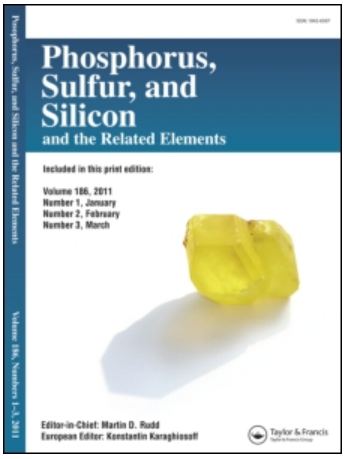

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COOXIDATION REACTION OF INDENE AND AROMATIC THIOLS IN THE PRESENCE OF OVOALBUMIN

Juanita Freer[a]; Cecilia Fuentealba[a]; Elizabeth González[a]; Jaime Baeza[a]
[a] Departamento de Química, Universidad de Concepción, Concepción, Chile

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COOXIDATION REACTION OF INDENE AND AROMATIC THIOLS IN THE PRESENCE OF OVOALBUMIN

JUANITA FREER, CECILIA FUENTEALBA, ELIZABETH GONZÁLEZ and JAIME BAEZA

Departamento de Química, Universidad de Concepción, Casilla 3-C, Concepción, Chile

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The thiol olefin cooxidation reaction (TOCO) between indene and aromatic thiols in presence of ovoalbumin has been studied in hexane. While this reaction under normal conditions leads to the formation of six products, in the presence of OVA gives stereospecifically only the *trans*-2-phenylmercapto-1-indanol derivative on the protein surface.

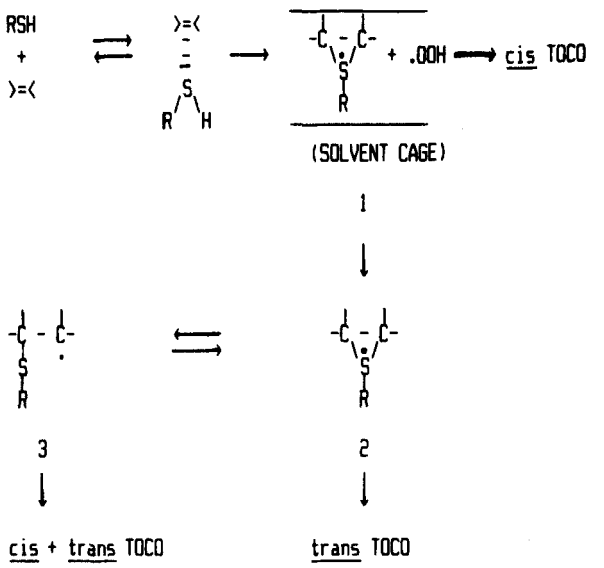
Key words: TOCO reaction; cooxidation reaction; oxidative addition of aromatic tiols to olefins; ovoalbumin; *trans*-2-mercapto-1-indanols.

INTRODUCTION

Reaction of cooxidation between thiols and olefins (TOCO reaction) has been extensively studied.[1–14] The mechanism of the reaction was originally suggested by Kharasch,[1] who proposed a typical free radical chain reaction which involves an intermediate hydroperoxide. Later, Fava[2] proposed the formation of a charge transfer complex and the abstraction of a hydrogen atom from this complex as the initiation step for the TOCO reaction. Extensive investigation of this reaction by Szmant and co-workers[4] found that this proposal was consistent with all the facts and necessary to explain some of the observations. A self-consistent mechanism for the reaction under nonradical-inducing conditions was proposed. This mechanism takes into account the observed structural and catalytic effects and permits to explain the product distribution in the interaction between a thiol and an olefin with each other and with oxygen to give the three major classes of products: TOCO products, anti-Markovnikov adduct and disulfide.

