

Organic Catalysis: Synthesis of Propylene Carbonate by the Carboxylation of Propylene Oxide in the Presence of Phenols and Fluorinated Alcohols

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Received March 22, 2018

Abstract—Phenol, polyphenols, as well as fluorinated alcohols actively catalyze the carboxylation of propylene oxide to form propylene carbonate in mild conditions (60°C, 7 at). The highest catalytic activity is characteristic of polyhydric phenols having neighbouring OH groups and alcohols with an enhanced acidity of OH protons. These catalysts in combination with tetrabutylammonium iodide exhibit activity at low concentrations (0.25 mol %) and ensure almost quantitative yields of propylene carbonate. The activity of the catalysts much increases with increasing ammonium salt amount (TOF up to 260), as well as temperature and initial CO₂ pressure (TON up to 370).

Keywords: propylene carbonate, propylene oxide carboxylation, phenol and fluorinated alcohol catalysts

DOI: 10.1134/S1070363218080029

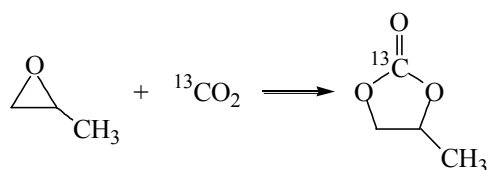
The reaction of propylene oxide with ¹³CO₂ to form propylene carbonate ¹³C-labeled in the carbonyl group (Scheme 1) is the first stage of production of ¹³C-urea [1, 2], which is the main component of medicines for the diagnosis of *Helicobacter pylori* and some other bacteria in the body [3, 4]. In view of the high cost of the isotopically labeled raw material, the carboxylation of propylene oxide is performed with a deficiency of ¹³CO₂. The most common catalysts are metals salts combined with ammonium salts [5–7].

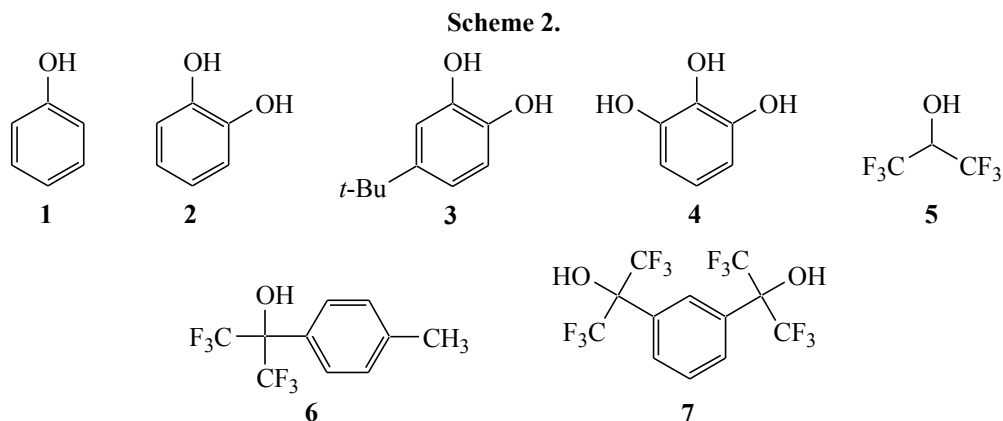
As known, the reaction of propylene oxide with CO₂ can be catalyzed by compounds able to form hydrogen bonds, especially alcohols and phenols with increased proton acidity [8, 9]. These organic catalysts exhibit activity when combined with ammonium salts, including Bu₄N⁺Br⁻ (TBAB) and Bu₄N⁺I⁻ (TBAI). The highest activity among phenols is characteristic of polyphenols having neighbouring OH groups in the aromatic ring (derivatives of pyrocatechol **2**, **3** and pyrogallol **4**, Scheme 2) [8, 9], and the most catalytically active alcohols are fluorinated isopropanols **5–7** and *tert*-butanols [9, 10]. For example, the first-order rate constant of the reaction of propylene oxide with CO₂ in the presence of TBAB–**2** or TBAB–**4** systems (3 mol % of each component, 60°C, 20 at) is 2.5 times

as high as that in the absence of these polyphenols (i.e. with TBAB alone, which is a low active catalyst). Fluorinated alcohols are even more active under the same conditions: perfluoro-*tert*-butanol and hexafluoro-(*p*-tolyl)isopropanol **6** increase the above-mentioned rate constant about 4 times and 1,3-bis(2-hydroxyhexafluoroisopropyl)benzene **7**, almost 6 times and an order of magnitude compared to its nonfluorinated analog. Perfluorinated trifluoromethyl derivatives were found to be the most active among the studied alcohols [9, 10].

