the solution was extracted with pentane (2 × 50 mL). The combined organic extracts were washed with 6 M hydrochloric acid (3 × 25 mL), 20% aqueous cadmium chloride (20 mL), 10% aqueous sodium sulfite (20 mL), saturated aqueous sodium hydrogen carbonate (20 mL), and saturated aqueous sodium chloride (30 mL) and then dried with magnesium sulfate. The solvent was removed under reduced pressure, the temperature rising by 5–10 °C. The resultant dark brown solution was stirred for 2 at ambient temperature, poured into saturated aqueous sodium chloride solution, and extracted with hexane; the extract was added to 20% aqueous cadmium chloride to precipitate the pyridine. After filtration, the organic layer was washed with bicarbonate and sodium chloride, dried, and reduced in volume to give a viscous dark liquid. It was passed through a silica gel column with hexane as eluant to give a light yellow oil that solidified in a vacuum desiccator. This compound was characterized as **26**: ^{1}H NMR δ 2.5–1.2 (br s, 14 H), 0.18 and 0.16 (ss, 18 H, two Me_3Si groups); MS, m/z 368 (M^+); ^{13}C NMR δ 88.87, 74.44, 74.35, 74.21, 71.33, 64.03, 61.96, 39.57, 37.54, 35.08, 26.63, 1.78, −0.49. The compound quickly darkened in solution upon exposure to fluoride ion; no products could be characterized.

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Registry No. 7-Cl, 1000-44-8; 7-OMe, 50398-61-3; **8a**, 79060-03-0; **16**-OH, 110391-14-5; **16**-Cl, 110372-96-8; **16**-$OSiMe_3$, 110373-03-0; **17**, 110372-97-9; **18** (n = 3), 110372-98-0; 18 (n = 4), 110372-99-1; **19**, 17047-96-0; **20**, 110373-01-8; **23**, 18243-59-9; **24**, 110391-15-6; **25**, 110373-04-1; **26**, 110373-02-9; **28**, 1066-54-2; **30**, 4526-07-2; 1,4-dichloro-2-butyne, 821-10-3; adamantanone, 700-58-3; tetramethylethylene, 563-79-1; ethynyltriethylsilane, 1777-03-3; 2-ethynyladamant-2-yl trimethylsilyl ether, 110373-00-7.

Solvent Effect in the Reduction of α-Keto Esters by Aqueous Titanium Trichloride

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In the reduction of 1 by Ti(III) ion the dimeric 3 or monomeric 4 reduction products could be made to predominate by the choice of the solvent. It is found that (a) dimerization, via coupling of two radicals 2, increases with increasing simultaneously the dielectric constant and the hydrogen ion concentration of the reaction medium and (b) alcohol formation, which occurs via electron transfer between radical species having different redox potentials, increases with decreasing the hydrogen ion concentration of the medium. Under appropriate reaction conditions, the dimerization process is partially stereoselective. Reaction mechanisms are proposed which account for the ratio of both dimer/alcohol and *meso*/*dl* under different experimental conditions.

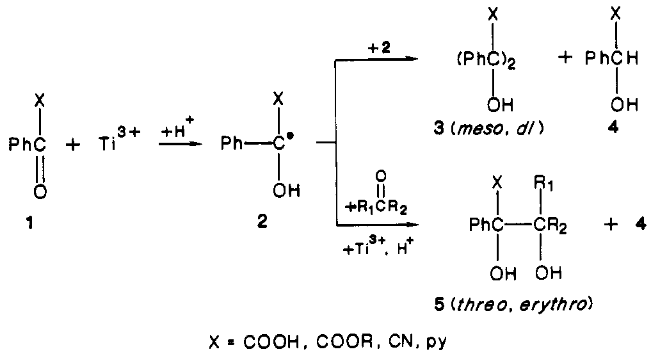
Carbonyl compounds **1**, activated toward reduction by an electron-withdrawing group X, are reduced by aqueous titanium trichloride to the corresponding dimers **3**[1,2] (Scheme I). If the reaction is carried out in the presence of simple ketones or aldehydes, the formation of symmetrical diols **3** is almost suppressed and radicals **2** selectively add to the carbonyl carbon of $R_1C(O)R_2$ to yield the unsymmetrical diols **5**.[2,3] The monomeric reduction products **4** are always present. The relative yields of **4** with respect to **3** or **5** are strongly solvent dependent:[4] higher in alcoholic or ethereal solvents, lower in carboxylic acid solvents.

In this paper we report our investigation of the role played by the solvent on the dimer/alcohol ratio in the reduction of **1** by Ti(III) ion with the aim to better understand the reaction paths and properties of the intermediates involved, in view of their possible use in carbon-to-carbon bond-forming reactions (Scheme I).

Results and Discussion

After preliminary experimentation, we selected methyl phenylglyoxalate (**1**, X = $COOCH_3$) as a suitable substrate for a detailed study since a precise method of products analysis has been found by using NMR spectroscopy: the methyl proton shifts of the substrate, *meso* dimer, *dl* dimer, and alcohol are well apart. The effect of the solvent on the ratio dimer/alcohol is shown by some representative reactions collected in Table I, all being performed under identical experimental conditions except for the solvent.

