DOI: 10.1002/adsc.200600575

Highly Efficient Direct Carboxylation of Propane into Butyric Acids Catalyzed by Vanadium Complexes

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Received: November 3, 2006

Abstract: A direct and highly efficient carboxylation of propane by carbon monoxide into butyric acids (mainly isobutyric and, in a smaller amount, *n*-butyric), in the presence of potassium peroxodisulphate ($K_2S_2O_8$) and in trifluoroacetic acid solution, has been achieved by using a vanadium catalytic system based on Ca[V{ON(CH(CH$_3$)COO)$_2$}$_2$] (synthetic *amavadine*), its model compounds Ca[V{ON(CH$_2$COO)$_2$}$_2$] or [VO{N(CH$_2$CH$_2$O)$_3$}] – other simpler vanadium compounds, such as [VO(acac)$_2$] or VOSO$_4$, are less active. Overall yields (based on propane) of carboxylic acids up to 70% and TON values up to 18.4×10^3 have been reached. The effects of various factors such as the propane and carbon monoxide pressures, temperature, time, catalyst amount and radical traps have been investigated, the reactions are shown to proceed *via* both *C*- and *O*-centred radicals, with $K_2S_2O_8$ playing the role of an oxidant *via* a free radical mechanism.

Keywords: butyric acids; carboxylation; homogeneous catalysis; propane; vanadium complexes

Introduction

The activation of gaseous alkanes is an important field in modern chemistry, since they are the most abundant and cheapest carbon raw materials.[1a–c] However, the difficulty of activation of the C–H and C–C bonds in alkanes prevents their broad usage for direct syntheses of added-value chemical products, and therefore gaseous alkanes are mainly used as fuels.[1] In particular, propane is applied for heating purposes and as an alternative and environmentally clean fuel for vehicles.[1b,2] To a lesser extent, it is used in the chemical industry, mainly for the production of ethylene and propylene,[2] whereas the direct transformations of propane to functionalised valuable chemicals still remain undeveloped fields of research.

Butyric acids are the expected products of carboxylation of propane and they are known to find application in the manufacture of various plastics, perfumes, lacquers, preservatives, etc.[2] The commercial production of *n*- and isobutyric acids is based on the oxidation of the corresponding aldehydes (almost exclusive processes for these acids),[2] thus employing starting materials with a considerable cost, that is, *n*-butyraldehyde and isobutyraldehyde. Therefore, the search for a direct synthesis of these acids from a cheap carbon raw material such as propane is a justifiable aim to be pursued.

A particularly interesting system (with significance for the current study) for the synthesis of *n*- and isobutyric acids from propane and carbon monoxide was discovered[3a] and developed by Fujiwara's group using $K_2S_2O_8/CF_3COOH$ (TFA) in the presence of a metallic compound [with, for example, Cu(II)/Pd(II),[3a,b] Mg(II),[3c] Co(II),[3d] or Ca(II)[3e]]. However, the obtained very low yields and TONs did not merit any further exploration. Besides, the mechanistic features of this reaction have remained unknown. Therefore, the search for more effective catalytic systems for propane carboxylation to the corresponding carboxylic acids and a study towards getting an insight into its mechanism are the main aims addressed in the current work.

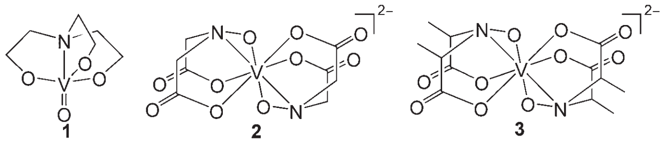
Recently, we have found some vanadium- and rhenium-based catalytic systems for the single-pot carboxylation, under mild conditions, of methane and ethane to acetic and propionic acids, respectively.[4] We have then observed that *amavadine* (a vanadium complex, see below, present in some *Amanita* fungi) and related compounds disclosed the highest activity not only for the carboxylation[4a,c] but also for the peroxidative oxidation[5] reactions of some alkanes (other than propane). Moreover, other vanadium compounds are also known[6] to act as efficient homogeneous catalysts for the latter type of reactions, but their use for alkane carboxylations has been reported[6f,7] only rather scarcely and not for propane.

By extending the above alkane carboxylation studies to propane, we now report a highly effective system for its direct (single-pot) conversion (by carboxylation with CO) into butyric acids, in the presence of $K_2S_2O_8$ and in TFA solution, based on the use, as catalysts or catalyst precursors, of *amavadine* and its model (see below) or other vanadium complexes with N,O- or O,O-ligands. Overall yields (based on propane) of carboxylic acids up to 70% and TON values up to 18.4×10^3 are achieved, and these systems constitute, as far as we are aware, the most efficient ones so far reported for the functionalisation of propane under mild or moderate conditions.

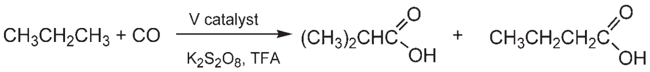
Results and Discussion

The following vanadium compounds were used as catalyst precursors: $[VO\{N(CH_2CH_2O)_3\}]$ (**1**), $Ca[V\{ON(CH_2COO)_2\}_2]$ (*amavadine* model) (**2**), $Ca[V\{ON(CH(CH_3)COO)_2\}_2]$ (synthetic *amavadine*) (**3**; Scheme 1), $[VO(acac)_2]$ (**4**; acac = acetylacetonate) and $VOSO_4 \cdot 5H_2O$ (**5**).

Each of them, in the presence of $K_2S_2O_8$ and in TFA, exhibits a high catalytic activity for the carboxylation of propane with carbon monoxide to give isobutyric and *n*-butyric acids as the main products, normally with a predominance of the former (Scheme 2, Table 1). Acetic acid is also formed, although in low yield, as a result of C–C bond cleavage and partial oxidation with peroxodisulphate. The formation of the TFA esters isopropyl trifluoroacetate and methyl trifluoroacetate was also detected, mainly when using pressures of CO lower than those normally employed. However, these esters are not formed by carbonylation, as shown by ^{13}CO experiments (see below), and the work focused on the preparation of the carboxylic acids which are also usually the main products.