One of the most interesting aspects of the TOCO reaction is its stereochemistry. It was generally accepted that the addition gives stereospecifically the *trans* adduct until Szmant and Rigau[5–6] isolated the *cis*-hydroxysulfoxide from TOCO reaction of indene and thiophenol. The formation of one or both isomers is dependent on the equilibrium between the open radical and the bridged radical. From the solvent cage bridged radical (**1**) the *cis* product is formed but the escape from the solvent cage results in bridged radicals (**2**) that are attacked by oxygen or hydroperoxide radicals preferentially from the backside to give the *trans* products. From the open radical (**3**) both two isomers can be formed (Scheme 1).

On the other hand, only in the last years the use of enzymes have been recognized as an important tool in organic synthesis.[15] Reactions using natural proteins and synthetic polypeptides are considered to be closely related and they represent



SCHEME 1

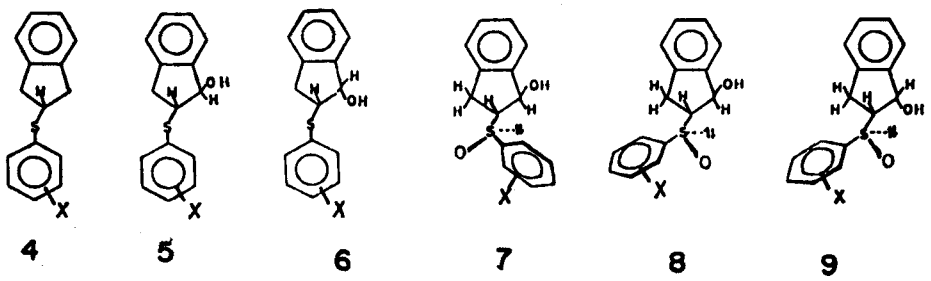
simplified models of enzymatic reactions. Typical examples are presented in the following cases: the enzyme-like behavior of human serum albumin and bovine serum albumin in hydrolysis reactions[16]; the use of bovine serum albumin in asymmetric reductions,[17] in oxidation of sulphides,[18] epoxidation[19] and *cis*-hydroxylations.[20] Synthetic polypeptides[21,22] have also been investigated as enzymatic models in organic reactions such as hydrogenation, oxidation, reduction and epoxidation.

In a previous short communication we reported that the oxidative addition of thiophenol to indene in the presence of ovoalbumin (OVA) produces only one isomer on the surface of the protein, which was informed as the *trans-anti*-2-phenylsulfinyl-1-indanol.[23] Then, we decided to investigate the effect of introducing substituents in thiols. In all cases, when the reaction was carried out with substituted thiophenols, from the surface of the protein was isolated only one product, the corresponding hydroxysulfide. With this in mind, we reinvestigated the reaction between indene and thiophenol.

RESULTS AND DISCUSSION

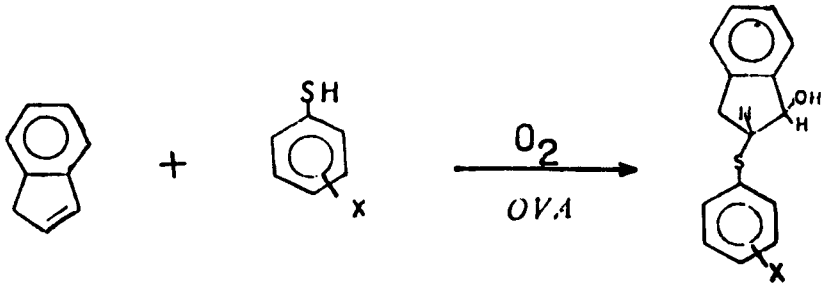
In normal cooxidation reactions of different aryl thiols and indene it is possible to isolate the sulfide (**4**), a mixture of *trans*-2-phenylmercapto-1-indanol (**5**) and *cis*-2-phenylmercapto-1-indanol (**6**) and three isomeric 2-phenyl-sulfinylindanols: *trans-syn* (**7**), *trans-anti* (**8**), and *cis-anti* (**9**) (Scheme 2).