Scheme I



Dimer **3** is the major product in carboxylic acid solvents, whereas alcohol **4** prevails in alcoholic or ethereal ones.

If radical **2** (X = $COOCH_3$, Scheme I) were the only reaction intermediate, the possible paths leading to **4** or **3** would be hydrogen atom abstraction of radical **2** from the solvent, further reduction of **2** by Ti(III) ion, and disproportionation or dimerization of **2**. From our experimental results, it comes out that substantially the same dimer/alcohol ratio is obtained in either isopropyl alcohol and *tert*-butyl alcohol, notwithstanding the former is a

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(1) Clerici, A.; Porta, O.; Riva, M. *Tetrahedron Lett.* **1981**, *22*, 1043.

(2) Clerici, A.; Porta, O. *Tetrahedron* **1982**, *38*, 1293.

(3) (a) Clerici, A.; Porta, O. *J. Org. Chem.* **1982**, *47*, 2852. (b) Clerici, A.; Porta, O. *Ibid.* **1983**, *48*, 1690. (c) Clerici, A.; Porta, O. *Chim. Ind. (Milan)* **1985**, *67*, 187.

(4) Clerici, A.; Porta, O.; Zago, P. *Tetrahedron* **1986**, *42*, 561.

Table I. Yields of Dimer 3 and Alcohol 4 in Different Solvents and in Binary Mixtures of Solvents

run[a]	solvent	% v/v	yields, %[b] 3	yields, %[b] 4	ratio 3/4
1	CH_3COOH		36	30	1.20
2	$CH_3COOH-H_2O$	90:10	55	26	2.12
3	$CH_3COOH-H_2O$	85:15	59	24	2.46
4	$CH_3COOH-H_2O$	70:30	63	20	3.15
5	$CH_3COOH-H_2O$	60:40	64	18	3.55
6	CH_3COOH-py	90:10	30	47	0.64
7	CH_3COOH-py	80:20	13	55	0.24
8	CH_3COOH-py	70:30	8	60	0.13
9	HCOOH		63	18	3.50
10	$HCOOH-H_2O$	90:10	72	14	5.14
11	$HCOOH-H_2O$	80:20	79	13	6.10
12	$HCOOH-H_2O$	70:30	80	11	7.27
13	CH_3OH		13	45	0.29
14	*i*-PrOH		13	49	0.26
15	*i*-PrOH-HCl[c]	70:30	18	36	0.50
16	*i*-PrOH-HCl[c]	60:40	27	24	1.12
17	*i*-PrOH-HCl[c]	50:50	32	15	2.13
18	*t*-BuOH		17	42	0.40
19	THF		12	29	0.41

[a] In all reactions 5 mmol of $PhCOCOOCH_3$, 6 mmol of aqueous $TiCl_3$, and 10 mL of solvent or binary mixture of solvents were used. [b] Calculated from the peaks area of the ^{1}H NMR spectra and based on the starting substrate; the difference to 100% is unreacted substrate. [c] 37% w/v HCl solution.

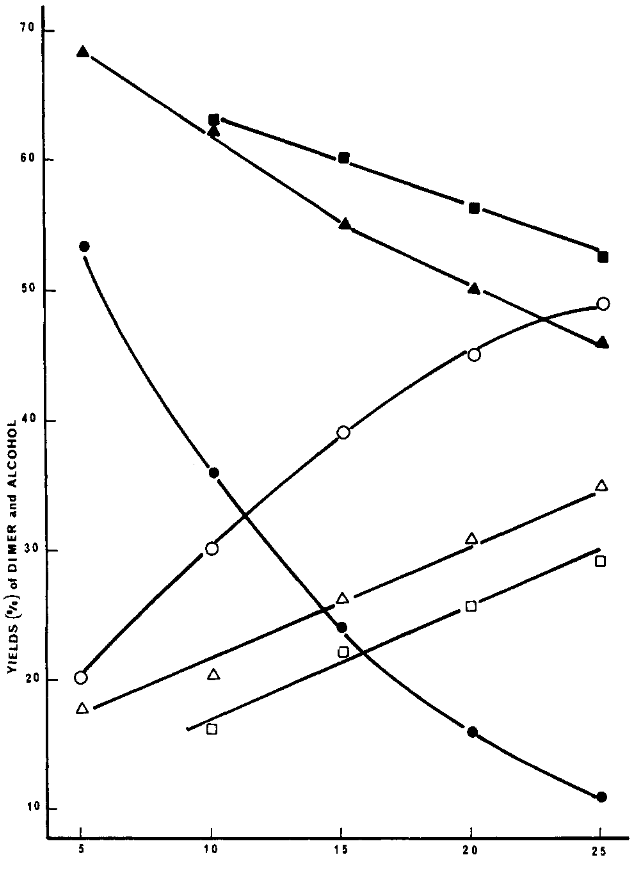

Figure 1. Yields (%) of dimer (●) and alcohol (○) in CH_3COOH, of dimer (▲) and alcohol (△) in $CH_3COOH-H_2O$ (70:30), and of dimer (■) and alcohol (□) in $CH_3COOH-H_2O$ (60:40) vs the volume of solvent or mixture of solvents (mL).

