").[31] On the basis of the present results, this well-known observation can be explained in term of partitioning of hydrophilic antioxidants in the aqueous phase, whereas the autoxidation reaction takes place only in the organic layer. Of course, in emulsified systems more complex phenomena are also expected, such as the relevance of the diffusion of inhibitors among the oil droplets, which gives rise to non-linear dependence of the antioxdant activity on its lipophilicity.[32]

In conclusion, we have demonstrated that properly substituted 4-thiaflavanes, prepared using industrial cardanol oil components as starting materials, are amphiphilic valuable antioxidants with rate constants, for the reaction with peroxyl radicals, from 50 to 70 times higher than cardanol **1**, independently from the medium used, an apolar solvent or a 1 : 1 H_2O/styrene mixture, to run the measures. The goal of this study to transform a waste into potentially useful fine chemicals has been achieved and the ability of this new class of amphiphilic antioxidants as fat stabilizers and/or lipid peroxidation inhibitors is currently under investigation.

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24 The use of excess of TBAF or temperatures higher than −10 °C cause the ring opening of the benzoxathiine ring.

25 In this case resorcinols **2** and **3** were monosilylated with DMTBSCl before sulfenylation with **4**. All the phenolic groups were then contemporary deprotected in the final step of the synthetic sequence. See experimental section on ESI.

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