When the reaction between indene and thiophenol is carried out in the presence of OVA, a stereoselective reaction occurs with the formation of only one product in the surface of the protein (Scheme 3). This corresponds to the *trans*-2-phenylmercapto-1-indanol (**5**) in which X=H (m.p. 101°C). Due that **5** and **8** have similar



4 5 6 7 8 9

SCHEME 2

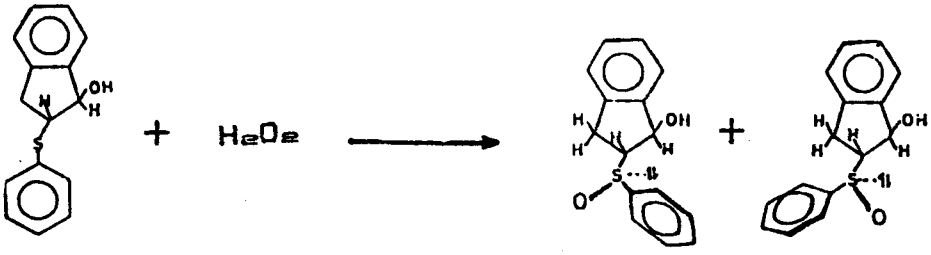


SCHEME 3

properties including a same melting point (mp = 101°C),[5] it was necessary to make a study to prove unequivocally the identity of the product.

The product obtained from the surface of the OVA was oxidated with H_2O_2. Two compounds were isolated, which correspond to the two isomeric hydroxysulfoxides **7** (m.p. 158°C)[5] and **8** (m.p. 101°C) (Scheme 4).

The compounds **7, 8, 9** were also isolated from a normal cooxidation reaction in which the three isomeric phenylindanyl sulfoxides were formed.[5] They were identified by comparison with the chromatographic and spectroscopic behavior given in literature.[5] The broadening of the OH 3000 cm^{-1} IR band in **8** as compared with the same **7** band, is in accord with the anticonfiguration of **8**.



SCHEME 4

It is important to distinguish in the infrared the peaks for the hydroxysulfide and for the hydroxysulfoxide. The hydroxysulfide shows a peak at 1060 cm^{-1}, but the compound obtained by oxidation of the sulfur moiety presents a peak at 1030 cm^{-1}, characteristic of the S=O group.

The compounds **5** (separated from the OVA surface) show by tlc (ethyl acetate:petroleum ether 50:50) a R_f of 0.80, while **8** gave a value of 0.32, and by HPLC (column octadecyl Si 100, acetonitrile:water (80:20) as eluent) the retention time observed were 12.36 min for **5** and 8.44 for **8**.

Reaction with Substituted Thiophenols

The stereoselectivity was observed also with substituted thiophenols. The reaction was carried out with different thiols in which X = *p*-CH_3, *p*-Cl, *p*-Br, *p*-F, *p*-OCH3. In all cases only one product was isolated from the OVA surface, the *trans*-2-phenylmercapto-1-indanol derivative. The R_f for tlc and the melting points are shown in Table I (as we indicated before the m.p. of the sulfide and of the sulfoxide derivatives when X=H are the same, the m.p. reported[3] for the 2-arylsulfinyl-1-indanols derivatives are indicated in the same table). The NMR^{1}H data appear in Table II.

Analysis of Mass Spectra[24]

The mass spectra of the products were measured. Diagnostic ions plus other major ions from the mass spectra are given in Table III. The main fragments for the *trans*-2-phenylmercapto-1-indanol (5, X=H) are: $[M]^{+\cdot}$, m/e 242; $[M-133]^+$, m/e 110; $[C_9H_9O]^+$, m/e 133; $[C_9H_7]^+$, m/e 115; $[C_5H_5]^+$, m/e 65; $[M-132]^{+\cdot}$, m/e 111; $[C_9H_8O]^+$, m/e 132; $[C_9H_8]^+$, m/e 116; $[C_7H_7]^+$, m/e 91. When X ≠ H the fragmentation is similar, but the relative intensities depend on the substituents.

The molecular ion $[M]^{+\cdot}$ presents two different possible important cleavages, the first with the generation of $[M-132]^{+\cdot}$, $[XC_6H_4SH]^+$, and the other with the generation of $[M-133]^{+\cdot}$, $[S{=}\langle\!=\!\rangle{-}X].^+$. Both fragmentation correspond to a C-S cleavage (Scheme 5).

