Reaction of dialkyl carbonates with alcohols: Defining a scale of the best leaving and entering groups*

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Abstract: A series of dialkyl and methyl alkyl carbonates has been synthesized and their reactivity investigated. The behavior of preferential leaving and entering groups for the newly synthesized carbonates has been accurately investigated. Both experimental and computational studies agreed that the scale of leaving groups follows the trend: $PhCH_2O^-$, $MeO^- \geq EtO^-$, $CH_3(CH_2)_2O^-$, $CH_3(CH_2)_7O^- > (CH_3)_2CHO^- > (CH_3)_3CO^-$.

Accordingly, the scale of the entering group has the same trend, with *t*-butoxide being the worst entering group. A preliminary attempt to rationalize the nucleofugality trends, limited to the $(CH_3)_3CO^-$ and CH_3O^- groups, has indicated that a likely origin of the observed trends lies in the different entropic contributions and solvation effects.

Keywords: computational studies; dimethyl carbonate; green chemistry; synthesis; theoretical chemistry.

INTRODUCTION

Since the 1980s, when dimethyl carbonate (DMC) was synthesized for the first time using a green process [1], its exploitation both in industrial [2] and laboratory scale [3] has grown exponentially. This is due to the fact that DMC chemistry incorporates several highly appealing green features: easy and clean synthesis [1,4], low toxicity [5], high selectivity, and flexible reactivity [6].

DMC is a well known environmentally benign substitute for dimethyl sulfate, methyl halides, and phosgene. In fact, in the presence of a nucleophile and a catalyst, DMC can act either as methylating agent (as a substitute of dimethyl sulfate) or carboxymethylating agent (as a substitute phosgene). In the first process, the nucleophile attacks the methyl group of DMC via $B_{Al}2$ mechanism, meanwhile in the second process the nucleophile reacts with the carbonyl group of DMC via $B_{Ac}2$ mechanism leading to the carboxymethylated product [7].

Factors that affect the reaction outcomes (i.e., methylation and/or carboxymethylation) are temperature, nature of the catalyst, and the nucleophile used.

The growing knowledge of the chemistry of DMC led the way to the use of similar carbonates such as: diethyl carbonate [8], diphenyl carbonate [9], diallyl carbonates [10], as well as the cyclic carbonate ethylene carbonate [11]. All these compounds are commercially available and have been used in several industrial processes or laboratory-scale reactions [8–11].

In this work we intend to further investigate the reactivity of alkyl carbonates. Thus, a string of dialkyl and methyl alkyl carbonates have been synthesized and their reactivity investigated by reacting with a simple nucleophile (i.e., ethanol). In this prospect, alkyl methyl carbonates have shown interesting behavior since in these reactions there is the possibility of different product formation depending on the preference of the leaving groups attached. Equally, competition reactions involving two nucleophiles (i.e., alcohols) and a dialkyl carbonate (i.e., DMC) showed distinct preference among the possible entering groups. In this prospect, a series of experimental and computational trials was conducted in order to define a scale of best leaving and entering groups for these newly synthesized carbonates.

EXPERIMENTAL

General information

All compounds used were ACS grade and were used without further purification. Gas chromatography-mass spectroscopy (GC-MS) analyses were performed at 70 eV (MS) with a 30 m HP 5 capillary GC column.

Infrared spectra were recorded on a Nicolet Magna 750 Fourier transform-infrared (FT-IR) spectrophotometer. NMR spectra (^{1}H, ^{13}C) were obtained on AVANCE 300 Bruker spectrometers at 25 °C and referred to internal tetramethylsilane.

Basic alumina type 5016A basic standard grade, 150 mesh was purchased from Merck.

If not otherwise specified, all the reactions were performed in batch conditions and at atmospheric pressure.

General procedures for the synthesis of methyl carbonates, dialkyl carbonates, as well as experimental details of the tables are reported in the Supplementary Information.

