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# The Effects of Intramolecular Hydrogen Bonding on the Reaction of Phenols with Epoxide in the Presence of Nano Calcium Carbonate

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The reaction of phenols and dihydroxybenzenes with epoxide in the presence of nano  $\text{CaCO}_3$  was studied. Catechol could react with epoxide and gave monochlorohydrin derivative; other dihydroxybenzenes and monomeric phenols had no reaction under the same conditions. The reaction of catechol with epoxide did not occur when nano  $\text{CaCO}_3$  was replaced by a normal one. These were attributed to the strong interaction between nano  $\text{CaCO}_3$  and the substrate as catechol possessed intrahydrogen bond and excess active hydrogen, which can induce the intramolecular proton transfer *via* the intramolecular hydrogen bond and promote the reaction of hydroxyl and epoxide. This is an example revealing the unique role of the hydrogen bond played in chemical reactions.

**Keywords:** Hydrogen bond; Phenol; Epoxide; Nano  $\text{CaCO}_3$

## INTRODUCTION

Hydrogen bonds act as a ubiquitous glue sustaining the intricate architecture [1] and functionality of proteins and nucleic acids [2] due in-part to their high selectivity, directionality and reversibility. The best-known example is the assembly of DNA [3]. As a consequence, hydrogen bonding can be used to construct long-range ordered architectures and supramolecular assemblies [4]. The function of a hydrogen bond has been discussed extensively in many reviews [5,6]. This is a field that is still expanding rapidly [7]. To date, this weak interaction is seldom used as a force for promoting a chemical reaction, although the contribution of hydrogen bonds in the transition state of an enzymatic system has been reported [8,9]. Hydrogen bonding was used

to explain the asymmetric catalytic activity of a prebiotic amino acid in the aldol condensation of glycolaldehyde [10]. An intramolecular hydrogen bond promotion has also been reported in both the allylation and the reduction of carbonyl compounds and also in regioselective allylation [11]. Activation of carbonyl compounds by double hydrogen bonding was described as an emerging tool in an asymmetric catalysis in Pihko's recent highlights [12]. These examples provide an insight into the unique role played by hydrogen bonding in chemical reactions.

We have reported that the use of nano  $\text{CaCO}_3$  promoted the reaction of *p*-*tert*-butylcalixarene with epoxide affording monochlorohydrin selectively [13,14]. The presence of intramolecular hydrogen bonds (Fig. 1) among residual hydroxyls and oxygen anion after the first deprotonization of the calixarene results in a decrease of the first ionization constant of calix[4]arene by ca. 2 pH units as compared with the corresponding acyclic analogue.  $Ka_1$  was much higher than  $Ka_2$  as evidenced by spectrographic methods [15,16]. The explanation put forward was that nano  $\text{CaCO}_3$  exhibits inherent basicity causing the first deprotonization of the calixarene [13,14]. What is the role of intramolecular hydrogen bond in the reaction? Is this restricted to the use of calixarenes? Such questions drove us to make further investigations into the role of nano  $\text{CaCO}_3$  and in particular the intramolecular hydrogen bond. We know a number of polyhydric phenols also possess very different  $pK_a$  values. For example, the  $pK_{a1}$  and  $pK_{a2}$  is 9.34 and 13.24 for catechol [17]. Spectroscopic data and theoretical calculations unequivocally

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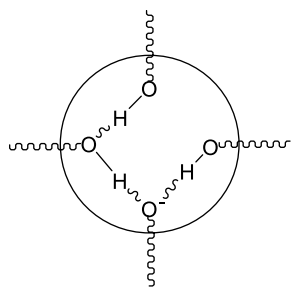


FIGURE 1 Schematic representation of intramolecular hydrogen bonds in calix[4]arene [13,14].

prove the presence of a relatively weak intramolecular hydrogen bond [18]. Can nano  $\text{CaCO}_3$  exhibit some special effect on the reaction of these polyhydric phenols with epoxide? Dihydroxybenzene, the simplest polyhydric phenol, was considered. The experimental results of catechol, resorcinol and hydroquinol as well as other phenols reacting with epichlorohydrin in the presence of nano  $\text{CaCO}_3$  are described in this report.