better hydrogen atom donor than the latter (Table I, runs 14 and 18); furthermore, the dimer/alcohol ratio remains unchanged upon addition of increasing amount of thiophenol, excellent hydrogen atom donor,[5] to the reaction

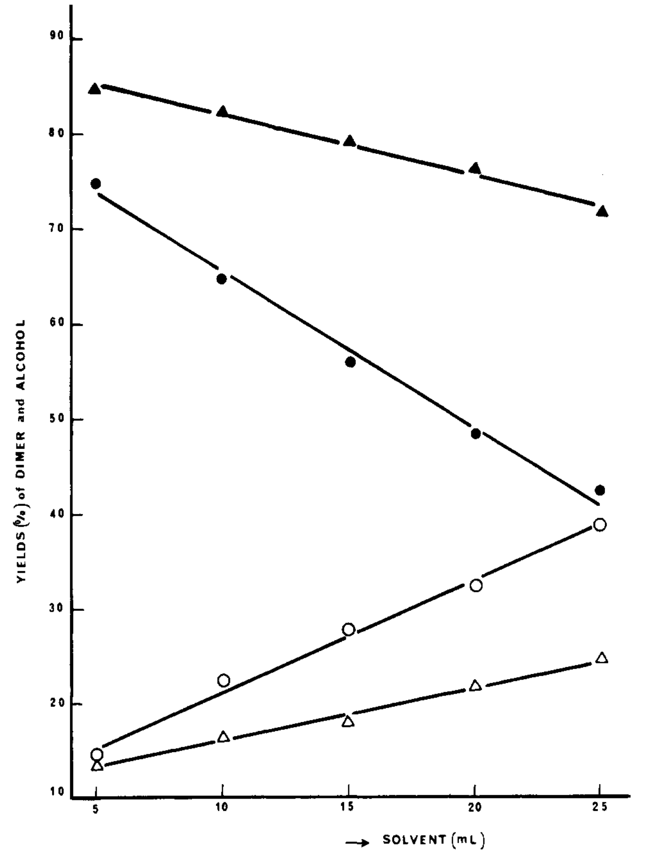

Figure 2. Yields (%) of dimer (●) and alcohol (○) in HCOOH and of dimer (▲) and alcohol (△) in $HCOOH-H_2O$ (80:20) vs the volume of solvent or mixture of solvents (mL).

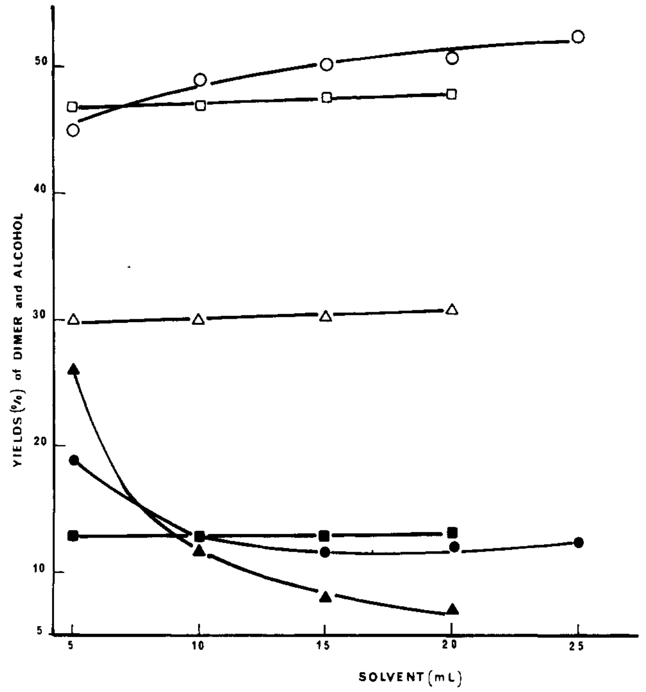

Figure 3. Yields (%) of dimer (●) and alcohol (○) in *i*-PrOH, of dimer (■) and alcohol (□) in CH_3OH, and of dimer (▲) and alcohol (△) in THF vs the volume of solvent (mL).

performed in acetic acid. Both these findings suggest that hydrogen atom abstraction is not the reaction responsible of alcohol formation even in isopropyl alcohol.

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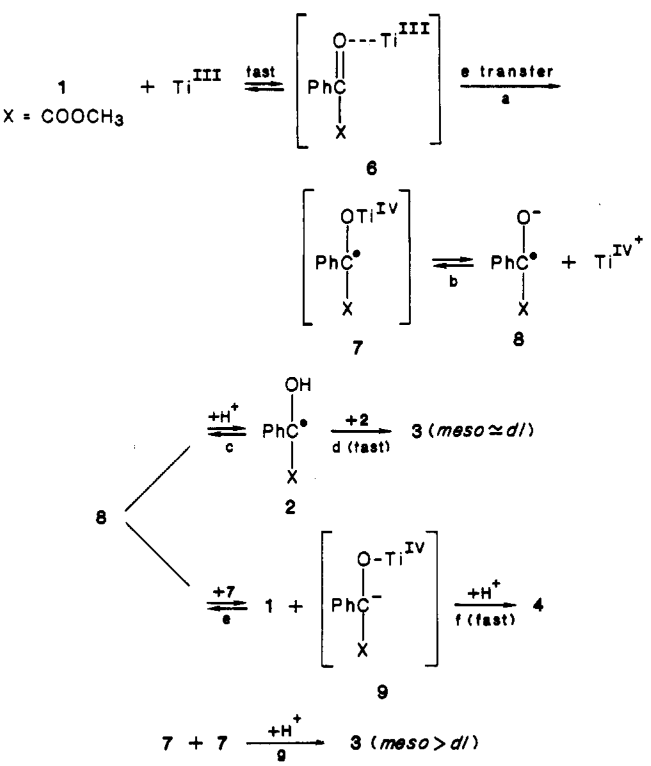
(5) Hammond, G. S.; Sen, J. N.; Boozer, C. E. *J. Am. Chem. Soc.* **1955**, *77*, 3244.

