

CARBONATION OF PHENOL: A NOVEL REACTION INVOLVING ENZYME MODEL CATALYSIS

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ABSTRACT

In the presence of an anion exchange resin, IR 45, indazolone and other structurally related compounds are observed to catalyse ortho carbonation of phenol in water under ambient conditions to produce salicylic acid alongwith, an unexpected product, benzoic acid.

THE industrial methods of production of salicylic acid involve very high pressures (80–90 atm) and high temperature (120–180°C) with scrupulous exclusion of moisture from the reaction mixture. Considering the demand of salicylic acid in the pharmaceutical industry, a process involving milder conditions seemed worth trying. Carbonation of polyhydric phenols in aqueous bicarbonate^{1,2} and of phenol in dimethyl formamide using sodium phenoxide³ have been reported; but, to the best of our knowledge, there is no report of carbonation of phenol in water.

Some mechanistic details of the catalysis of carbon dioxide transfer and fixation in enzymes such as carbonic anhydrase and methylmalonyl-CoA carboxy-transferase are known. The carboxy-transferase has been shown to capture carbon dioxide through a biotin nitrogen and transfer it to a pyruvate moiety^{4,5}. Application of this concept led to the design of some model compounds with appropriate structural features to catalyse the carbonation (figure 1 and table 2). These compounds were expected to, on the one hand, associate with phenol through hydrophobic or stacking interactions and hydrogen bonding *via* a molecule of water (from the medium) and, on the other, juxtapose its basic nitrogen atom to the ortho position of phenol for capturing and positioning of a carbon dioxide molecule in favourable geometry for the carbonation (figure 2). To drive the reaction forward by removing the produced acid from the medium, an anion exchange resin, IR 45, was used. Quite unexpectedly, benzoic acid was obtained as the major product alongwith, salicylic acid. No para carbonation was observed in any case. The estimation of the resultant acids was made from the UV spectrum of the product in a known volume of chloroform. The absorptions at 308 nm for salicylic acid and 275 nm for

benzoic acid were considered for the estimation^{6,7}.

The identity of the products was confirmed by HPLC separation of the acids using a reverse phase μ bondapak C₁₈ column and 4% methanol in chloroform as solvent for elution. In the process the two products were separately isolated.

Experiments with uniformly ¹⁴C-labeled phenol showed that the radioactivity of the reacting phenol

MODEL COMPOUNDS USED

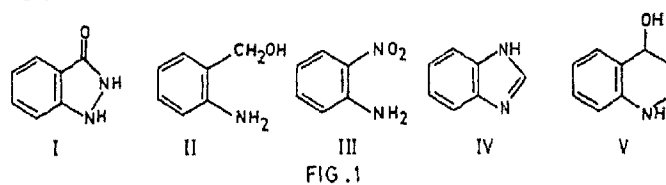


FIG. 1

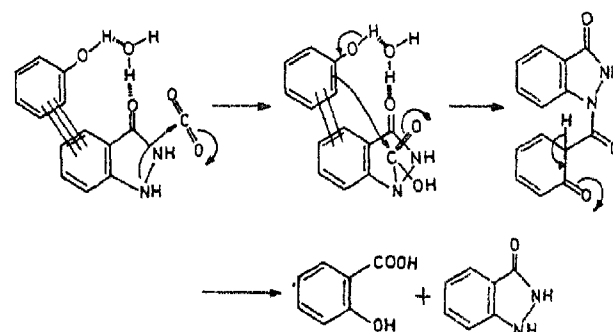


FIG. 2

Table 1 Carbonation experiments in 250 ml. of water

Phenol (mole)	Catalyst(I) (mole)	Resin (IR 45) (wet volume) ml.	Product (24 hour run)
0.04	Nil	100	Nil
Nil	0.01	100	Nil
0.01	0.01	Nil	Nil
Nil	Nil	100	Nil
Nil	0.01	Nil	Nil
0.01	Nil	Nil	Nil

was distributed, uniformly, between the benzoic and salicylic acids formed. Thus, it was confirmed that the benzoic acid was also produced from phenol. The unreacted phenol as well as the catalyst could be recovered quantitatively. The yields of benzoic and salicylic acids were 94.5% and 5.5% respectively, taking into account the recovered phenol. The overall yield of the acids was about 3%. A set of six blank experiments (table 1) proved that both the products were arising out of phenol under the influence of the catalyst and the anion exchanger.

While the mechanism of formation of salicylic acid was expected to be as in figure 2, the formation of benzoic acid was intriguing. Involvement of a hydride seemed the only way to explain the deoxygenation cum carbonation of phenol to produce benzoic acid (figure 3). Among the compounds present in the reaction mixture, *i.e.* phenol, the anion exchanger, the catalyst, carbon dioxide and water, only the catalyst or the resin can be conceived to donate the hydride. Phenol was excluded as there was no evidence of quinone formation. The catalysts, *o*-amino-benzyl alcohol (II) or 4-hydroxy-1,2,3,4-tetrahydroquinoline (V) could, possibly, donate a hydride from the benzylic position. The partial structure of the resin, IR 45, shows the presence of a benzylic hydrogen atom which could, probably, be transferred as hydride to give rise to a Schiff base (figure 4). To test the possibility of hydride transfer from the catalyst, a compound, *o*-(*N,N*-dimethylamino) α,α -benzyl alcohol (figure 5), was used as catalyst. Here, though there was a theoretical possibility of transfer of a methyl group to yield *o*-toluic acid, a mixture of salicylic and benzoic acids was obtained again. Incubation of salicylic acid in the reaction mixture, instead of phenol, did not yield any