The published results showed that the reaction between catechol, resorcinol or hydroquinol with epoxide were quite different [19]. For example, reacting resorcinol and hydroquinol with 4 equiv. of epichlorohydrin and 2 equiv. of base, afforded as the main products bisglycidyl ethers **7** and **8** (Fig. 2) [19]. Reacting resorcinol and hydroquinol with an equal equiv. of epichlorohydrin and base, leads to a convenient preparation of monoglycidyl ether **9** and **10** (Fig. 2) [20]. The reaction of catechol with epichlorohydrin was quite complicated (Fig. 2). Using the same procedures as for preparing **7** and **8**, the synthesis of bisglycidyl ethers **6** of catechol was unsuccessful. The bischlorohydrin **2** was obtained by reacting catechol with an excess of epichlorohydrin and catalytic amounts of base [21]. Bischlorohydrin **2**

could be converted to bisglycidyl **6** *via* ring-closing reaction under specific condition [22]. The monochlorohydrin **1** and monoglycidyl ether **4** were easily converted to benzomethylol-dioxane **5** in the presence of the base [19,21].

From these results, we could see that the reaction of the dihydric phenols with epichlorohydrin was sensitive to the number of equiv. of the epichlorohydrin used, the reaction time and the temperature. In particular, the nature and the amount of base used was a determining factor. It was interesting to see what happened when nano  $\text{CaCO}_3$  was used.

Better activity was exhibited in the catechol reaction than for resorcinol and hydroquinol. Only a small amount of product was observed for resorcinol by GC-MS and could not be isolated. The product of the hydroquinol reaction could not be detected even by GC-MS. No reaction could be observed with normal  $\text{CaCO}_3$  or in the absence of  $\text{CaCO}_3$ .

When reacting catechol with epoxide, only monochlorohydrin was isolated. The structure of the monochlorohydrin ether of catechol was proved by FAB-MS and  $^1\text{H}$  NMR spectroscopy. The reaction was investigated in details. The results are listed in the Table I.

From Table I we find the yields of catechol monochlorohydrin differed with different amount of nano  $\text{CaCO}_3$  used up to 10 equiv. amounts of nano  $\text{CaCO}_3$ . When a catalytic amount of nano  $\text{CaCO}_3$  was used, only a little amount of product was obtained (entry 3). When the amount of nano  $\text{CaCO}_3$  was increased to 4 equiv., the yield increased to 25% (entry 5), the yield reached a maximum when 10 equiv. of nano  $\text{CaCO}_3$  was used (entry 6). Lengthening the reaction time produced similar effects (entry 2,5). Although increasing the reaction temperature was favorable to the conversion of catechol (entry 4,5),

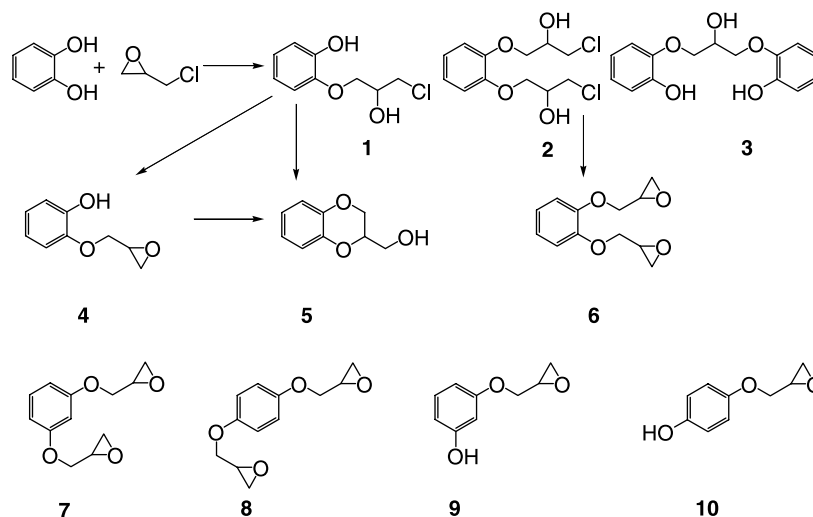


FIGURE 2 Some possible products of dihydric phenols.