Scheme II



Further reduction of 2 by Ti(III) ion, as a possible route to alcohol, has to be discarded also. In fact, dilution of the reagents with increasing volume of solvent leads to a decrease of dimer and to an increase of alcohol yields (Figures 1–3). If reduction of 2 were operative, just the opposite trend would be observed since the lower the Ti(III) ion concentration, the lower the reducing power of the reaction medium. Besides 2 being a capto-dative radical,[6] which mostly enjoys thermodynamic stabilization, its dimerization is by far favored over its disproportionation,[7] independently of the solvent.[8] Accordingly, data from the literature[9] give a coupling decay rate of 3.5 × 10^8 L mol^{-1} s^{-1} for 2.

Now, considering that radical 2, once formed, terminates almost entirely by coupling, to justify the high yields of alcohol obtained in some cases, we have to admit the existence of other species, in equilibrium with 2, responsible for the formation of alcohol.

As a result of our study we believe that the principal reaction paths leading to 3 or 4 under our working conditions are as illustrated in Scheme II.

Condition sine qua non for the reduction to occur is the formation of an inner sphere complex 6 between 1 and Ti(III) ion.[10,11] Chemical evidence of its formation is provided by the addition of fluoride ions to the reaction mixture: the blue color of $Ti(H_2O)_6^{3+}$ changes[12] into a persistent green attributable[13] to the complex TiF_6^{3-}, which is inert toward further substitution, and 1 is recovered unreacted. Thus, when the coordination sphere of Ti(III) ion is blocked, the entry of the ligand 1 is prevented, and its reduction does not occur.

Following the activation of the precursor complex 6, electron transfer takes place[14] from the metal to the ligand, yielding complex 7 (path a). 6 and 7 must be considered as empirical formulae, since the coordinative valences of Ti(III) and Ti(IV) ions are presumably completed by water, chloride ions, and molecules of the solvent in which the reaction occurs.

The extent of bond-breaking (path b) between the metal ion and the developing substrate radical anion 8 will strongly depend on the ion-solvating power and dielectric constant of the solvent,[15] 7 and 8 being the limit cases,[16] while the equilibrium concentration of 8 and its protonated form 2 (path c) is mainly related to the acidity of the medium.

The pK_a value of radical 2 is unknown, but it is undoubtedly lower than that of ethyl lactate radical $CH_3\dot{C}(OH)COOC_2H_5$ ($pK_a \simeq 6$)[17] for the conjugation of the unpaired electron with the aromatic ring further increases the acidity of the hydroxyl group. Thus, 2 being a relatively strong acid, only solvents with a relatively low pK_a will promote protonation of 8 and favor the formation of dimer 3.

In fact, dimerization of 2 is a very fast process,[9] whereas dimerization of 8, for reason of electrostatic repulsion is either very slow or does not occur.[18] Only when equilibrium b of Scheme II is by far shifted to the left, formation of 3 can occur by coupling of 7, but, in this case, as we will discuss later, the dimerization process becomes partially stereoselective (*meso* > *dl*), owing to steric hindrance (path g). With regard to the formation of alcohol 4, we have already discarded, on experimental findings, either hydrogen atom abstraction from the solvent, further reduction by Ti(III) ion or disproportionation of radical 2.[19]

In view of the fact that interaction of the developing substrate radical anion 8 with the metal ion considerably enhances its electron affinity, we have to deal, under our experimental conditions, with radical intermediates having different redox potentials: the redox potential[20] of 7 is higher than that of its dissociated form 8, making this latter a powerful reducing agent and the former an easily reducible species. Thus, the reaction leading to alcohol 4 can be seen, in our case, as an electron transfer from one to another radical provided the latter has higher redox

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(6) Viehe, H. G.; Merenyi, R.; Stella, L.; Janousek, Z. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 917.

(7) (a) Greene, F. D.; Berwick, M. A.; Stowell, J. C. *J. Am. Chem. Soc.* **1970**, *92*, 867. (b) Nelsen, S. F.; Bartlett, P. D. *Ibid.* **1966**, *88*, 137. (c) Shelton, J. R.; Liang, C. K.; Kovacic, P. *Ibid.* **1968**, *90*, 354. (d) Bickel, A. F.; Waters, W. A. *Recl. Trav. Chim. Pays-Bas* **1950**, *69*, 1490.

(8) Kochi, J. K. *Free Radicals*; New York, 1973; Vol. 1, p 51 and references cited therein.