Scheme 1.



$$CH_3CH_2CH_3 + CO \xrightarrow[K_2S_2O_8,\ TFA]{V\ catalyst} (CH_3)_2CHC(=O)OH + CH_3CH_2CH_2C(=O)OH$$

Scheme 2.

Carbon monoxide is the source of the carbonyl groups for the butyric acids but not for the acetic acid and the esters, as clearly established by experiments with ^{13}C-labelled CO (see below). Blank tests were performed under typical reaction conditions and different CO pressures and indicated that neither *n*-bu-

Table 1. Effect of propane pressure on the yield of carboxylic acids.[a]

Entry	Catalyst	pC_3H_8 [atm][b]	pCO [atm][b]	Yield of products[c] [%] Isobutyric acid	*n*-Butyric acid	Acetic acid	Total	TON[d]
1	**1**	0.0	20	0	0	0	0	-
2	**1**	3.0	20	4.9	5.7	5.2	15.8	7.3
3	**1**	5.0	20	11.8	6.5	4.4	22.7	17.4
4	**1**	8.5	20	27.7	20.4	1.4	49.5	64.3
5	**1**	10.7	20	22.6	16.3	1.1	40.0	65.5
6[e]	**1**	8.5	20	0	0	1.7	1.7	2.2
7[f]	**1**	8.5	20	23.1	16.2	0.9	40.2	52.3
8[g]	**1**	8.5	20	5.5	3.5	8.3	17.3	22.5
9	**2**	8.5	20	19.2	19.2	1.6	40.0	52.0
10	**3**	8.5	20	23.0	14.6	0	37.6	49.0
11	**4**	8.5	20	27.4	16.9	5.3	49.6	64.5
12	**5**	8.5	20	25.0	17.7	3.0	45.7	59.4

[a] *Reaction conditions (unless stated otherwise)*: metal complex catalyst (20.00 μmol), $K_2S_2O_8$ (4.00 mmol, that is, 200:1 molar ratio of oxidant to metal catalyst), CF_3COOH (5.0 mL), 80 °C, 20 h, in an autoclave (13 mL capacity).

[b] Measured at 25 °C (amounts of C_3H_8 or CO gases correspond to $0.306\ mmol \cdot atm^{-1}$).

[c] The values given are for molar yield [%] based on C_3H_8, that is, moles of product per 100 moles of propane (determined by GC or GC-MS). If required, molar yields [%] based on $K_2S_2O_8$, that is, moles of product per 100 moles of $K_2S_2O_8$, can be estimated (by taking into account that the $K_2S_2O_8$:metal catalyst molar ratio is 200:1) as TON × 0.5 (except for run 8), for example, 32.8% for run 5.

[d] Turnover number (moles of isobutyric, *n*-butyric and acetic acids per mol of metal catalyst precursor).

[e] $CBrCl_3$ was used in the same molar amount as that of propane.

[f] $(NH_4)_2S_2O_8$ (4.00 mmol) was used instead of $K_2S_2O_8$.

[g] $K_2S_2O_8$ was used in the amount of 6 mmol; molar yield [%] based on $K_2S_2O_8$ is 7.5%.

tyric nor isobutyric acid were formed unless the vanadium catalyst was added. Only acetic acid in an almost negligible yield (less than 1%) was detected in the absence of catalyst.

The most active systems are provided by *amavadine* **3** and its model **2** and by complex **1**, which can lead to overall yields of carboxylic acids up to 70% based on propane (or 55% based on the oxidant $K_2S_2O_8$) and TONs up to 18.4×10^3 (see Tables). The simpler vanadium compounds (**4** and **5**), under the same conditions, are less active, although still providing yields of *ca.* 50% (Table 1, entries 11 and 12).

Replacement of TFA or of $K_2S_2O_8$ by another acid or oxidant, respectively, even similar ones, results in a decrease or loss of activity. For instance, the use of $(NH_4)_2S_2O_8$ instead of the analogous potassium salt leads to a lower yield and TON (compare runs 7 and 4, Table 1). The relative amounts of the reagents are also important and, in particular, 4.0 mmol $K_2S_2O_8$/5.0 mL TFA provides the most adequate ratio. The use of a higher amount of the oxidant results in a lowering of activity (compare runs 8 and 4, Table 1), conceivably due to its limited solubility in TFA which hampers an effective stirring of the suspension. The impact of other factors on the activity of the system (comprising any of the catalysts **1**–**3**), aiming at the optimisation of the reaction conditions and getting information with mechanistic significance, was also investigated in detail, as discussed below.

Effect of Propane Pressure

The investigation of the effect of propane pressure, for catalyst **1** and at a constant CO pressure (20 atm), reveals its significant influence on the yields of carboxylic acids and on the total conversion of propane (Table 1, Figure 1). At a low C_3H_8 pressure (3 atm) the yields of all carboxylic acids are also rather low (*ca.* 5% each) and similar. An increase of propane pressure promotes the formation of both iso- and *n*-butyric acids, whose maximum yields of *ca.* 28 and 20%, respectively, are reached at 8.5 atm of C_3H_8 (Table 1, entries 3 and 4). A further increase of propane pressure up to *ca.* 10.5 atm results in a slight yield drop of these acids. Isobutyric acid is the predominant product above 3 atm of propane. The yield of acetic acid is maximum at this propane pressure, beyond which it becomes the minor product. Since the maximum overall yield of carboxylic acids (*ca.* 50%, under the conditions of Table 1) has been achieved at 8.5 atm of propane, the subsequent studies (see below) of the effects on the yields and TONs of the other reaction parameters have been performed typically at this alkane pressure.

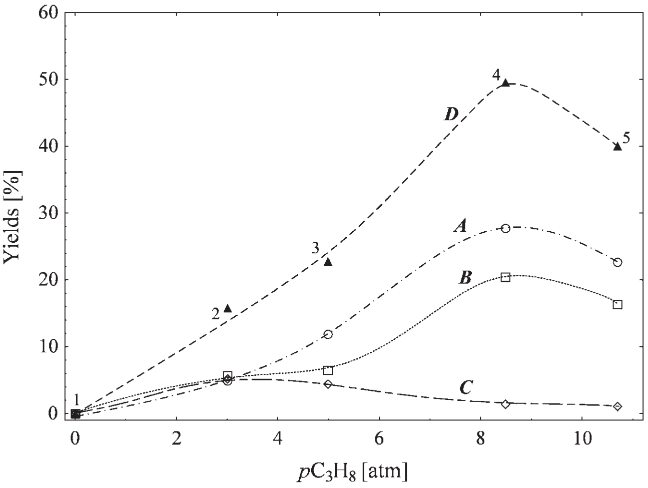


Figure 1. Effect of the C_3H_8 pressure on the yields of isobutyric (curve ***A***), *n*-butyric (curve ***B***) and acetic (curve ***C***) acids and on the total yield (curve ***D***) for the propane carboxylation catalysed by complex **1** (pCO = 20 atm). Reaction conditions and point numbers are those of the Table 1 entries.