TABLE I Results of catechol with epoxide under different reaction conditions

Entry	Epichlorohydrin (equiv.)	Base (nano CaCO <sub>3</sub> equiv.)	Temp. (°C)	Time (days)	Yield <sup>†</sup> (%)
1	4	4 normal CaCO <sub>3</sub>	100	5	0
2	4	4	100	2	18
3	4	0.1	100	5	4
4	4	4	85	5	19
5	4	4	100	5	25
6	4	10	100	5	27

<sup>†</sup> The data were calculated from the isolated monochlorohydrin, this product was the only main product from TLC.

the b.p. of epichlorohydrin was restrictive. In all cases, the chlorohydrin **1** was the main product. In other words, the amount of base did not effect the composition of the products, this is different from the situation when using a normal base.

As the same nano CaCO<sub>3</sub> was used in these reactions, the different activity of dihydroxybenzenes could be attributed to the existence of either intramolecular bonding or differences in acidity. The situation was less clear in the case of catechol. In order to make clear this problem, a series of substituted phenols (phenol, *p*-nitrophenol, resorcinol, hydroquinol, salicylic acid, salicylaldehyde, *o*-nitrophenol, *o*-methoxyphenol) with various ionization constant comparable to that of catechol were used. The substituted phenols and their respective ionization constants are listed in Table II. Phenol, resorcinol, hydroquinol, salicylaldehyde and *o*-methoxyphenol have higher *pKa* than *pKa*1 of catechol, and no reaction was observed with these phenols. No reaction could be observed even for *p*-nitrophenol owing to the high acidity (7.15, similarly *o*-nitrophenol (*pKa* = 7.2)). The *pKa* of phenol hydroxyl of salicylic acid was 13.40, but salicylic acid exhibited better activity (the yield of chlorohydrin was 30%). The acidity appears not to be the determining factor in these reactions.

Can we say that the intramolecular hydrogen bond was enough to be responsible for these phenomena? Although catechol and salicylic acid exhibited some activity and both have intramolecular hydrogen bond, guaiacol (2-methoxyphenol) and salicylic aldehyde also have intramolecular hydrogen bonding but show no activity. Further investigations were necessary.

It should be mentioned that there were two types of phenols containing intramolecular hydrogen bonding (Fig. 3), the first type are calixarene and catechol ligands, and the second type existed in

guaiacol (2-methoxyphenol) and salicylic aldehyde. At first sight these seem very similar, but it should be mentioned that an *exo* active hydrogen of hydroxyl exists in the first type, which is absent in the second type. The effect of the *exo* active hydrogen is discussed below.

It was obvious that nano CaCO<sub>3</sub> and as the first type phenols both were essential. Without the use of nano CaCO<sub>3</sub>, no detectable change was observed. So nano CaCO<sub>3</sub> played an undoubted role in the reaction of phenols with epichlorohydrin. The first type phenols have intramolecular hydrogen bonding which provided enough acidity and difference between *pKas*, the latter may be responsible for the selectivity. However, increasing acidity cannot explain why there is no reaction with nitrophenols. In other words, the intramolecular hydrogen bond should play another more important role.

Nano size calcium carbonate used was prepared by the High Gravity Reactive Precipitation Technology [23], its surface was modified by treatment with 1% stearic acid by weight of the reaction mixture. The XRD pattern of CaCO<sub>3</sub> nanopowders agreed with that of the calcite crystal structure in the JCPDS database. The XRD pattern remained unchanged after the reaction. We observed no effect when the surface modifier was added accompanying with normal CaCO<sub>3</sub>. The effect of surface modifier could be excluded.

There was clear experimental evidence that the surface of calcium carbonate contained a thin layer of hydroxides and bicarbonate species formed by the dissociative adsorption of water, and the hydroxyl groups remained even after treatment with acid [24,25]. The Energy minimization calculations predicted the formation of a maximum of two hydroxyl ions over a surface area of 1.0 nm<sup>2</sup> during chemisorption at low surface coverage [26]. With the particle size