(9) Fujisawa, T.; Monroe, B. M.; Hammond, G. S. *J. Am. Chem. Soc.* **1970**, *92*, 542.

(10) Ti(III) ion is present in aqueous solution as $Ti(H_2O)_6^{3+}$, and this last is classified among the cations for which activated complexes must be considered for electron-transfer reactions in water involving them. (a) Taube, H. *Chem. Rev.* **1952**, *50*, 69. (b) Haim, A. *Acc. Chem. Res.* **1975**, *8*, 264.

(11) Vanadous ion belongs to the same category of cations,[10] and a rapid equilibrium between V(II) and phenylglyoxylic acid has been shown to precede the reduction step to diphenyltartaric acid. Konstantatos, J.; Astra, E. V.; Katsaros, N.; Katatis, D. *J. Am. Chem. Soc.* **1980**, *102*, 3035.

(12) UV spectra of an aqueous solution of $TiCl_3$ containing fluoride ions show the disappearance of the band at 20 408 cm^{-1} due to $Ti(H_2O)_6^{3+}$ and the appearance of two new bands at 15 538 and 23 810 cm^{-1}.

(13) Fenske, R. F.; Coulton, K. G.; Radtke, D. D.; Sweeny, C. C. *Inorg. Chem.* **1966**, *5*, 951.

(14) The rate of path a is independent from the solvent used: addition of $TiCl_3$ solution or $TiCl_3$ solution preequilibrated with the solvent for 1 h afforded the same dimer/alcohol and *meso*/*dl* ratios.

(15) Reichardt, C. *Solvent Effect in Organic Chemistry*; Verlag Chemie: Weinheim, 1979; pp 30–36.

(16) The ionization of an ionogen and its subsequent dissociation, according to path b of Scheme II, could be further elaborated. Between the covalently bonded species 7 and the independently solvated free radical anion 8 there will be several steps of progressive loosening of the ion pairs by penetration of solvent molecules between the ions.

(17) Hayon, E.; Simic, M. *Acc. Chem. Res.* **1974**, *7*, 114.

(18) (a) Chauduri, J.; Klume, S.; Groznisky, J. J.; Szwarc, M. *J. Am. Chem. Soc.* **1968**, *90*, 6421. (b) Szwarc, M. *Acc. Chem. Res.* **1969**, *2*, 87. (c) Bowers, K. W.; Giese, R. W.; Grimshaw, J.; House, H. O.; Konodny, N. H.; Kronberger, K.; Roe, D. K. *J. Am. Chem. Soc.* **1970**, *92*, 2783.

(19) The same reasoning holds for any radicalic species involved in Scheme II.

(20) Rao, P. S.; Hayon, E. *J. Am. Chem. Soc.* **1974**, *96*, 1287.

Table II. Dependence of Dimer 3 and Alcohol 4 Yields on the Flow Rate of $TiCl_3$ Addition for the Reactions in CH_3COOH[a]

flow rate, mL/h	yields, %[b] 3	yields, %[b] 4	ratio 3/4
c	36	30	1.20
30	31	35	0.89
10	24	38	0.63
5	18	43	0.42

[a] 6 mmol of $TiCl_3$ (5 mL) was added dropwise to 5 mmol of $PhCOCOOCH_3$ in 10 mL of CH_3COOH. [b] See note *b* of Table I. [c] $TiCl_3$ added at once.

potential than the former (path e).

Carbanion 9 is, on the whole, a stronger base than 8, and its protonation (path f) is a fast process even at low hydrogen ion concentration: alcohol 4 and the regenerated substrate 1 are the disproportionation products.

On the grounds of both redox considerations and reports from the literature,[21] disproportionation between two 7 or two 8 is less favored than path e.

Therefore, depending on the solvent-dependent degree of ionization and dissociation, and on the acidity of the medium, we have to deal with different equilibrium concentrations of 7, 8, and 2 and, hence, with different dimer/alcohol ratios.

Keeping in mind all the above considerations, is now easier to rationalize the results obtained in the reduction of methyl phenylglyoxalate 1 by aqueous titanium trichloride and discuss their significance depending on the experimental conditions employed.

Reactions in Carboxylic Acid Solvents. The higher the acidity and dielectric constants of the solvent are, the higher the equilibrium concentration of 2 is. As a consequence, the yields of dimer are higher in formic acid (ϵ = 58.15 and $K_a = 2.1 \times 10^{-4}$) than in acetic acid (ϵ = 6.5 and $K_a = 1.8 \times 10^{-5}$) (Table I, runs 1 and 9). This finding is confirmed by the results of experiments carried out in CH_3COOH/H_2O and $HCOOH/H_2O$ mixtures (Table I, runs 2–5 and 10–12, respectively).

Water being both a good ionizing and dissociating solvent, its addition to CH_3COOH or HCOOH shifts equilibrium b of Scheme II to the right and simultaneously increases the dissociation constant of both CH_3COOH or HCOOH and HCl.[22] Thus, the dimer/alcohol ratio increases by increasing the volume ratio of water in the reaction medium. In percentage, such an increase is lower for water addition to HCOOH than to CH_3COOH since both hydrogen ion concentration and dielectric constant of the medium increase less upon addition of water to the former than to the latter carboxylic acid solvent. Addition of pyridine to CH_3COOH leads to a decrease of dimer and to an increase of alcohol yields (Table I, runs 6–8), exactly the opposite of what water does. Upon addition of pyridine (ϵ = 12.4), although the dielectric constant of the medium does not substantially change, protonation of the added base ($pK_a = 6.1$) competes with protonation of 8 ($pK_a < 6$) lowering the equilibrium concentration of 2.