However, even though the best of the above-mentioned systems make it possible to obtain the highest possible yields of propylene carbonate in mild conditions, they are still much less active than metal-containing catalysts [5, 6]. Thus, the quantitative yield of propylene carbonate in the TBAB–**7** system was obtained after 100-min reaction at 3 mol % catalyst

Scheme 1.





component concentrations (60°C, 20 at) [9], whereas the same yield in the TBAI–4 system could be reached only for 18 h at 5 mol % catalyst component concentrations (45°C, 10 at, solvent ethyl methyl ketone) [8]. At the same time, taking into account the requirement to ensure as low as possible concentrations of heavy metal impurities in drugs, we considered it interesting to study in more detail the behavior of the most active of the mentioned metal-free catalytic systems the carboxylation of propylene oxide under the conditions of synthesis of ¹³C-propylene carbonate.

In the preliminary experiments the activities of phenols and fluorinated alcohols as organic catalysts were compared, in combination with TBAI, which is a component of the most active catalytic systems (Scheme 1) [5], under the conditions of the commercial ¹³C-propylene carbonate production process (100°C, CO₂ : propylene oxide ~ 1 : 1, mol/mol) [2]. The resulting data showed that Bu₄N⁺I⁻ is scarcely active under the chosen condition, but its activity much increases in the presence of organic catalysts (Fig. 1). Therewith, the systems involving monohydric alcohols **5** and **6** and phenol **1** were much less active than those with dihydric alcohols **2** and **7** (the component concentrations in all the TBAI–catalyst systems were 1 mol %).

It should be noted that phenol-containing systems proved to be unstable at high temperatures, especially those involving pyrogallol and *tert*-butylpyrocatechol: by the end of reactions, the reaction mixtures got appreciably dark and those involving pyrogallol even got black. At the same time, the reactions abruptly slowed down. Yet in the case of fluorinated alcohols the reaction mixture did not change color during reaction. Taking this into account, further experiments with phenols were performed under milder conditions.

Figure 1b compares the activities of phenol-containing systems at 60°C and the initial CO₂ pressure of 7 at. As seen, polyphenols are much more active than phenol and, therewith, the systems on the basis of pyrocatechols **2** and **3** and pyrogallol **4** are close in activity.

Figure 2 shows the dependences of the reaction rate on the concentration of the highly active catalytic systems involving alcohol **7** and phenol **2** at a 1:1 TBAI/catalyst ratio. In the case of pyrocatechol, the reaction rate increases linearly with the concentration of the catalytic system (Fig. 2b), whereas in the case of fluorinated dihydric alcohol **7**, enhanced growth of catalytic activity is observed (Fig. 2a), and, therewith, the quaternary salt TBAI alone is an order of magnitude less active than an equimolar TBAI–catalyst system.

We also studied the effect of the component ratio in the TBAI–**2** and TBAI–**7** catalytic systems on the reaction rate of propylene oxide with CO₂. The TBAI/catalyst ratio was widely varied, but other reaction conditions (mild) were the same (Fig. 3). At low catalyst concentrations (0.25 mol %), equimolar systems involving dihydric fluorinated alcohols and phenols (as exemplified by compounds **2** and **7**) show close activities. However, as the concentration of TBAI is increased, the activity of the system with fluorinated alcohol **7** increases faster compared to the system with pyrocatechol **2**. It is interesting to note that the activity of the TBAI–**2** system containing 1 mol % of each component is close to the activity of the same system containing 2.5 mol% of TBAI and 0.25 mol % of compound **2** at 60°C (Figs. 2b and 3). From the practical viewpoint, this finding implies that the catalyst composition can be chosen on the basis of economic reasons (costs, availability, etc.) without sacrifice of catalytic activity.