Computational information

Stables and transition structures (TSs) were fully optimized in the gas phase by gradient procedures within the density functional theory (DFT), by using the B3LYP functional [12]. The polarized 6-311+G(2df) basis set [13] was used both in the DFT optimizations and in the solvent simulation. The nature of the critical points was checked by vibrational analysis.

Solvent effects were taken into account via the self-consistent reaction field (SCRF) method, by using the integral equation formalism-polarizable continuum model (IEF-PCM) [14]. The relevant single-point energy calculations were carried out on the gas-phase geometries.

Natural bond orbital analysis [15] was performed to obtain reliable atomic and group charges. All calculations were carried out using the GAUSSIAN 03 system of programs [16].

RESULTS AND DISCUSSION

Laboratory investigations

A first set of experiments was carried out in order to investigate the reactivity of the unsymmetrical carbonates using a simple primary alcohol (i.e., ethanol) (Scheme 1). In the context of this investigation, "unsymmetrical" refers to hetero-disubstitute carbonates. In a typical experiment, an excess of ethanol was added to a mixture containing the organic carbonate and potassium carbonate. The product distribution was monitored over 6 h both by GC and GC-MS analysis, and the results are reported in Table 1.
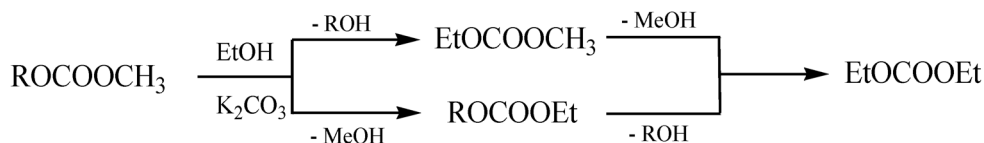
Scheme 1 Reaction of unsymmetrical carbonates with a primary alcohol.

Table 1 Reaction of unsymmetrical carbonates with ethanol in the presence of K_2CO_3.

Carbonate	Product distribution (% mol) after 6 h			
	Carbonate			
$ROCO_2Me$	$EtOCO_2Me$	$ROCO_2Et$	$EtOCOOEt$	$ROCO_2Me$
n-$PrOCO_2Me$	3.8	4.5	91.7[a]	–
$OctOCO_2Me$	–	–	100[b]	–
$PhCH_2OCO_2Me$	–	–	100[c]	–
i-$PrOCO_2Me$	3.1	10.1	86	–
t-$BuOCO_2Me$	–	69	10	21

$ROCO_2Me$ /K_2CO_3 1/0.25, T = 60 °C.
[a]Reaction reached equilibrium after 60 min.
[b]Reaction reached equilibrium after 60 min.
[c]Reaction reached equilibrium after 30 min.

When ethanol was reacted with carbonates derived from primary alcohols (i.e., propyl methyl carbonate and octyl methyl carbonate), a significant preference among the two leaving groups was not observed (i.e., RO^- and MeO^-). In fact, after 6 h, the unsymmetrical carbonates were both converted quantitatively to diethyl carbonate. The reactions resulted quite fast since complete conversion to diethyl carbonate was achieved after 1 h. The same trend was observed for the benzyl methyl carbonates. In this case, the reaction was even faster, reaching completion after 30 min with the exclusive formation of diethyl carbonate (100 %) as final product. In all cases, the reaction intermediates (i.e., $EtOCO_2Me$ and $ROCO_2Et$) were observed during the reaction; they formed quickly and then were slowly converted to diethyl carbonate.

Accordingly, reaction of propan-2-yl methyl carbonate with ethanol led to the formation of diethyl carbonate as the main product. However, after 6 h the mixture showed also traces of propan-2-yl ethyl carbonate (11 %). Finally, when t-butyl methyl carbonate was used, the reaction was the slowest compared to the other carbonates reaching completion after 6 h. In this case, diethyl carbonate was formed in about 10 % yield while the main product was t-butyl ethyl carbonate. These results showed that t-butyl methyl carbonate is the least reactive compound possibly due to the low ability of the t-butyl as leaving group.