TABLE I

Melting points and R_f values of *trans*-2-phenylmercapto-1-indanols

X	mp (°C)		R_f*
F	111		0.63
Cl	110	(159-160)*	0.62
Br	115-117		0.63
H	101	(101)*	0.63
CH_3	77	(155-156)*	0.63
OCH_3	97	(117-119)*	0.57

* Silica gel, ethyl acetate (30%): petroleum ether (70%).

* m.p. of the 2-arylsulfinyl-1-indanols[3]. The yield range between 20–30% depending on the substituent.

TABLE II

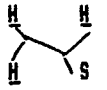
Principal ions in the electron impact mass spectra of some *trans*-2-phenylmercapto-1-indanols

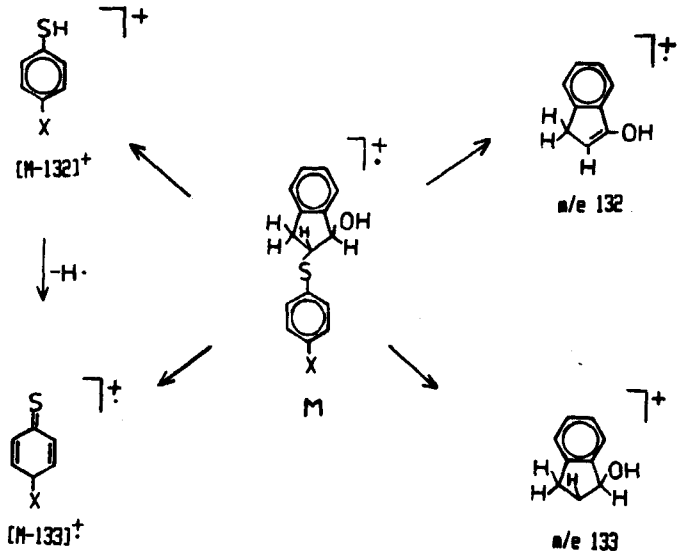
X	[M]⁺	[M+1]⁺	[M+2]⁺	[M-132]⁺	[M-133]⁺	$[C_9H_8O]^+$	$[C_9H_9O]^+$	$[C_9H_8]^+$	$[C_9H_7]^+$	$[C_7H_7]^+$	$[C_6H_5]^+$		
F	260 (68.4)	261 (10.5)	262 (3.4)	128 (28.9)	127 (15.8)	132 (94.7)	133 (100)	116 (10.5)	115 (36.8)	91 (13.2)	65 (9.2)		
Cl	276 (68.4)	277 (10.5)	278 (3.4)	144 (28.9)	143 (15.8)	132 (94.7)	133 (100)	116 (10.5)	115 (29.0)	91 (13.2)	65 (9.2)	145 (3.1)	146 (8.7)
Br	320 (68.4)	321 (10.5)	322 (3.4)	188 (28.9)	187 (15.8)	132 (94.7)	133 (100)	116 (10.5)	115 (27.3)	91 (13.2)	65 (9.2)	190 (15.7)	323 (9.3)
H	242 (47.7)	243 (9.1)	244 (3.2)	111 (36.4)	110 (4.3)	132 (100)	133 (65.9)	116 (4.5)	115 (2.0)	91 (12.3)	65 (6.4)		
CH_3	256 (60.7)	257 (10.7)	258 (3.6)	124 (16.1)	123 (12.5)	132 (100)	133 (67.9)	116 (11.8)	115 (28.9)	91 (35.7)	65 (8.9)		
OCH_3	272 (100)	273 (19.2)	274 (7.6)	140 (11.5)	139 (73)	132 (50)	133 (15.4)	116 (16.8)	115 (40.9)	91 (25.6)	65 (12.4)		

[a] Relative intensities in parentheses.
[b] Taken in a Varian Mat 311A, 70 eV, 120°C (entrance temperature), 90°C)probe temperature).