Effect of Carbon Monoxide Pressure

The CO pressure influences significantly the yields of carboxylic acids (Table 2, Figure 2). The carboxylation of propane proceeds even in the absence of CO, although to a very low extent, when TFA behaves as the carbonylating agent[4a] for both iso- (0.3%) and *n*-butyric (1.5%) acids, whereas acetic acid is then the main product (3.1%). However, CO promotes the formation of both butyric acids (Figure 2 for catalyst **1** and $pC_3H_8 = 8.5$ atm), and the maximum yields of isobutyric (*ca.* 38%) and *n*-butyric (*ca.* 20%) acids are observed at 40 and 20 atm of CO, respectively, the highest overall yield of products (*ca.* 57%) being achieved at 40 atm.

At this value of CO pressure (40 atm), the increase of pC_3H_8 above 8.5 atm is still favourable and, at 10 atm of this gas, the total yield of acids is *ca.* 70% (Table 2, entry 8). Under these reaction conditions, the activity of complex **1** is higher in comparison with those of catalysts **2** and **3** which lead to a total yield of *ca.* 37 and 56%, respectively (Table 2, entries 8–10).

Effect of the Reaction Temperature

The study of the temperature effect (Table 3, Figure 3) reveals its important role in terms of the achieved activity and selectivity. Thus, the carboxylation proceeds even at 40°C, but with low yields of both isobutyric (1.9%) and *n*-butyric (1.1%) acids and without formation of acetic acid (Table 3,

Table 2. Effect of carbon monoxide pressure on the yield of carboxylic acids.[a]

Entry	Catalyst	pC_3H_8 [atm][b]	pCO [atm][b]	Yield of products[c] [%]				TON[d]
				Isobutyric acid	n-Butyric acid	Acetic acid	Total	
1	**1**	8.5	0	0.3	1.5	3.1	4.9	6.0
2	**1**	8.5	10	7.3	6.9	2.8	17.0	24.0
3	**1**	8.5	20	27.7	20.4	1.4	49.5	64.3
4	**1**	8.5	30	33.1	18.5	1.6	53.2	69.0
5	**1**	8.5	40	37.7	17.7	1.1	56.5	73.0
6	**1**	8.5	50	34.2	16.3	0.6	51.1	66.4
7	**1**	10.0	25	27.1	16.0	1.1	44.2	67.7
8[e]	**1**	10.0	40	46.7	20.9	2.3	69.9	214
9[e]	**2**	10.0	40	23.9	12.4	0.9	37.2	114
10[e]	**3**	10.0	40	35.3	19.3	1.0	55.6	170

[a] *Reaction conditions (unless stated otherwise)*: metal complex catalyst (20.00 μmol), $K_2S_2O_8$ (4.00 mmol, that is, 200:1 molar ratio of oxidant to metal catalyst), CF_3COOH (5.0 mL), 80 °C, 20 h, in an autoclave (13 mL capacity).

[b] Measured at 25 °C (amounts of C_3H_8 or CO gases correspond to 0.306 mmol·atm^{-1}).

[c] The values given are for molar yield [%] based on C_3H_8, that is, moles of product per 100 moles of propane (determined by GC or GC-MS). If required, molar yields [%] based on $K_2S_2O_8$, that is, moles of product per 100 moles of $K_2S_2O_8$, can be estimated (by taking into account that the $K_2S_2O_8$:metal catalyst molar ratio is 200:1) as TON × 0.5 (except for runs 8–10), for example, 36.5 % for run 5.

[d] Turnover number (moles of isobutyric, n-butyric and acetic acids per mol of metal catalyst precursor).

[e] 10.0 μmol of catalyst were used. Molar yields [%] based on $K_2S_2O_8$ can be estimated as TON × 0.25, for example, 53.5 % for run 8.

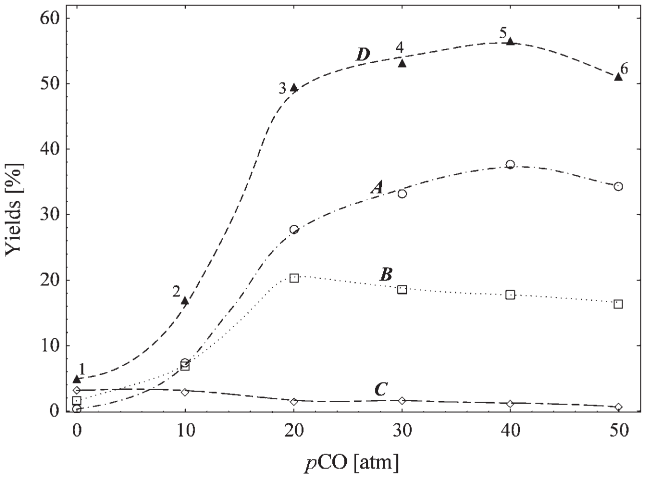


Figure 2. Effect of the CO pressure on the yields of isobutyric (curve ***A***), n-butyric (curve ***B***) and acetic (curve ***C***) acids and on the total yield (curve ***D***) for the propane carboxylation catalysed by complex **1** ($pC_3H_8 = 8.5$ atm). Reaction conditions and point numbers are those of the Table 2 entries.

entry 1). The increase of the temperature up to 80 °C results in a considerable growth of the total yield of carboxylic acids up to *ca.* 50 %, with the prevailing formation of isobutyric acid (*ca.* 28 %) over n-butyric (*ca.* 20 %) and acetic (*ca.* 1 %) acids. However, above 80 °C, the yield of isobutyric acid starts to decrease whereas that of n-butyric acid continues to grow, the latter acid becoming the dominant one above 90 °C (at 100 °C, the yields of n-butyric and isobutyric acids are 28 % and 18 %, respectively; Table 3, entries 2 and 3, Figure 3). Nevertheless, the overall yield of carboxylic acids remains constant within the 80–100 °C range. The activity of catalyst **3** still increases above 80 °C, the total yield of carboxylic acids at 100 °C (*ca.* 47 %) being *ca.* 10 % higher that at 80 °C (Table 3, entries 6 and 7).