In order to confirm the results obtained, a similar set of experiments was conducted using cesium carbonate. For this series of trials, we decided to use 5 % mol of base instead of 25 % mol employed in the previous table since cesium carbonate is renowned as a stronger base.

Table 2 reports the results obtained. The data collected were very similar to the ones reported in Table 1. Cesium carbonate is a more soluble and active catalyst for the reaction. In fact, despite the lower amount of base used, the reaction was faster than those with potassium carbonate and the results are comparable with Table 1.

Table 2 Reaction of unsymmetrical carbonates with ethanol in the presence of Cs_2CO_3.

| Carbonate	Product distribution (% mol) after 6 h			
	Carbonate			
$ROCO_2Me$	$EtOCO_2Me$	$ROCO_2Et$	$EtOCOOEt$	$ROCO_2Me$
n-$PrOCO_2Me$	4	–	96[a]	–
n-$OctOCO_2Me$	–	–	100[b]	–
$PhCH_2OCO_2Me$	–	–	100[c]	–
i-$PrOCO_2Me$	3	11.6	88	–
t-$BuOCO_2Me$	–	75.8	9.3	14.7

$ROCO_2Me/Cs_2CO_3$ 1/0.25, $T = 60$ °C
[a]Reaction reached equilibrium after 30 min.
[b]Reaction reached equilibrium after 30 min.
[c]Reaction reached equilibrium after 10 min.

To support the data obtained, some competitive experiments were also conducted employing equal amounts of symmetric carbonates and ethanol as the nucleophile. Dialkyl carbonates (i.e., dioct-1-yl carbonate, dipropan-2-yl carbonate, dibenzyl carbonate, and di-t-butyl carbonate) were synthesized according to the procedure reported in the Experimental section. According to Scheme 2, reaction of ethanol with either DMC or the competitor dialkyl carbonate should result first in the formation of unsymmetrical carbonates (i.e., ethyl methyl carbonate and/or alkyl ethyl carbonate) and then in their conversion to diethyl carbonate.
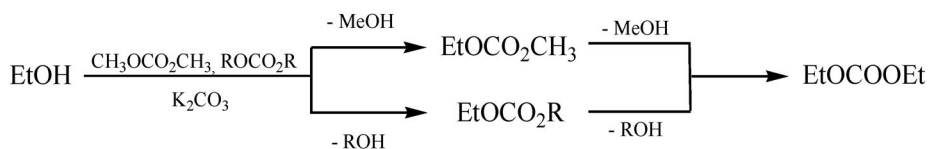
Scheme 2 Competitive reaction of ethanol with different carbonates.

Results of the experiments are reported in Table 3. Competition between dioct-1-yl carbonate and DMC resulted in the quick formation of unsymmetrical carbonates ethyl methyl carbonate and octyl methyl carbonate which were then converted to diethyl carbonate. The reaction was complete after 2 h. The molar percentage of diethyl carbonate reported (i.e., 187.2 % mol) is due to the fact that the initial % mol for both DMC and dioct-1-yl carbonate was considered to be 100 % mol.

Table 3 Competition of carbonates with ethanol in the presence of K_2CO_3

| Carbonate 1	Carbonate 2	Product distribution (% mol) after 6 h				Alcohol
	(R)	Carbonate				
		$EtOCO_2CH_3$	$EtOCO_2Et$	$ROCO_2Et$	$ROCO_2R$	ROH
$CH_3OCO_2CH_3$	$OctOCO_2Oct$	12,8	187,2	–	–	200
$CH_3OCO_2CH_3$	$PhCH_2OCO_2CH_2Ph$	10,5	189,5	–	–	200
$CH_3OCO_2CH_3$	i-$PrOCO_2Pr$-i	8,7	79	12,3	62,9	19,3
$CH_3OCO_2CH_3$	$^tBuOCO_2{}^tBu$	5,4	94,6	–	100	–

DMC/$ROCO_2R$ 1/1; K_2CO_3 0.25 mol % $T = 60$ °C

As expected, isoproxide was not as good a leaving group as the methoxide or the octanoxide and ethanol did not react at all with di-*t*-butyl carbonate, which was confirmed to be the less reactive carbonate, possibly due to the two bulky *t*-butyl groups.