TABLE II *pKa* of phenols used in our experiments<sup>†</sup>

	Phenol	<i>p</i> -Nitrophenol <sup>‡</sup>	Catechol	Resorcinol	Hydroquinol	Salicylic acid <sup>¶</sup>	Salicylic aldehyde	<i>o</i> -Nitrophenol <sup>‡</sup>	<i>o</i> -Methoxyphenol <sup>‡</sup>
<i>pKa</i> 1	9.89	7.151	9.12	9.40	9.91	2.98	8.14 <sup>¶</sup>	7.2	10.0
<i>pKa</i> 2			12.08	11.4	12.03	13.40			

<sup>†</sup> All data were cited from Ullmann's Encyclopedia of Industrial Chemistry except <sup>‡</sup> and <sup>¶</sup>. <sup>‡</sup>The data were cited from <http://www.mhhe.com/physsci/chemistry/carey/student/olc/ch24phenols.html>. <sup>¶</sup> The datum was cited from Kirk-Othmer Encyclopedia of Chemical Technology.

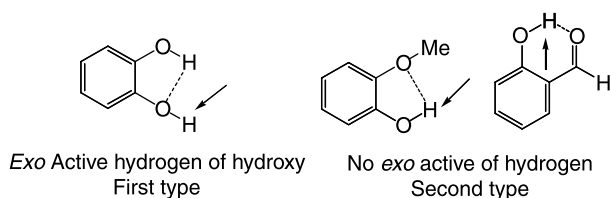


FIGURE 3 First-Type phenols: calixarene and catechol and Second type phenols: guaiacol and salicylic aldehyde.

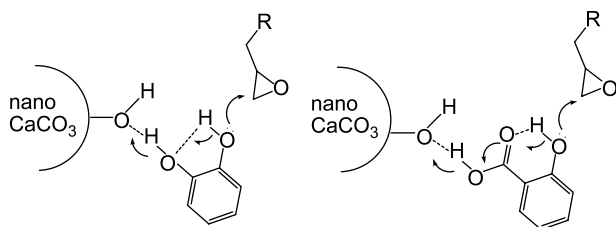


FIGURE 4 Possible mechanism of the reaction.

reduced to the nano scale, the surface area increased by orders of magnitude along with the amounts of surface hydroxyl ions. Thus, the interaction between the substrate and nano  $\text{CaCO}_3$  increased remarkably, which should be helpful for the reaction.

Perhaps, the special interaction between the intramolecular hydrogen bond and nano  $\text{CaCO}_3$  may be taken into account. It was rational to postulate that a strong interaction existed between the *exo* active hydrogen of catechol and hydroxyl ions on the surface of nano  $\text{CaCO}_3$ , and is caused the breakage of another hydroxyl of substrate, making the oxygen atom of this hydroxyl more negative, thereby promoting its reactivity towards epoxides. In other words, the proton transfer process was activated by the nano  $\text{CaCO}_3$  (Fig. 4). The effect of the presence of intramolecular hydrogen bonds on the rates of acid–base reactions was recognized and discussed by Eigen *et al.* dealing with proton-transfer kinetics in aqueous solution [27]. Catechol and

calix[4]arene both have this type of structure, and the one oxygen atom had more nucleophilicity towards epoxides. On the other hand, the compounds with the second type of hydrogen bond such as guaiacol and salicylic aldehyde cannot exhibit any activity in the mentioned reaction because of the absence of *exo* active hydrogens. Such a hypothesis was discussed by Frederick with regard to drinking water treatment. It was reported that the adsorption effect by hydrogen bonding of adjacent hydroxyl and carboxyl was great, and even larger than that of the strongest complexing ligand (phthalate) [28].

How about salicylic acid? There are intermolecular hydrogen bond and intramolecular hydrogen bond coexisting, each of them possessed two types of intramolecular hydrogen bonding as shown in Fig. 5, and tautomer **b** could suffer the analog process of first type phenol, which had *exo* active hydrogen. This seems to be the rational explanation for the activity of salicylic acid in Fig. 4.

## CONCLUSION

The different effect to the reaction of phenol with epoxide between normal and nano  $\text{CaCO}_3$  was found. The special role of intramolecular hydrogen bonding played in this reaction can be attributed to the strong interaction between nano  $\text{CaCO}_3$  and the molecule with an *exo* active hydrogen, which could induce the intramolecular proton transfer *via* the intramolecular hydrogen bond and promoted the reaction of hydroxyl and epoxide. Acidity only plays an auxiliary role in this reaction.