TABLE III

H¹NMR spectral data of *trans*-2-phenylmercapto-1-indanols

X	H (aryl)				X
F	7.28 (8, m)	5.10 (1, d)	2.20 (1, m)	3.18 (3, m)	
Cl	7.45 (8, m)	5.30 (1, d)	2.38 (1, m)	3.22 (3, m)	
Br	7.40 (8, m)	5.12 (1, d)	2.52 (1, m)	3.40 (3, m)	
H	7.30 (8, m)	5.12 (1, d)	2.50 (1, m)	3.42 (3, m)	
CH_3	7.28 (8, m)	5.18 (1, d)	3.00 (1, m)	3.68 (3, m)	2.33 (3, s)
OCH_3	7.20 (8, m)	5.08 (1, d)	2.80 (1, m)	3.30 (3, m)	3.72 (3, s)



SCHEME 5

EXPERIMENTAL

Nuclear magnetic resonance spectra were recorded on a Bruker 90 MHz, using tetramethylsilane as an internal standard. The mass spectra were recorded on a Varian Mat311A.

All compounds reported here gave satisfactory microanalysis results.

Cooxidation of Indene and Thiophenol. For 48 h oxygen was bubbled at room temperature into a mixture of 2.46 g (0.022 mol) of thiophenol and 2.6 g (0.022 mol) of indene in 60 ml of hexane. The reaction mixture was allowed to rest for seven days and a solid was formed that was separated by decantation The solid was a mixture of *trans-syn*-2-phenylsulfinyl-1-indanol and *cis-anti*-2-phenylsulfinyl-1-indanol, both with the same mp., 158°C. Evaporation of the liquid gave a solid that by crystallization from petroleum ether-toluene gave the *trans-anti*hydroxy sulfoxide, mp. 101°C.

Cooxidation of Indene and Thiophenol in the presence of Ovoalbumin (OVA). Equimolar amounts (0.022 mol) of indene and thiophenol were added to a heterogeneous mixture of 27 g of OVA in 60 ml of hexane. After stirring this mixture at 5°C for two days with continuously bubbling of oxygen through it, the solid phase was separated from the solution and washed with hexane. The hexane phase was washed with a diluted NaOH (aq) solution and water and dried over drierite and the solvent was evaporated. The residue showed to be a typical mixture of cooxidation products. On the other hand, the solid phase (OVA) was extracted with chloroform. The chloroform phase was worked up in the same way yielded only as shown by TLC and HPLC only one product, identified as the *trans*-2-phenylmercapto-1-indanol, mp. 101°C. [H-NMR (60 MHz) $CDCl_3$) δ (ppm): 2.50 (s, 1H, OH identified by exchange with D_2O); 2.76 (dd, 1H, H-3, J_{2-3} = 3.8 Hz, J_{3-3} = 8.5 Hz); 3.45 (dd, 1H, H-3', $J_{2-3'}$ = 3.8 Hz $J_{3-3'}$ = 8.5 Hz); 3.72 (m, 1H, H-2); 5.03 (d, 1H, H-1; J = 2.87 Hz); 7-7.7 (m, 9H, aryl); Hydrogens 1, 2, and 3 were identified by displacement with $Eu(DPM)_3$. IR(KBr) shows bands at 3250 cm^{-1} (OH), 1060 cm^{-1} (sulfide). MS is given in Table II. Elemental analysis: found (%) C: 74.13, H: 5.79, S: 13.24; calculated: C: 74.38, H: 5.78, S: 13.22, O: 6.61].

Oxidation of trans-2-phenylmercapto-1-indanol. In a typical reaction, 0.0047 mol of sulfide was stirred overnight at room temperature with 0.005 mol of H_2O_2 (30%) and 60 ml of acetic acid. Saturated sodium bicarbonate solution was added carefully to neutralize the acid. The sulfoxides were extracted with dichloromethane. Both isomers, *trans-anti* and *trans-syn* were separated by recrystallization, using petroleum ether and toluene. They were identified by comparison with the compounds isolated from the normal cooxidation reaction.[5]

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