From the data collected it is thus possible to build up the following scale of leaving groups for dialkyl carbonates:

$$PhCH_2O^-, MeO^- > CH_3(CH_2)_2O^-, CH_3(CH_2)_7O^- > (CH_3)_2CHO^- > (CH_3)_3CO^-$$
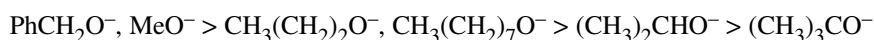
Also, some competitive experiments on the reactivity of different nucleophiles (i.e., alcohols) with DMC were performed (Scheme 3). The alcohols selected for this investigation are the parent alcohols used to obtain the asymmetric carbonates (i.e., octan-1-ol, propan-2-ol, *t*-butyl alcohol, and benzyl alcohol).
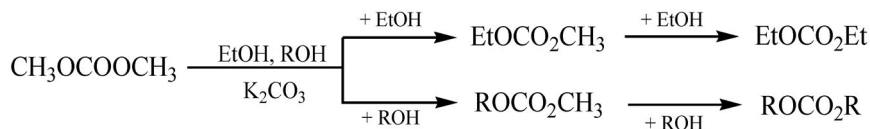
Scheme 3 Competitive reaction of DMC with different alcohols.

These sets of experiments embrace a double intent: investigate the reactivity of different alcohols (i.e., primary, secondary, tertiary and benzylic alcohols) with DMC and confirm the results obtained regarding the best leaving group.

In a typical experiment, a mixture containing the two alcohols, DMC and potassium carbonate, were stirred and heated at 60 °C over a time of 24 h, taking samples at time intervals. The results obtained are reported in Table 4. Competition between ethanol and octan-1-ol showed no significant difference since their reactivity as nucleophiles is comparable. In fact, the main products formed were the ones related to the mono-substitution of DMC. Neither dioct-1-yl carbonate nor diethyl carbonate were observed.

Table 4 Competitive reaction of DMC with different alcohols in the presence of K_2CO_3.

Alcohol 1	Alcohol 2	Product distribution (% mol) after 6 h				
	(R)	Carbonate			Alcohol	
		$EtOCO_2CH_3$	$ROCO_2Me$	$ROCO_2R$	ROH	EtOH
EtOH	OctOH	73.6	65.5	–	34.5	26.4
EtOH	$PhCH_2OH$	72	90	–	10.2	27.6
EtOH	*i*-PrOH	57	16.2	–	83.8	43
EtOH	*t*BuOH	34.4	–	–	97	65.6

EtOH/ROH/DMC 1/1/50; K_2CO_3 0.25 mol %, $T = 60$ °C

Benzyl alcohol showed a better reactivity toward DMC compared to ethanol. In fact, benzyl methyl carbonate formed very quickly and in almost quantitative yield.

On the other side, when the competitive reaction was performed using ethanol and a secondary alcohol (i.e., propan-2-ol), the difference in reactivity was more evident. After 24 h it was possible to identify ca. 16 % mol of the propan-2-yl methyl carbonate, meanwhile, the amount of ethyl methyl carbonate was ca. 50 % mol. Finally, competition between *t*-butyl alcohol and ethanol resulted in a very slow reaction. The tertiary alcohol did not react with DMC, and the only product formed was ethyl methyl carbonate even if the yield was lower than in the other reactions.

The results obtained confirmed that the scale of the best entering group follows the same trend of the best leaving group previously reported:

$$PhCH_2O^-, MeO^- > EtO^-, CH_3(CH_2)_2O^-, CH_3(CH_2)_7O^- > (CH_3)_2CHO^- > (CH_3)_3CO^-$$

Computational studies

To interpret part of the experimental data, a computational study was also carried out. In particular, the nucleofugality [17] of t-BuO$^-$ and MeO$^-$ groups from the tetrahedral intermediate generated by ethoxide attack onto t-butyl methyl carbonate, was the focus. This means that reference is made to the experimental results of Table 1, last entry. More precisely, we investigated the barriers for competitive loss of the alkoxide anions MeO$^-$, EtO$^-$, and t-BuO$^-$ from the tetrahedral intermediate t-BuO·EtO·MeO·CO$^-$ in the gas phase and in ethanol solution.