At temperatures above 100 °C, the product yields are expected to be significantly lower due to the thermal decomposition of $K_2S_2O_8$,[8] but accurate analyses of the reaction mixture were prevented by the formation of a highly viscous suspension.

Effect of the Reaction Time

The effect of the reaction time on the yields of carboxylic acids was studied in the presence of catalyst **1**, at 8.5 and 30 atm of propane and CO pressures, correspondingly (Table 4, Figure 4). The accumulation of acids occurs during the first 8 h, remaining practically invariable beyond this time, without a lowering effect of overoxidation of the products being observed. The high conversions of propane achieved already after 2–4 h of reaction time are worthy of mention.

Effect of the Catalyst Amount

One should stress that the carboxylation of propane does not proceed in the absence of any catalyst (just a very small amount of acetic acid, *ca.* 1 %, Table 5,

Table 3. Effect of the temperature on the yield of carboxylic acids.[a]

Entry	Catalyst	T [°C]	Yield of products[b] [%]				TON[c]
			Isobutyric acid	*n*-Butyric acid	Acetic acid	Total	
1	**1**	40	1.9	1.1	0	3.0	4.0
2	**1**	60	19.6	9.6	1.1	30.3	39.4
3	**1**	80	27.7	20.4	1.4	49.5	64.3
4	**1**	100	17.9	27.9	2.7	48.5	63.1
5	**1**	120	n.d.	n.d.	n.d.	n.d.	n.d.
6	**3**	80	23.0	14.6	0	37.6	49.0
7	**3**	100	19.5	24.3	2.7	46.5	60.4

[a] *Reaction conditions :* propane (8.5 atm), carbon monoxide (20 atm) (amounts of C_3H_8 or CO gases, measured at 25 °C, correspond to 0.306 $\mathrm{mmol \cdot atm^{-1}}$), metal complex catalyst (20.00 μmol), $K_2S_2O_8$ (4.00 mmol, that is, 200:1 molar ratio of oxidant to metal catalyst), CF_3COOH (5.0 mL), 20 h, in an autoclave (13 mL capacity).

[b] The values given are for molar yield [%] based on C_3H_8, that is, moles of product per 100 moles of propane (determined by GC or GC-MS). If required, molar yields [%] based on $K_2S_2O_8$, that is, moles of product per 100 moles of $K_2S_2O_8$, can be estimated (by taking into account that the $K_2S_2O_8$:metal catalyst molar ratio is 200:1) as TON × 0.5, for example, 32.2 % for run 3.

[c] Turnover number (moles of isobutyric, *n*-butyric and acetic acids per mol of metal catalyst precursor).

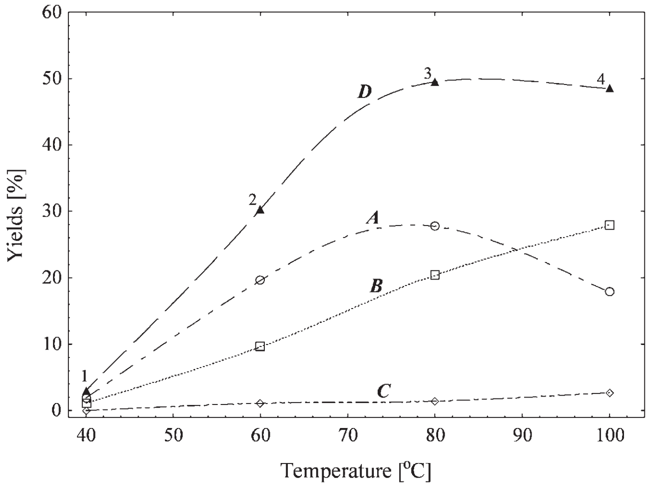


Figure 3. Effect of the temperature on the yields of isobutyric (curve ***A***), *n*-butyric (curve ***B***) and acetic (curve ***C***) acids and on the total yield (curve ***D***) for the propane carboxylation catalysed by complex **1** ($pC_3H_8 = 8.5$ atm, $pCO = 20$ atm). Reaction conditions and point numbers are those of the Table 3 entries.

entry 1, was then detected). A typical catalyst amount corresponds to a C_3H_8/catalyst molar ratio of 130 but we have investigated, at a wide range of this ratio (up to 66,600), the effect of the amount of catalysts **1–3** on the yields of carboxylic acids and TONs, at constant propane and CO pressures of 8.5 and 20 atm, respectively (Table 5, Figure 5, Figure 6, Figure 7, Figure 8, and Figure 9). The obtained results show an unprecedented activity even in the presence of a negligible amount of the catalyst. Thus, the decrease of the amount of catalyst **1** (corresponding to the propane-to-catalyst molar ratio change from 130 to 26.4×10^3) leads to a drastic growth of the TONs (from 64 to 5.62×10^3) (Table 5, entries 2–5, Figure 5), corresponding to TOF (turnover frequency) values up to 281 h^{-1}, although with a fall of the overall yield (from *ca.* 50 % to 21 %). The increase of the propane-to-catalyst molar ratio from 130 to 66.6×10^3 for catalysts **2** and **3** results in extremely high TONs (18.4×10^3 and 14.4×10^3, respectively) corresponding to TOFs of 920 and 720 h^{-1}, respectively, still with preservation of high total yields of carboxylic acids (*ca.* 28 % and 22 %, respectively) (Table 5, entries 6–9 and 10–13, Figure 6 and Figure 7). At low catalyst amounts in the reaction systems, complex **2** appears to exhibit the highest activity, being followed by complexes **3** and **1** (Figure 8 and Figure 9).

Mechanistic Considerations

Although the detailed mechanism could not yet be established, evidence has been accumulated in favour of a radical process, at least for some of the steps.