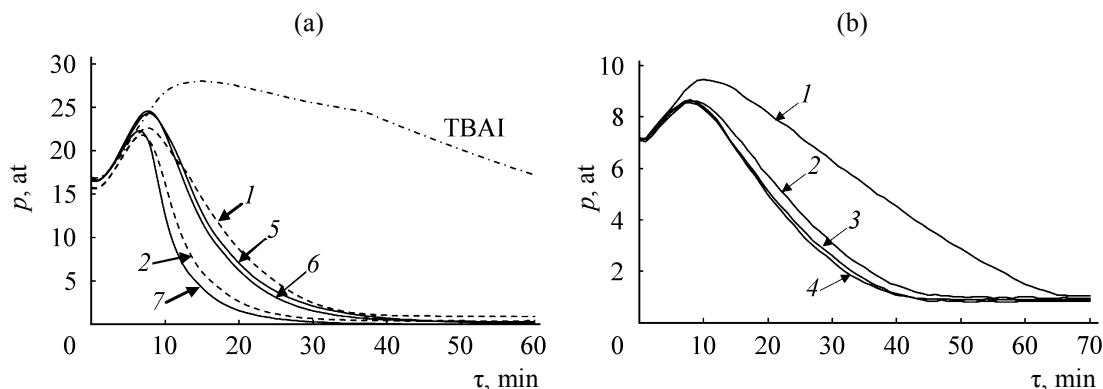


Fig. 1. (a) Dependence of the pressure in the reactor on time in the course of carboxylation of propylene oxide with different catalysts under severe conditions at 100°C and p_0 16–17 at and (b) comparison of the activities of systems based on phenols under mild conditions at 60°C and p_0 7 at. Concentrations of TBAI and catalyst 1 mol %, CO_2 /propylene oxide molar ratio ≤ 1 .

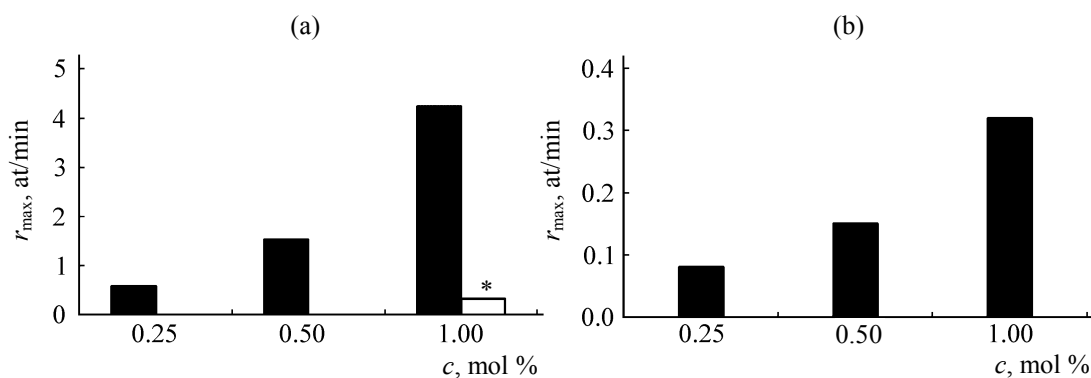


Fig. 2. Dependence of the rate of carboxylation of propylene oxide at the TBAI/catalyst ratio of 1:1 on the concentration of (a) alcohol 7 [(*) in the presence of TBAI alone] at 103°C and p_0 16 at and (b) alcohol 2 at 60°C and p_0 7 at.

The table shows the results of the carboxylation of propylene oxide under the conditions of the production of ^{13}C -propylene carbonate (i.e. with the deficiency of CO_2 with respect to propylene oxide) in the presence of the TBAI–catalyst systems studied in the present work.