Gas-phase results

In the gas phase, the loss of alkoxide requires the energy barriers (ΔE_{gas}) of 4.5 and 5.6 kcal mol^{-1} to be overcome for t-BuO$^-$ and MeO$^-$, respectively (Table 5), while the experimental results in solution (EtOH) indicate that t-butoxide leaves less easily than methoxide. However, the free energy barriers (ΔG_{gas}, at 333 K) imply the reverse trend of the leaving group rates: MeO$^-$ > t-BuO$^-$. On the basis of an estimate of the rate constant ratio, the MeO$^-$ loss can be estimated to be faster than the t-BuO$^-$ loss: $k_{MeO}/kt_{BuO} = 1.8$.

Table 5 Energies and free energy differences (in kcal mol^{-1}) with respect to the same tetrahedral intermediate, in the gas phase and in solution at DFT(B3LYP)/6-311+G(2df) level. Solvent = ethanol, T = 333 K.

	ΔE_{gas}	ΔH_{gas}	ΔG_{gas}	ΔG_{solv}	r_{C-O}[a]
TS MeO loss	5.6	4.5	3.9	2.2	2.19
TS t-^{t}BuO loss	4.5	3.9	4.3	4.0	1.95

[a]Distance (in Å) between the alkoxy group and the carbonate in the TS.

We can tentatively offer a rationalization of this inversion. Considering the gas-phase energy reaction profile, MeO$^-$ is a worse leaving group than t-BuO$^-$ (Fig. 1, open diamond): hence, the length of the cleaving C–O bond in the TS, which is determined on the E hypersurface, is larger (later TS in a geometrical sense: r_{C-O} = 2.19 vs. 1.95 Å). The TS geometry is looser and gives rise to lower vibrational frequencies. These contribute in turn to the definition of the enthalpy and entropy contributions (dashed lines), actually to different extents (Fig. 1). In the t-BuO$^-$ case, the contribution to the enthalpy is negative, as is the case for MeO$^-$.

Thus, both contribute in lowering the barrier. However, the –$T\Delta S$ term has positive sign in the t-BuO$^-$ case, thus bringing about some elision with the enthalpy contribution: consequently, the resulting G barrier is only slightly lower than the E barrier (Fig. 1, left).

In the MeO$^-$ case, by contrast, the –$T\Delta S$ term is lower than zero and strengthens the effect seen for enthalpy. These vibrational effects cause the ordering inversion in the barrier heights, defining MeO$^-$ as the best leaving group.
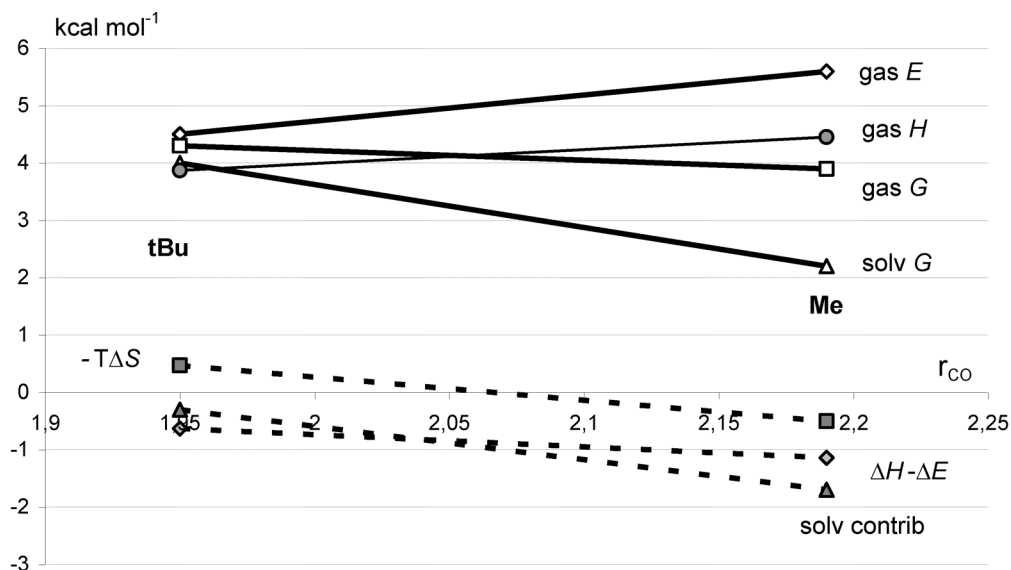
Fig. 1 Energy and free energy barrier height trends and enthalpic, entropic, and solvation contributions.