This is immediately suggested by the common higher yield of isobutyric acid, in comparison with *n*-butyric acid, indicating that the unique secondary carbon atom of the propane molecule undergoes carboxylation preferably to the two primary carbon atoms, as expected for a radical process that should proceed mainly *via* the isopropyl radical $(CH_3)_2CH^{\bullet}$ in preference to the *n*-propyl radical $CH_3CH_2CH_2^{\bullet}$. Similarly, although the isopropyl ester of trifluoroacetic acid, that is, $CF_3COOCH(CH_3)_2$, has been detected by ^1H NMR of the final reaction mixture, the resonances due to the *n*-propyl ester $CF_3COOCH_2CH_2CH_3$ were not observed, also in accord with the higher reactivity of the secondary carbon of propane, in comparison with the primary carbons, towards esterification.

Table 4. Effect of the reaction time on the yield of carboxylic acids.[a]

Entry	Time [h]	Yield of products[b] [%]				TON[c]
		Isobutyric acid	*n*-Butyric acid	Acetic acid	Total	
1	2	13.4	7.9	0.5	21.8	26.2
2	4	22.1	13.6	0.7	36.4	47.3
3	8	31.4	18.4	0.7	50.5	65.6
4	20	33.1	18.5	1.6	53.2	69.0

[a] *Reaction conditions:* propane (8.5 atm), carbon monoxide (30 atm) (amounts of C_3H_8 or CO gases, measured at 25 °C, correspond to 0.306 mmol·atm^{-1}), metal complex catalyst **1** (20.00 μmol), $K_2S_2O_8$ (4.00 mmol, that is, 200:1 molar ratio of oxidant to metal catalyst), CF_3COOH (5.0 mL), 80 °C, in an autoclave (13 mL capacity).

[b] The values given are for molar yield [%] based on C_3H_8, that is, moles of product per 100 moles of propane (determined by GC or GC-MS). If required, molar yields [%] based on $K_2S_2O_8$, that is, moles of product per 100 moles of $K_2S_2O_8$, can be estimated (by taking into account that the $K_2S_2O_8$:metal catalyst molar ratio is 200:1) as TON × 0.5, for example, 34.5 % for run 4.

[c] Turnover number (moles of isobutyric, *n*-butyric and acetic acids per mol of metal catalyst precursor).

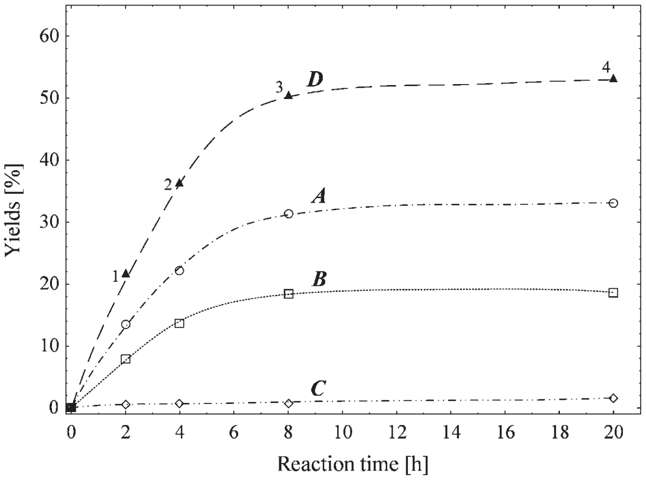


Figure 4. Effect of the reaction time on the yields of isobutyric (curve ***A***), *n*-butyric (curve ***B***) and acetic (curve ***C***) acids and on the total yield (curve ***D***) for the propane carboxylation catalysed by complex **1** ($pC_3H_8 = 8.5$ atm, $pCO = 30$ atm). Reaction conditions and point numbers are those of the Table 4 entries.

Effect of Radical Traps

Another argument for the involvement of a radical process is the full suppression of the formation of both isobutyric and *n*-butyric acids when the experiments are performed in the presence of either a carbon-radical trap[9] like TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) or $CBrCl_3$,[6d] or an oxygen-radical trap[9] such as Ph_2NH or BHT (2,6-di-*tert*-butyl-4-methylphenol).

The formation of the isopropyl and *n*-propyl radicals was proved by the detection by ^{1}H NMR of $(CH_3)_2CHBr$ and $CH_3CH_2CH_2Br$ as the main products when the reaction was carried out in the presence of $CBrCl_3$ (Scheme 3, Table 1, entry 6).

Role of $K_2S_2O_8$

$K_2S_2O_8$ plays a fundamental role in the radical formation, apparently in contrast with the metal catalyst. In fact, without that oxidant no products (namely no organohalide derivative of propane when the reaction is performed in the presence of $CBrCl_3$) are detected, while in the absence of the metal catalyst but in the presence of $K_2S_2O_8$ the corresponding organohalides are formed in high yields. The colourless crystalline material isolated from the reaction solutions in a high yield was proved by IR spectroscopy and elemental analysis to be $KHSO_4$. These observations are consistent with the involvement of $K_2S_2O_8$ as a radical initiator and an oxidant. In the former case, $S_2O_8^{2-}$ can lead to the sulphate radical $SO_4^{-\bullet}$ on heating[10] (Scheme 4, a), while the latter behaviour results in the formation of the reduced sulphate form (hydrogen sulphate HSO_4^- in the acidic solvent medium, leading to the precipitation of the salt $KHSO_4$).

The $SO_4^{-\bullet}$ radical can abstract a hydrogen atom from the alkane (Scheme 4, b) which thus is oxidised to the isopropyl and *n*-propyl radicals, $(CH_3)_2CH^\bullet$ and $CH_3CH_2CH_2^\bullet$, with predominance of the former (secondary *vs.* primary carbon radical). Carbonylation of those radicals would lead to the corresponding acyl radicals $(CH_3)_2CHCO^\bullet$ and $CH_3CH_2CH_2CO^\bullet$ (Scheme 4, c) which upon further oxidation and reaction with TFA could form the respective acids, as suggested[1i,4b] for the carboxylation of the methyl radical.