All the alcohols and phenols tested as catalysts (in combination with TBAI) allowed efficient carboxylation of propylene oxide, ensuring a high yield of propylene carbonate. Fluorinated alcohols work both in mild and in rather rigid conditions (at $t > 100^\circ\text{C}$) without loss of activity, whereas the activities of the systems based on phenols are unstable at high temperatures, and, therefore, their activities can only be compared in mild conditions. The results of exp. nos. 10–13 show that the catalytic activities of phenols, including reaction rate and reaction frequency (TOF), increase with increasing number of OH groups, which is completely consistent with the data in [8, 9]; therewith, the reaction time decreases. Dihydric alcohol 7, too, is more active than monohydric

fluorinated alcohols 5 and 6 (exp. nos. 5–7) and ensures a high yield of propylene carbonate even at low concentrations (0.25 mol %) of the components of the TBAI–7 system (exp. no. 9); the turnover number (TON) of this catalyst reaches 370. As readily seen from a comparison of exp. nos. 11 and 16, the component ratio in the TBAI–2 catalytic system can be varied without changing the total efficiency of the process, specifically its rate and time (Figs. 2b and 3). At the same time, simultaneous increase of the TBAI concentration 2.5 times and decrease of the pyrocatechol concentration 4 times much increase the catalytic activity of the system: the TON and TOF increase more than 3 times. These results together with the results of exp. nos. 15–18 provide evidence for an important role of the quaternary base: increasing TBAI/catalyst (alcohol or phenol) ratio much increases the catalytic activity of the system. Thus, the TOF of pyrocatechol 2 at a concentration of 0.25 mol % increases from 77 to 209, when the TBAI/2 ratio is increased from 4 to 10 (exp. nos. 15 and 16), and the

TOF of alcohol **7** increases from 62 to 259, when TBAI/**7** ratio is increased from 1 to 10 (exp. nos. 17 and 18).

The mechanism of the reaction of propylene oxide with CO₂, catalyzed by hydroxyl-containing organic catalysts, has been studied in [8, 10–13]. It was found that the α -oxide is activated due to hydrogen bonding between the catalyst protons and epoxide oxygen followed by three-membered ring opening, CO₂ insertion, the formation of the target carbonate, and regeneration of the organic catalyst (Scheme 3); therewith, the anion of the ammonium salt facilitates α -oxide ring opening by attacking the methylene carbon of the substrate [8]. Increasing acidity of the OH groups in the catalyst increases the catalytic activity (*p*-nitrophenol vs. phenol [8, 9], fluorinated vs. nonfluorinated alcohols [9, 10], *m*-hydroxypyridine vs. its *o*- and *p*-isomers [14]). However a more important factor is the presence in the catalyst molecule of several OH groups capable for chelating the epoxide ring oxygen. Thus, an enhanced catalytic activity is characteristic of polyphenols and naphthols with neighbouring OH groups [8, 9], fluorinated diol **7** [9, 10], sugars [9], ethanolamines [9, 15, 16], and silanediol Ar₂Si(OH)₂ [12].

Our results provide evidence for published data. Thus, phenol is the least active among the tested phenols: under comparable conditions, the TON and TOF are 38 and 41 at a concentration of 1 mol %