Further evidence that the ratio dimer/alcohol strongly depends on the polarity[23] and acidity of the medium is obtained by changing the time of mixing the reagents (Table II). The slower the $TiCl_3$ solution is added to 1 dissolved in CH_3COOH, the lower the acidity[22] and the dielectric constant of the medium are at the time the reduction of 1 occurs; consequently, the dimer/alcohol ratio decreases as the flow rate (mL/h) of $TiCl_3$ addition decreases (Table II).

Either slow addition of the reducing solution to 1 or dilution of the reagents (1 and $TiCl_3$ solution) with increasing amount of carboxylic acid solvents produce the same effect on the ratio dimer/alcohol. In fact, when the $TiCl_3$ solution is added at once to 1 dissolved in increasing amount (5–25 mL) of CH_3COOH (Figure 1) or HCOOH (Figure 2), a marked decrease of dimer yield and increase of alcohol yield are observed upon dilution. Comparing these results with those obtained on equivalent dilution with aqueous acetic or aqueous formic acid (Figures 1 and 2), we observe that the slopes of the plots corresponding to the decrease of 3 and increase of 4 lessen in the order $CH_3COOH > HCOOH \simeq CH_3COOH/H_2O$ (70:30) $> CH_3COOH/H_2O$ (60:40) $> HCOOH/H_2O$ (80:20). This experimental finding is an accord with the fact that both the hydrogen ion concentration and dielectric constant of the reaction medium decrease in the same order on dilution of the reagents with the above solvents or binary mixture of solvents. The more the dielectric constant and hydrogen ion concentration decrease, the more the electron transfer from 8 to 7 (path e) competes with protonation of 8 (path c), leading to the higher percentage of 4. Indeed, electron transfer is usually faster[24] than radical anion protonation, even more so in our case owing to the relatively low pK_a of 2. Since the dimer/alcohol ratio strongly depends on dilution, to evaluate the effect that an excess of $TiCl_3$ with respect to 1 has on such a ratio, we performed a series of reactions in which the same amount of 1 was used and the molar ratio $TiCl_3/1$ was increased in such a way that the volume ratio $CH_3COOH/TiCl_3$ remained constant in a set of three reactions (Table III).

For a given volume ratio $CH_3COOH/TiCl_3$, the dielectric constant, hydrogen ion concentration of the medium and, consequently, equilibrium concentration of 2 do not change, thus yields of 3 remain practically the same independently of the molar ratio $TiCl_3/1$ (Table III, runs 1–3, 4–6, and 7–9).

On the contrary, yields of 4 increase with increasing the $TiCl_3/1$ ratio, for disproportionation equilibrium e of Scheme II is continuously shifted to the right by an excess of Ti(III) ion, which reduces back to 7 the regenerated substrate 1. The same trend is observed (runs 10–12) when CH_3COOH/H_2O (70:30) mixture is used instead of glacial acetic acid.

In line with this reasoning, the results of Table IV show that yields of 4 decrease and yields of 3 increase by working with an excess of 1 with respect to Ti(III) ion. An excess of 1, shifting equilibrium e to the left, maintains an appreciable concentration of 8 in the reaction medium[25] and the higher the molar ratio $1/TiCl_3$, the more the protonation of 8 competes with disproportionation.

Reactions in Alcoholic Solvents and Tetrahydrofuran. The dimer/alcohol ratio is completely reversed on going from carboxylic acid solvents to methanol, isopropyl

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(21) Levin, G.; Claesson, S.; Szwarc, M. *J. Am. Chem. Soc.* **1972**, *94*, 8672.

(22) The acidity of the $TiCl_3$ solution is due to HCl. In acetic acid, HCl is only partially ionized ($pK_a = 8.55$), and the autoprotolysis constant of CH_3COOH is 3.5×10^{-15}. Bruckenstein, S.; Kolthoff, I. M. *J. Am. Chem. Soc.* **1956**, *78*, 2974.

(23) The term "polarity" is used taking into account both the dielectric constant and the coordinating ability of the solvent, e.g., its ionizing and dissociating power.

(24) Electron-transfer processes proceed with biomolecular rate constants higher than 10^7 L mol^{-1} s^{-1}, while the bimolecular rate constants of radical anion protonation are lower, rarely reaching values as high as 10^6 L mol^{-1} s^{-1}. (a) Szwarc, M. *Ions and Ion Pairs in Organic Reactions*; Wiley: New York, 1974; Vol. II, p 222. (b) Arai, S.; Grew, D. A.; Dorfman, L. M. *J. Chem. Phys.* **1967**, *46*, 2572.

(25) Cserbegyi, A.; Chauduri, J.; Franta, E.; Grodzinsky, J. J.; Szwarc, M. *J. Am. Chem. Soc.* **1967**, *88*, 7129.