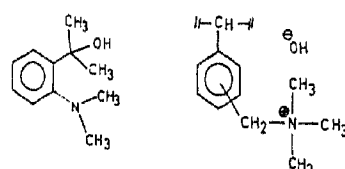
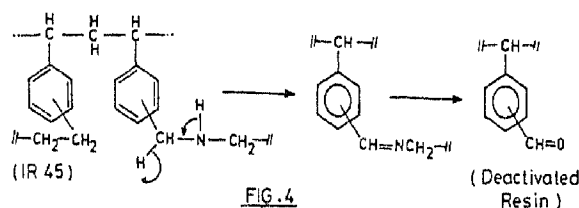
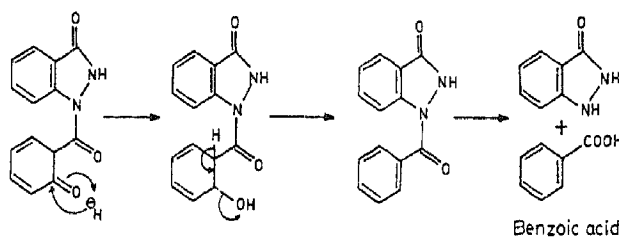
Dowex 1 ($^{\ominus}\text{OH}$)

FIG. 6

benzoic acid. So, it is most likely that both the acids are derived through a common intermediate.

Experiments with a different anion exchanger with quaternary ammonium group, Dowex 1 (OH^-) (figure 6) (a fresh lot was used in each case), resulted in the formation of salicylic acid, only, and when the catalyst was indazolone, the yield was 100% taking into account the recovered phenol. The overall yield was about 5% (table 2). Taking note of all the observations, a mechanism involving hydride transfer from the resin, IR 45, can be suggested for the formation of benzoic acid (figure 3). After a number of recyclings, the resin became inactive. This was caused, probably, by the loss of the amino side arm by hydrolysis of the Schiff base

Table 2 The results of Carbonation

Conc. of phenol (M)	Catalyst used	Conc. of catalyst (M)	Anion Exchange Resin	Overall yield (per cent) after bubbling CO_2 for 24 hours	
				Salicylic acid*	Benzoic acid*
0.100	I (Indazolone)	0.075	IR 45	0.167	2.873
0.144	II (<i>o</i> -Aminobenzyl alcohol)	0.036	IR 45	0.183	0.880
0.200	III (<i>o</i> -Nitroaniline)	0.100	IR 45	0.183	0.670
0.040	IV (Benzimidazole)	0.040	IR 45	0.250	1.900
0.175	V (4-Hydroxy-1,2,3,4-tetrahydro-quinoline)	0.040	IR 45	0.035	0.305
0.100	I	0.036	Dowex 1 (OH^-)	5.100	0.000

* In each case, the experiment was repeated with uniformly ^{14}C -labeled phenol (Amersham) to obtain radioactive products. The specific activity of the phenol used as well as that for each of the products, salicylic and benzoic acids, was approximately 174000 counts/mg., in each experiment.

formed (figure 4). Comparison of the IR spectrum of the deactivated resin with that of fresh IR 45 showed corroborant effects. There was a pronounced increase of absorption in the carbonyl region in the case of the former.

Every carbonation experiment was carried out by keeping the reaction mixture saturated with carbon dioxide by bubbling the gas at about 25°C under ambient pressure. After this, the resin was subjected to the following treatment:-

(i) a neutral water-wash, (ii) washing with methanol, (iii) elution with 2N aqueous ammonia, (iv) washes with water till neutral. The first fraction, after extraction of phenol with ether, yielded the recovered catalyst, the second yielded the rest of the recovered phenol, and the third and the fourth yielded salicylic and benzoic acids which were extracted with ether after acidification of the eluate, and then sublimed twice to purity.

Association between phenol and the catalyst, indazolone, in water, was monitored using UV. At pH 9, a new absorption maximum was observed to appear at 296 nm. With varying concentrations of phenol and indazolone, at 25°C and 45°C, the following values of free energy and equilibrium constant for the association were arrived at:

$$\begin{aligned} K_{25^\circ\text{C}} &= 4.46 \times 10^4 \text{ M}^{-1}, \\ K_{45^\circ\text{C}} &= 4.826 \times 10^4 \text{ M}^{-1} \\ \Delta G_{25^\circ\text{C}} &= -6.341 \text{ Kcal/mole}, \\ \Delta G_{45^\circ\text{C}} &= -6.816 \text{ Kcal/mole}. \end{aligned}$$

The moderate values of binding constant indicate that in the enclave of the resin, where the effective pH may

be alkaline, the binding of the catalyst with phenol is, probably, facilitated. The observed values of free energy of association were comparable with those reported earlier for phenyl-phenyl interactions⁸.

The catalysts were also found to effect carbonation of thiophenol to benzoic and thiosalicylic acids but were ineffective with aniline.

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ANNOUNCEMENT

NATIONAL AERONAUTICAL LABORATORY, BANGALORE—NEW DIRECTOR

Prof. Roddam Narasimha, Chairman, Department of Aerospace Engineering, Indian Institute of Science, Bangalore, assumed charge as the Director of the National Aeronautical Laboratory, Bangalore, on October 19, 1984.

Prof. Narasimha is associated with various aerospace organisations in India and abroad as a consultant and serves as India's Executive Delegate to the Commonwealth Aeronautical Advisory Research

Council. He is a member of Editorial Board of *Current Science*.

Prof. Narasimha is the recipient of the Burmah Shell Award of the Aeronautical Society of India, the Bhatnagar Prize in Engineering Sciences, and the Homi Bhabha Award for Research in Applied Sciences; during 1982-83 he was Sherman Fairchild Distinguished Scholar at the California Institute of Technology.