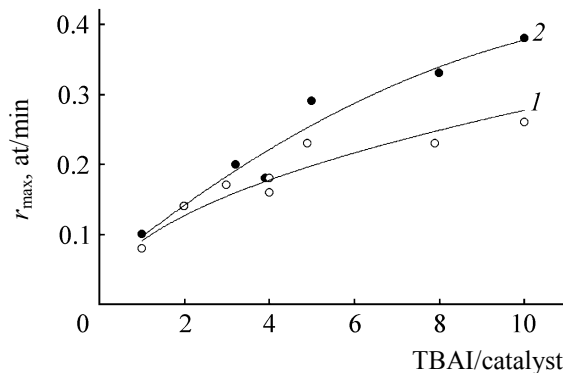
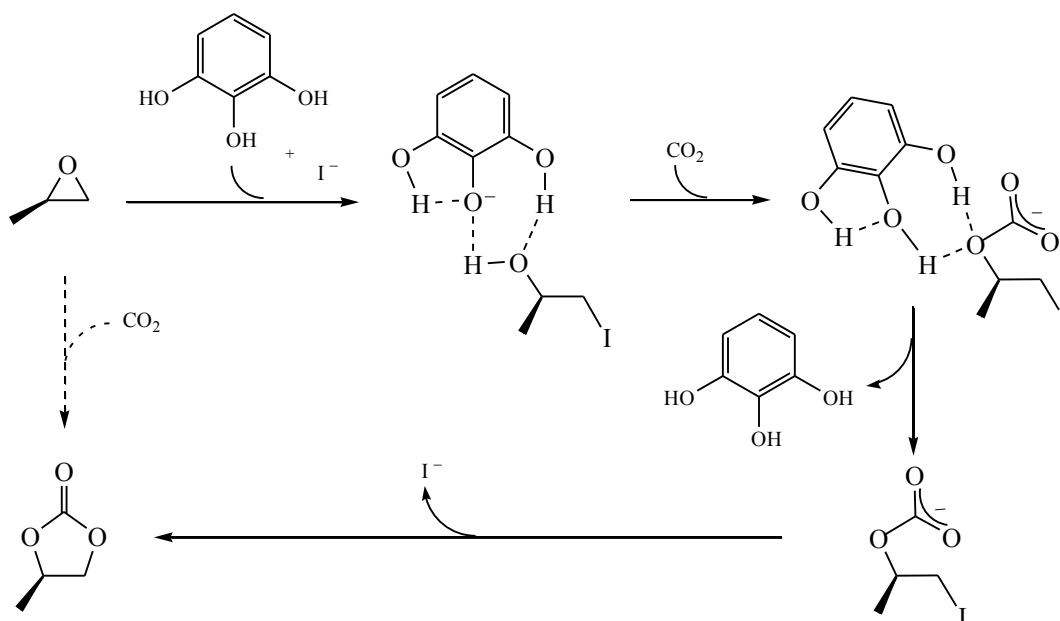


Fig. 3. Dependence of the rate of carboxylation of propylene oxide on the TBAI/catalyst ratio at 60°C and p_0 7 at. Catalyst: (1) **2** and (2) **7** (*c* 0.25 mol %).

(Table 1, exp. no. 10), and fluorinated dihydric alcohol **7** is the most active: TON 134 and TOF 259 at a concentration of 0.25 mol % (see table; exp. no. 18). Furthermore, comparison of pyrocatechol **2** and hexafluoroisopropanol **5**, which have close pK_a values (~9.3 [17, 18]), shows (exp. nos. 2 and 5) that pyrocatechol is much more active under similar conditions and ensures higher reaction rate (almost 1.5 times) and turnover frequency (231 vs. 133) than monohydric alcohol **5**.

Our results show that organic compounds capable of hydrogen bonding in combination with quaternary ammonium salts efficiently catalyze the synthesis of cyclic carbonates by the carboxylation of α -oxides.

Scheme 3.



Synthesis of propylene carbonate by the carboxylation of propylene oxide in the presence of TBAI–catalyst systems^a

Exp. no.	Catalyst		TBAI, %	TBAI/catalyst	<i>t</i> , °C	<i>p</i> ₀ ^b , at	CO ₂ /propylene oxide, mol/mol	Time, min	Yield of propylene carbonate ^c , %	<i>r</i> _{max} , at/min	TON	TOF, h ⁻¹
	comp. no.	<i>c</i> , mol %										
1	1	1	1	1	103	16	0.85	50	93.0	1.42	78	151
2	2	1	1	1	104	16	0.89	40	94.7	3.00	85	231
3	3	1	1	1	104	17	0.98	60	94.3	2.14	93	112
4	4	1	1	1	103	16	0.90	240 ^d	92.7 ^d	0.84	83	25
5	5	1	1	1	103	17	0.91	60	99.2	2.07	91	133
6	6	1	1	1	103	17	0.93	50	95.2	2.27	90	174
7	7	1	1	1	102	17	0.90	40	98.7	4.24	89	231
8	7	0.5	0.5	1	105	17	0.99	90	95.5	1.54	182	138
9	7	0.25	0.25	1	105	17	0.98	180	94.8	0.58	370	131
10	1	1	1	1	60	7	0.38	65	98.7	0.20	38	41
11	2	1	1	1	58	7	0.39	50	95.6	0.32	46	66
12	3	1	1	1	58	7	0.44	45	93.6	0.35	42	82
13	4	1	1	1	58	7	0.40	45	93.7	0.37	38	71
14	2	0.5	0.5	1	58	7	0.40	100	95.0	0.15	76	51
15	2	0.25	1	4	59	7	0.40	140	94.9	0.16	154	77
16	2	0.25	2.5	10	59	7	0.37	55	93.1	0.26	139	209
17	7	0.25	0.25	1	61	7	0.38	150	92.3	0.10	145	62
18	7	0.25	2.5	10	59	7	0.36	35	92.3	0.38	134	259