Table III. Yields of Dimer 3 and Alcohol 4 in CH_3COOH at Different $TiCl_3$/1 Molar Ratios and at Constant $CH_3COOH/TiCl_3$ Volume Ratio for Each Set of Reactions

run[a]	CH_3COOH, mL	$TiCl_3$,[b] mL	vol ratio $CH_3COOH/TiCl_3$	molar ratio $TiCl_3$/1	yields, %[c] 3	4	ratio 3/4
1	5	5	1	1.2	53	20	2.65
2	10	10	1	2.4	51	35	1.46
3	15	15	1	3.6	52	45	1.15
4	15	5	3	1.2	24	39	0.61
5	30	10	3	2.4	26	67	0.39
6	45	15	3	3.6	26	74	0.35
7	10	2	5	0.48	11	17	0.65
8	25	5	5	1.2	11	49	0.22
9	37.5	7.5	5	1.8	10	67	0.15
10	5[d]	5	1	1.2	68	18	3.78
11	10[d]	10	1	2.4	70	24	2.92
12	15[d]	15	1	3.6	70	30	2.33

[a] In all reactions the same amount of $PhCOCOOCH_3$ (5 mmol) was used. [b] The 15% aqueous $TiCl_3$ solution used was exactly 1.2 N. [c] See note *b* of Table I. [d] $CH_3COOH-H_2O$ (70:30) was used instead of glacial CH_3COOH.

Table IV. Yields of Dimer 3 and Alcohol 4 in CH_3COOH at Different 1/$TiCl_3$ Molar Ratios[a]

start substrt 1, mmol	molar ratio 1/$TiCl_3$	yields, mmol %[b] 3	4	unreactd 1	ratio 3/4
5	0.83	1.2	2.0	1.8	0.60
10	1.66	2.0	1.9	6.1	1.05
15	2.50	2.8	1.8	10.4	1.56
20	3.33	3.7	1.5	14.8	2.47

[a] 6 mmol of $TiCl_3$ (5 mL) was added at once to variable amount of $PhCOCOOCH_3$ in 15 mL of CH_3COOH. [b] See note *b* of Table I.

alcohol, *tert*-butyl alcohol, or tetrahydrofuran (Table I).

Owing to the lower dielectric constant and higher basicity of these solvents, equilibria b and c of Scheme II are shifted to the left, thus protonation of radical anion 8 becomes more and more difficult as compared with electron transfer from 8 to 7. Accordingly, addition of aqueous HCl to the reaction performed in isopropyl alcohol increases the yield of 3 and decreases the yield of 4 (Table I, runs 15–17), though an higher amount of unreacted substrate 1 is recovered.[26]

After the reagents were diluted (as described for CH_3COOH and HCOOH) with an increasing amount of alcoholic solvents or tetrahydrofuran (Figure 3), the increase of alcohol and the decrease of dimer yields are still discernible but are very less pronounced as compared with Figures 1 and 2.

By assuming that, upon dilution, the decrease of hydrogen ion concentration[27] is very modest and of the same order of magnitude for dilution with either methanol, isopropyl alcohol, or tetrahydrofuran, the decrease of 3 and increase of 4 yields have to be ascribed to the decrease of the dielectric constant of the medium. In fact, the higher the dielectric constant of the solvent, the less is the decrease of the dielectric constant of the medium on dilution, and, in line with this reasoning, the yields of 3 decrease in the order: THF (ϵ = 7.58) > *i*-PrOH (ϵ = 17.93) > MeOH (ϵ = 32.7) (Figure 3).

Stereoselective Dimerization in Isopropyl Alcohol. The ratio of meso to racemic dimers formed in all the reactions so far reported is always 1.1, as it has to be expected on statistical ground. In isopropyl alcohol, such a ratio is 1.0–1.1 only when the $TiCl_3$ solution is added at once (Table V, runs 1, 4, 7, 10, and 13). On the contrary, with a decrease in the flow rate (mL/h) of $TiCl_3$ addition to 1 dissolved in isopropyl alcohol, the meso dimer increases and the racemic remains practically unchanged, while the alcohol yield decreases with a consequent increase of both dimer/alcohol and *meso*/*dl* ratios.

The trend is verified for four different 1/$TiCl_3$ molar ratios (Table V). Since dilution with an increasing amount of isopropyl alcohol (Figure 3) leads to a slight decrease of the dimer/alcohol ratio, one would expect, by comparison with the experiments in carboxylic acid solvents, that dropwise addition of $TiCl_3$ solution to 1 dissolved in isopropyl alcohol, at least, slightly decreases such a ratio. In fact, as observed for carboxylic acid solvents, both dilution of the reagents (Figures 1 and 2) and dropwise addition of $TiCl_3$ solution (Table II) lead to a decrease of the dimer/alcohol ratio. The opposite trend found here, along with the preferential formation of the meso isomer, not only indicates that polar and/or steric effects intervene at the time of dimerization but also strongly suggest that a different mechanism is operative in the route to 3 (Scheme II, path g).