Experiments with ^{13}C-Labelled CO

In order to clearly establish the origin of the carbonyl group in the formed carboxylic acids, ^{13}C-labelling experiments were performed with ^{13}CO and the products were identified by $^{13}C\{^1H\}$ NMR spectroscopy. Hence, from the reaction of C_3H_8 and ^{13}CO (at the low pressure of 2.0 atm), catalysed by complex **2**, the

Table 5. Effect of the catalyst amount.[a]

Entry	$n(C_3H_8)/n(\text{catalyst})$	Yield of products[b] [%] Isobutyric acid	 *n*-Butyric acid	 Acetic acid	 Total	TON[c]
1	no catalyst	-	-	1.1	1.1	-
Catalyst **1**						
2	130	27.7	20.4	1.4	49.5	64.3
3	260	26.3	16.9	1.5	44.7	116
4	520	25.8	16.9	1.4	44.1	229
5	26.4×10^3	12.0	7.0	2.3	21.3	5.62×10^3
Catalyst **2**						
6	130	19.2	19.2	1.	40.0	52
7	260	25.4	15.8	2.2	43.4	113
8	520	31.1	21.4	0.5	50.5	276
9	66.6×10^3	15.0	9.8	2.9	27.7	18.4×10^3
Catalyst **3**						
10	130	23.0	14.6	-	37.6	49
11	260	26.6	17.3	3.4	47.3	123
12	520	21.2	16.5	1.7	39.4	205
13	66.6×10^3	9.2	5.2	7.2	21.6	14.4×10^3

[a] *Reaction conditions:* propane (8.5 atm), carbon monoxide (20 atm) (amounts of C_3H_8 or CO gases, measured at 25 °C, correspond to 0.306 mmol·atm^{-1}), metal complex catalyst (20.00–0.04 μmol), $K_2S_2O_8$ (4.00 mmol), CF_3COOH (5.0 mL), 80 °C, 20 h, in an autoclave (13 mL capacity).

[b] The values given are for molar yield [%] based on C_3H_8, that is, moles of product per 100 moles of propane (determined by GC or GC-MS). If required, molar yields [%] based on $K_2S_2O_8$ that is, moles of product per 100 moles of $K_2S_2O_8$, can be estimated (by taking into account that the C_3H_8:$K_2S_2O_8$ molar ratio is 0.65) as total yield (based on C_3H_8) × 0.65, for example, 32.2 % for run 2.

[c] Turnover number (moles of isobutyric, *n*-butyric and acetic acids per mol of metal catalyst precursor). TOF (moles of products/mol of catalyst per hour) can be estimated as TON/20 h^{-1}, for example, 920 h^{-1} for run 9.

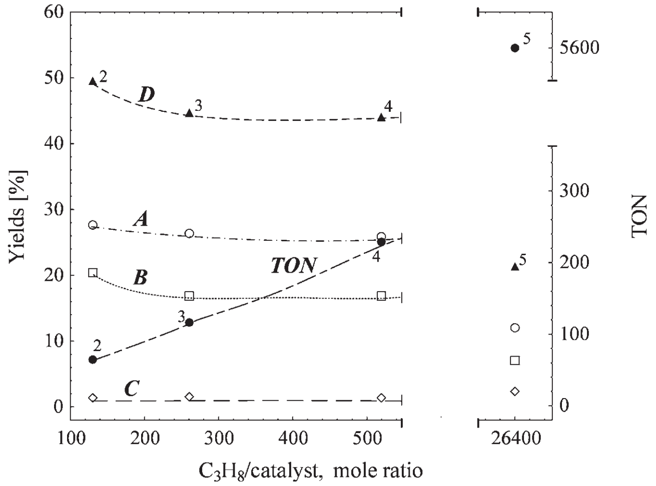


Figure 5. Effect of the catalyst **1** amount on the overall TON (points ●) and on the yields of isobutyric (curve ***A***, points ○), *n*-butyric (curve ***B***, points □) and acetic (curve ***C***, points ◇) acids and on the total yield (curve ***D***, points ▲) for the propane carboxylation ($pC_3H_8 = 8.5$ atm, $pCO = 20$ atm). Reaction conditions and point numbers are those of the Table 5 entries.

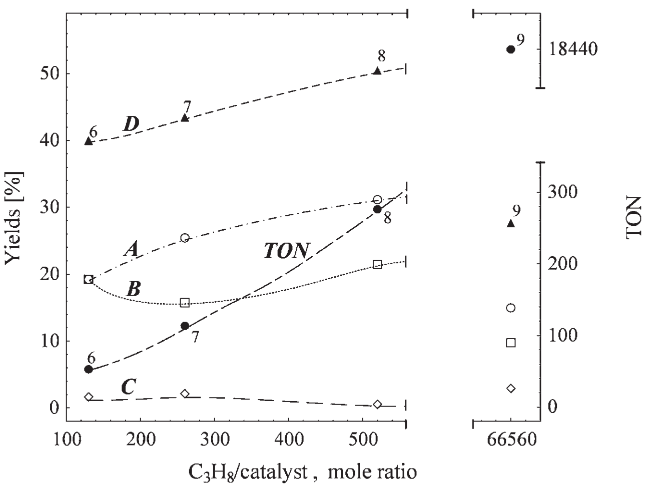


Figure 6. Effect of the catalyst **2** amount on the overall TON (points ●) and on the yields of isobutyric (curve ***A***, points ○), *n*-butyric (curve ***B***, points □) and acetic (curve ***C***, points ◇) acids and on the total yield (curve ***D***, points ▲) for the propane carboxylation ($pC_3H_8 = 8.5$ atm, $pCO = 20$ atm). Reaction conditions and point numbers are those of the Table 5 entries.

main products (Scheme 5) are $(CH_3)_2CH^{13}COOH$ and $CH_3(CH_2)_2{}^{13}COOH$, thus indicating that the carbonyl moieties of both isobutyic and *n*-butyric acids are derived from ^{13}CO. CH_3COOH, $CF_3COOCH(CH_3)_2$ and CF_3COOCH_3 are also detected, but without ^{13}C enriched atoms, showing that these products were not derived from carbonylation by ^{13}CO. Thus, acetic acid was formed by C−C bond cleavage and oxidation,