^a Propylene oxide 20 mL. ^b Initial CO₂ pressure at room temperature. ^c Isolated yield per loaded CO₂. ^d The process was terminated but the reaction was not complete, the reaction mixture got black.

The catalysts used in the present work (alcohols and phenols together with tetrabutylammonium iodide), allow the synthesis of ¹³C-propylene carbonate (for the subsequent synthesis of ¹³C-urea, a popular diagnostic preparation) under mild conditions (60°C, 7 at) with a nearly quantitative yield without the use of solvents (which enhances the process performance). The highest activity is characteristic of polyatomic phenols and alcohols with increased acidity of hydroxyl protons. Such catalysts, unlike their known analogs [8–16], can work at low concentrations (≤0.25 mol %) and much enhance their activity with increasing ammonium salt amount (TOF up to 260), temperature, and initial CO₂ pressure (TON up to 370); therewith, complete gas consumption takes place, which is required, for example, in the synthesis of ¹³C-labeled products for saving the isotopically labeled raw materials.

From the practical viewpoint, the lack of metals in the catalyst composition, mild conditions, and sufficiently high performance of the tested catalysts open up prospects for their use in the synthesis of cyclic carbonates from CO₂, in particular, for drug production.

EXPERIMENTAL

Analysis of the gas phase in the reactor for the residual concentration of CO₂ was performed by gas chromatography on a Kristallyuks-4000M chromatograph with a thermal conductivity detector and a 3 m × 3 mm column packed with activated carbon (Shimadzu, 60–80 mesh); carrier gas helium (60 mL/min); the oven temperature was ramped from 35°C (hold 2.5 min) to 150°C at a rate of 45 deg/min; detector temperature 150°C; detector current 70 mA; injection (loop)

volume 1 mL. The ^1H NMR analysis of propylene carbonate was performed on a Bruker AVANCE 600 MHz instrument using a Bruker WIN-NMR software package.

The reaction rate was determined as a maximum gas consumption rate in the inflection point of the dependence of the pressure in the reactor (p) on time (τ), using a SYSTAT TableCurve 2D v5.01.05 software [20] by the best fit of the $p = f(\tau)$ dependence and calculation of the maximum first derivative.

$$r_{\max} = \left| -\frac{dp}{d\tau} \right|_{\max}$$

The reactions were performed in a stainless steel pressure reactor (volume 200 mL) equipped with sensors for recording the temperature and pressure at 1-min steps. The reactor was loaded with the catalyst components, closed, and evacuated, after which propylene oxide was loaded through a vent from a measuring tank and CO_2 was fed until a required pressure had been reached and then the gas inlet vent was closed and stirring and heating were initiated. After completion of the process (pressure drop is no longer observed), the reactor was cooled down, unreacted propylene oxide was removed in a water-jet-pump vacuum, and the residue was taken out and subjected to vacuum distillation to isolate propylene carbonate, bp 82–84°C (3 mmHg) {bp 241.7°C (760 mmHg) [19]}. The purity of the product was no less than 99% (^1H NMR data), n_D 1.4209 (n_D^{20} 1.4209 [19]). ^1H NMR spectrum (DMSO- d_6), δ , ppm: 1.37 d (3H, CH_3 , 3J 6.1 Hz), 4.06 m (1H, CH_2 , $^2J \approx ^3J = 7.3$ –8.6 Hz), 4.57 t (1H, CH_2 , $^2J \approx ^3J = 7.9$ –8.6 Hz), 4.89 m (1H, CH).

CONFLICT OF INTERESTS

No conflict of interest was declared by the authors.

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