## EXPERIMENTAL SECTIONS

NMR was recorded on Varian Mercury VX300 instrument at ambient temperature.  $^1\text{H}$  NMR chemical shifts are given in ppm and referenced to internal

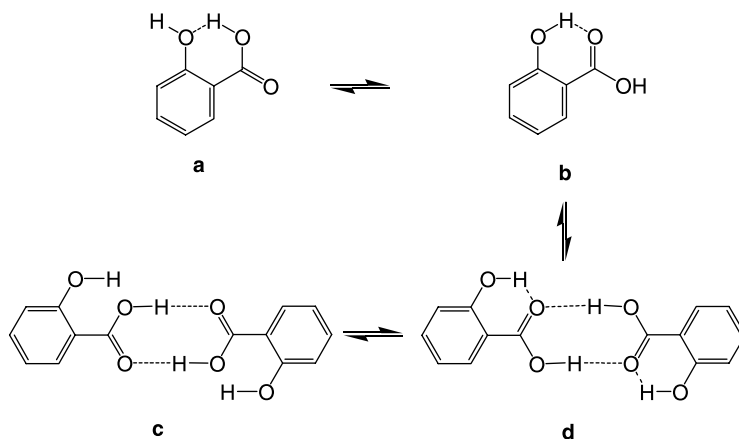


FIGURE 5 Hydrogen bonds existing in salicylic acid.



$\text{CHCl}_3$  ( $\delta = 7.27$ ) for  $\text{CDCl}_3$  solutions. FAB-MS spectra were obtained from a Kratos MS80RF mass spectrometry service, with *m*-nitrobenzyl alcohol as a matrix. Modified nano calcium carbonate (average particle size was 20 nm) was supplied by Inter Mongolia Mengxi High-tech materials Co. Ltd., China. Anhydrous solvents were purified by standard procedures and were freshly distilled prior to use. All other chemicals were analytically pure and used without further purification.

### General Procedure for the Reaction with Epichlorohydrin

To a suspension of nano  $\text{CaCO}_3$  in dry toluene (50 mL), phenol (0.01 mol) and epoxide were added. The reaction was stirred for 5 days at  $100^\circ\text{C}$ . Nano  $\text{CaCO}_3$  was removed by centrifugation. After evaporation of the solvent and the excess of epoxide, the residue was purified by column chromatography.

### Compound 1

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$ : 3.54–3.60 (m, 2H,  $\text{ClCH}_2$ ), 3.97 (dd, 1H,  $^2J = 6\text{ Hz}$ ,  $^3J = 1.2\text{ Hz}$ , Ar–O– $\text{CH}_2$ ), 4.01 (dd, 1H,  $^2J = 6\text{ Hz}$ ,  $^3J = 2.1\text{ Hz}$ , Ar–O– $\text{CH}_2$ ), 4.08–4.13 (m, 1H,  $\text{CH}(\text{OH})$ ), 4.82–5.12 (br, 2H, OH), 6.64–6.82 (m, 4H, ArH); MS (FAB)  $m/z$  202 for  $\text{M}^+$ .

### Chlorohydrin of Salicylic Acid

30% yield  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ , TMS)  $\delta$ : 2.75–3.38 (br, 1H, OH), 3.67 (dd, 1H,  $^2J = 11.1\text{ Hz}$ ,  $^3J = 5.4\text{ Hz}$ ,  $\text{ClCH}_2$ ), 3.74 (dd, 1H,  $^2J = 11.1\text{ Hz}$ ,  $^3J = 5.4\text{ Hz}$ ,  $\text{ClCH}_2$ ), 4.18–4.27 (m, 1H,  $\text{CH}(\text{OH})$ ), 4.45–4.48 (m, 2H, Ar–O– $\text{CH}_2$ ), 6.84–6.89 (m, 1H, ArH), 6.95–6.98 (m, 1H, ArH), 7.42–7.48 (m, 1H, ArH), 7.79–7.83 (m, 1H, ArH), 10.52 (s, 1H, COOH); MS (FAB)  $m/z$  231 for  $[\text{M} + \text{H}]^+$ .

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