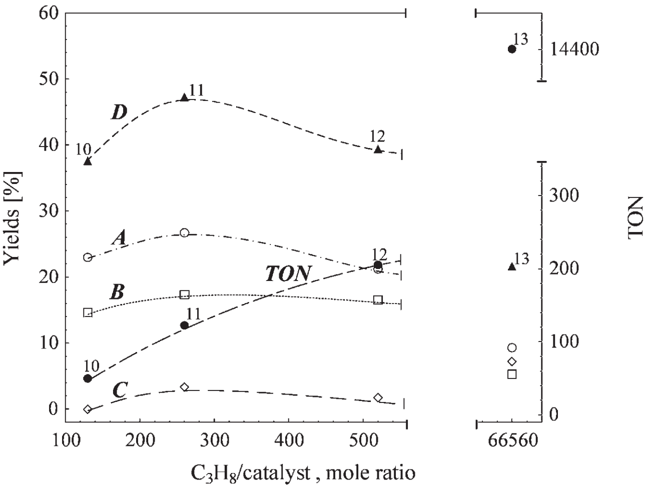


Figure 7. Effect of the catalyst **3** amount on the overall TON (points ●) and on the yields of isobutyric (curve ***A***, points ○), *n*-butyric (curve ***B***, points □) and acetic (curve ***C***, points ◇) acids and on the total yield (curve ***D***, points ▲) for the propane carboxylation ($pC_3H_8 = 8.5$ atm, pCO = 20 atm). Reaction conditions and point numbers are those of the Table 5 entries.

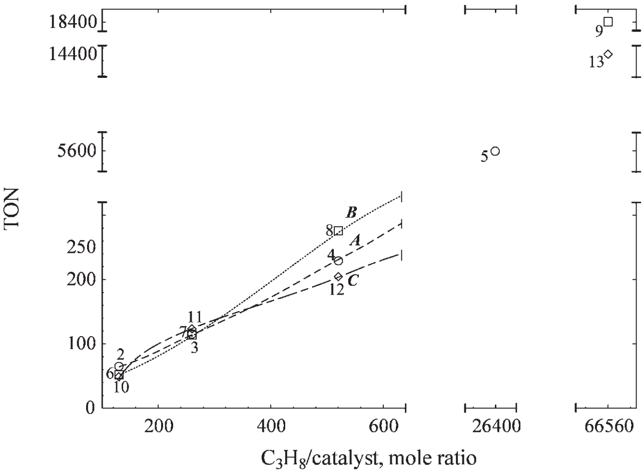


Figure 8. Effect of the catalyst amount on the TON for the propane carboxylation ($pC_3H_8 = 8.5$ atm, pCO = 20 atm) catalysed by complex **1** (curve ***A***, points ○), **2** (curve ***B***, points □), **3** (curve ***C***, points ◇). Reaction conditions and point numbers are those of the Table 5 entries.

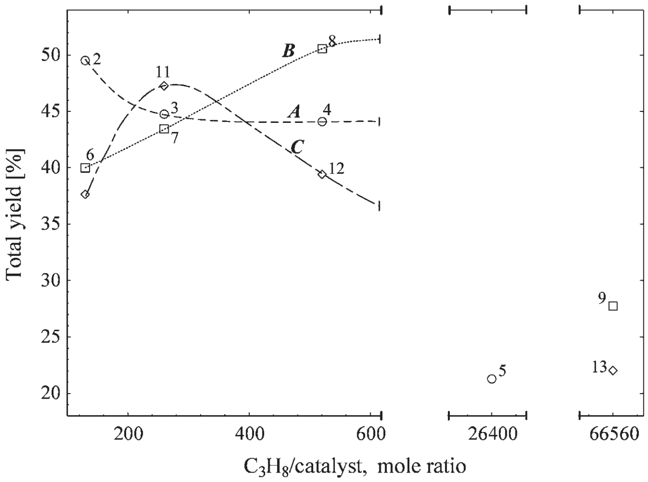
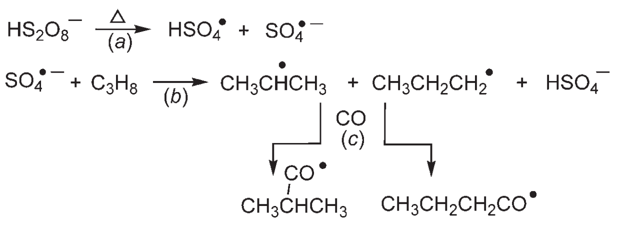


Figure 9. Effect of the catalyst amount on the total yield of carboxylic acids for the propane carboxylation ($pC_3H_8 = 8.5$ atm, pCO = 20 atm) catalysed by complex **1** (curve ***A***, points ○), **2** (curve ***B***, points □), **3** (curve ***C***, points ◇). Reaction conditions and point numbers are those of the Table 5 entries.



Scheme 4.

whereas the esters were obtained upon esterification of TFA and not by carbonylation. In accord, the esters are obtained mainly for CO pressures below those normally used. In particular, methyl trifluoroacetate was detected only at very low pCO and even in the absence of this gas.

Conclusions

This study indicates that vanadium complexes with N,O- or O,O-ligands can behave as strikingly active

$$CH_3CH_2CH_3 + CBrCl_3 \xrightarrow[K_2S_2O_8,\ TFA]{CO,\ catalyst\ \mathbf{1}} (CH_3)_2CHBr + CH_3CH_2CH_2Br + (CH_3)_2CHCl$$

Scheme 3.

$$CH_3CH_2CH_3 + {}^{13}CO \xrightarrow[K_2S_2O_8,\ TFA]{catalyst\ \mathbf{2}} \begin{array}{l}(CH_3)_2CH^{13}COOH + CH_3CH_2CH_2{}^{13}COOH + \\ CH_3COOH + CF_3COOCH(CH_3)_2 + CF_3COOCH_3\end{array}$$

Scheme 5. (For the conditions, see Experimental Section).

catalysts (or catalyst precursors) for the single-pot carboxylation of propane to a mixture of butyric acids and, to a much smaller extent, to acetic acid, under rather mild conditions. The overall yield, based on propane, can reach 70% and the catalysts remain active even for very low concentrations affording remarkably high TONs (up to 18.4×10^3), still with corresponding high yields. The measured catalysts activities, to our knowledge, are the highest so far achieved in the field of propane functionalisation under mild conditions.

The process could be optimised by studying the effects of various factors (e.g., optimal propane and CO pressures of *ca.* 8.5 and 40 atm, respectively, for the formation of butyric acids, optimal temperature of *ca.* 80 °C).