Solvent effects

Free energies in ethanol solution also describe the MeO⁻ loss as easier with respect to the *t*-BuO⁻ loss. The effect is such to enhance the trend already discussed for the free energy barriers in the gas phase. The effect is due to a larger solvation energy of the MeO⁻ loss TS (-41.7 kcal mol^{-1}) compared with the *t*-BuO⁻ loss (-40.3 kcal mol^{-1}). Solvent simulation, makes the MeO⁻ loss even easier: $k_{MeO}/k_{t\text{-BuO}}$ (EtOH) = 14.2, which compares well with the experimental findings.

In the MeO⁻ case, the TS has a larger charge localized in the oxygen of the leaving alkoxy group than *t*-BuO⁻ (Chart 1). The solvent enhances this localization with respect to the gas phase, to a lesser extent in the case of *t*-BuO⁻ loss.
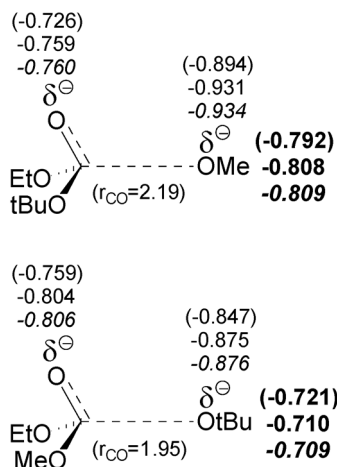

Chart 1 Q_{NAO} of the oxygen atoms: (1) for the gas-phase *t*BuO·EtO·MeO·C–O⁻ cleaving system (TS), in parentheses; (2) for system (1) solvated in EtOH (IEF-PCM); (3) in bold, sum of charges for the whole leaving group.

CONCLUSIONS

Several alkyl methyl carbonates and dialkyl carbonates have been synthesized. The behavior of preferential leaving and entering groups for the newly synthesized carbonates has been accurately investigated. Both experimental and computational studies agreed that the scale of leaving groups follows the trend

$$PhCH_2O^-, MeO^- > CH_3(CH_2)_2O^-, CH_3(CH_2)_7O^- > (CH_3)_2CHO^- > (CH_3)_3CO^-$$
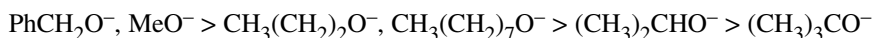
It appears that the trend follows a basicity function of the alkoxide, i.e., the best leaving group is that with the lowest basicity, methoxide whereas *t*-butoxide, the stronger base is a poorer leaving group.

The nucleofugality trend was also investigated computationally, limited to the $(CH_3)_3CO^-$ and CH_3O^- groups, indicating that a likely origin of the observed trends lies in the different entropic contributions and solvation effects. Accordingly, the scale of the entering group has the same trend, with *t*-butoxide being the poorer entering group.

The results collected are promising for the use of the newly synthesized unsymmetrical alkyl carbonate such as octyl methyl carbonate, propan-2-yl methyl carbonate, and *t*-butyl methyl carbonate. From here we intend to further investigate the utility of this concept in other reactivities.

SUPPLEMENTARY INFORMATION

Supplementary information is available online (doi:10.1351/PAC-CON-08-12-02).

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