The carbonyl groups of both isobutyic and *n*-butyric acids are derived from the carbon monoxide gas, as shown by experiments with ^{13}CO which also indicate that acetic acid (a minor product) was formed by C–C bond cleavage and oxidation rather than by carbonylation by CO gas, and that the esters (other minor products) were derived upon esterification of TFA and not by carbonylation. In the absence of CO, TFA can act as an alternative, although rather weak, carbonylating agent.

Both C- and O-centred radicals are key intermediates as shown by radical trap experiments and the product distribution. A relevant role of $K_2S_2O_8$ was recognised, as an oxidising agent of the alkane *via* a free radical mechanism, that is, behaving as a source of the sulphate radical ($SO_4^{-\bullet}$) which upon further H-atom abstraction from propane could lead to the isopropyl and *n*-propyl radicals, with predominance of the former. The formation of these organic radicals was proved by trapping with $CBrCl_3$.

The work also corroborates the potentiality of propane as a promising starting material for the preparation of butyric acids, in the presence of CO and under rather mild conditions. Nevertheless, the process has to be further developed, namely by searching for cheaper solvents and oxidants, and elaboration of an effective recycling method for the reagents. Moreover, the study has, for the first time, extended to propane the catalytic activity of *amavadine* for the carboxylation and oxidation of alkanes,[4a,c,5] eventually contributing towards the recognition of a biological role for this intriguing natural vanadium complex present in some *Amanita* fungi.[11]

Experimental Section

The catalysts **1**,[12] **2**,[13] and **3**[13] were prepared according to published methods. [VO(acac)$_2$] (**4**) (Aldrich), $VOSO_4{\cdot}5H_2O$ (**5**) (Merck), propane (AlphaGaz), carbon monoxide (Air Products), ^{13}C-enriched carbon monoxide (Aldrich) and dinitrogen (Air Liquid Portugal) gases, potassium peroxodisulphate (Fluka), trifluoroacetic acid (Aldrich), $CBrCl_3$ (Fluka), 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (Aldrich), Ph_2NH (Fluka), 2,6-di-*tert*-butyl-4-methylphenol (BHT) (Aldrich) and *n*-heptanoic acid (Aldrich) were obtained from commercial sources and used as received.

Typical Catalytic Experiment

The reaction mixtures were prepared as follows: to 20.00–0.04 μmol of catalyst [used (i) in the solid form, (ii) as a fine solid mixture with $K_2S_2O_8$ ($K_2S_2O_8$:catalyst = 100:1), or (iii) as a 0.0020 M TFA solution] contained in a 13.0-mL stainless steel autoclave, equipped with a Teflon-coated magnetic stirring bar, were added 4.00 mmol (1.08 g) $K_2S_2O_8$ and 5.0–7.5 mL of TFA. Then the autoclave was closed and flushed with dinitrogen three times for removing the air and finally pressurised with 0–10.5 atm of propane and 0–50 atm of carbon monoxide. The reaction mixture was vigorously stirred for 2–20 h at 40–120 °C using a magnetic stirrer and an oil bath. After the selected reaction time, the autoclave was cooled in an ice bath, then degassed and opened. To 1 mL of the reaction mixture were added 5 mL of diethyl ether and 90 μL of n-heptanoic acid (as internal standard). The obtained mixture was stirred, then filtered and analysed by gas chromatography (internal standard method) using a Fisons Instruments GC 8000 series gas chromatograph with a DB WAX fused silica capillary column (P/N 123–7032) and the Jasco-Borwin v.1.50 software. In some cases, products were also identified by GC-MS, ^{1}H and ^{13}C-{^{1}H} NMR techniques using a Trio 2000 Fisons mass spectrometer with a coupled Carlo Erba (Auto/HRGC/MS) gas chromatograph, and a Varian UNITY 300 NMR spectrometer, respectively.

Experiments with ^{13}C-Enriched Carbon Monoxide

The experiments with ^{13}C-enriched carbon monoxide were performed for $p^{13}CO = 2.0$ atm and $pC_3H_8 = 6.3$ atm, using catalyst **2** (0.020 mmol) and $K_2S_2O_8$ (4.0 mmol), in CF_3COOH (5.0 mL), contained in the 13.0-mL stainless steel autoclave equipped with a Teflon-coated magnetic stirring bar, at 80 °C (20 h reaction time). The detected compounds are: $CH_3(CH_2)_2{}^{13}COOH$ [$\delta_C = 13.0$, 18.2, 36.4 (all weak) and 183.3 (strong)], $(CH_3)_2CH^{13}COOH$ [$\delta_C = 19.4$, 35.7 (both weak) and 186.6 (strong)], CH_3COOH [$\delta_C = 181.0$ (weak)], $CF_3COOCH(CH_3)_2$ ($\delta_C = 20.8$, 75.4) and CF_3COOCH_3 ($\delta_C = 55.9$).

A ^{1}H NMR spectrum illustrative of all the detected products is provided for example, by the solution in the final reaction mixture after carboxylation in the presence of catalyst **2** (Table 5, entry 8), as follows. Apart from the signals due to the obtained carboxylic acids [that is, $(CH_3)_2CHCOOH$: $\delta_H = 1.285$ (d, $J = 7.5$ Hz, 6H), 2.730 (heptet, $J = 7.4$ Hz, 1H); $CH_3CH_2CH_2COOH$: $\delta_H = 1.041$ (t, $J = 7.4$ Hz, 3H), 1.761 (sextet, $J = 7.4$ Hz, 2H), 2.485 (t, $J = 7.4$ Hz, 2H); CH_3COOH: $\delta_H = 2.353$ (s, 3H)], the resonances relevant to the isopropyl ester of trifluoroacetic acid [that is, $CF_3COOCH(CH_3)_2$: $\delta_H = 1.433$ (d, $J = 6.0$ Hz, 6H), 5.302 (heptet, $J = 6.0$ Hz, 1H)] were also detected. No signals relevant to *n*-propyl trifluoroacetate were found in the ^{1}H NMR spectrum.

Acknowledgements

This work has been partially supported by the Fundação para a Ciência e a Tecnologia (FCT) and its POCI 2010 (FEDER funded) Programme, Portugal. We also thank Prof. Yuzo Fujiwara (University of Kyushu, Japan) for stimulating discussions at the earlier stage of the carboxylation work, and Mr. Indalécio Marques for the GC-MS analyses.

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