When the $TiCl_3$ solution is added dropwise to 1 in isopropyl alcohol, at the very beginning of the reduction, hydrogen ion concentration is to the point of vanishing and the dielectric constant of the medium very low. In these conditions, free radical anions 8 barely exist,[15] being all the reduced substrate still bonded to Ti(IV) ion (7). In the absence of any process which converts 7 into the more reactive intermediates 8 and 2, dimerization of 7 (path g) occurs, leading to the preferential formation of the meso isomer, owing to steric control in the dimerization step.[28]

According to this interpretation, the *meso*/*dl* ratio becomes again 1.1 (Table V, runs 14 and 15) when the $TiCl_3$ solution is added dropwise to 1 dissolved in a mixture of 37% HCl/*i*-PrOH (30:70). Being the reaction medium strongly acidic from the beginning, the flow rate of $TiCl_3$ addition does not effect either the *meso*/*dl* ratio for the dimer is formed by coupling of two radicals 2 or the dimer/alcohol ratio in agreement with the dilution experiments depicted in Figure 3.

The fact that the dimer/alcohol ratio becomes independent from the flow rate of $TiCl_3$ addition (Table V, runs 13–15) removes the doubt that the excess of 1, present at the beginning of the reduction when the $TiCl_3$ solution is added very slowly, may shift the disproportionation equilibrium e to the left, diminishing the yields of 4. This

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(26) Most likely, an excess of chloride ions complexes Ti(III) ion, making increasingly difficult the formation of the activated complex 6 and, consequently, the reduction of 1.

(27) In isopropyl alcohol, as well as in methanol and tetrahydrofuran, the acidity is due only to the HCl contained in the $TiCl_3$ solution, and HCl is almost completely ionized in these solvents. Since no dissociation constants of acids are involved, as it was with acetic and formic acids, hydrogen ion concentration diminishes very slightly on dilution.

(28) Clerici, A.; Porta, O. *J. Org. Chem.* **1985**, *50*, 76.

Table V. Dependence of *meso,dl* Dimer and Alcohol Yields on the Flow Rate of $TiCl_3$ Addition for the Reaction in *i*-PrOH.

			yields, %[c]				
run[a]	flow rate, mL/min	$TiCl_3$,[b] mL	*meso*-3	*dl*-3	4	ratio 3/4	ratio *meso*/*dl*
1	*d*	2	5	5	20	0.50	1.0
2	1	2	16	6	17	1.29	2.7
3	0.1	2	19	6	13	1.92	3.2
4	*d*	3	6	6	28	0.43	1.0
5	1	3	19	7	27	0.96	2.7
6	0.1	3	22	8	20	1.50	2.8
7	*d*	4	7	6	36	0.36	1.1
8	1	4	22	8	31	0.97	2.7
9	0.1	4	25	9	29	1.17	2.8
10	*d*	5	7	6	44	0.29	1.1
11	1	5	21	8	37	0.78	2.6
12	0.1	5	24	9	32	1.03	2.7
13	*d*	3[e]	7	6	19	0.68	1.1
14	1	3[e]	7	6	19	0.68	1.1
15	0.1	3[e]	7	6	19	0.68	1.1

[a] In all reactions the same amount of $PhCOCOOCH_3$ (5 mmol) and the same amount of *i*-PrOH (10 mL) were used. [b] The 15% aqueous $TiCl_3$ solution was exactly 1.2 N. [c] See not *b* of Table I. [d] $TiCl_3$ was added at once. [e] *i*-PrOH–37% HCl (70:30) was used instead of *i*-PrOH.

possibility, if ever it might be, is greater in acetic acid than in isopropyl alcohol since equilibrium e is more shifted to the right in the latter than in the former solvent. Accordingly, in acetic acid (Table IV) the yields of **4** decrease by working with a moderate excess of **1** with respect to Ti(III) ion,[29] whereas in isopropyl alcohol, as we have observed, the same excess of substrate (3–4-fold) does not substantially change the yields of **4**.

Conclusions

All the results presented strongly support our working hypothesis (Scheme II) that radical anion **8** is the common intermediate involved in competitive equilibria shifted in favor of dimerization or disproportionation, depending on the reaction conditions. The higher the polarity and hydrogen ion concentration of the medium, the higher the equilibrium concentration of **2** is, which leads to the dimer **3** by a very fast process. Any factor that diminishes the acidity of the medium hinders protonation of **8**, so that disproportionation, leading to alcohol **4**, favorably competes with dimerization.

However, at low polarity and very low hydrogen ion concentration of the medium, equilibria b and c of Scheme II are by far shifted to the left and a different mechanism to **3** becomes operative (e.g., dimerization of **7**), resulting in the preferential formation of the meso isomer.

Since we are dealing with extremely fast processes, a quantitative evaluation of the different reaction rates by conventional techniques seems rather difficult at present.

Experimental Section

General Methods. The titanium(III) chloride solution (15% w/v, C. Erba) was titrated against 0.1 N cerium(IV) sulfate solution. Methyl phenylglyoxalate **1** was a commercial sample distilled before use. The solvents employed were reagent grade. All the reactions were run at room temperature under N_2 and, after the times reported for each procedure, were extracted with ethyl acetate (3 × 100 mL), washed with distilled water, dried over anhydrous Na_2SO_4, and evaporated in vacuo. Yields of **3** and **4** and the *meso*/*dl* dimer ratios were determined by ^1H NMR spectroscopy on an aliquot of the crude reaction mixtures, taking advantage of the fact that the methyl protons peaks of **1**, *meso*-**3**, *dl*-**3**, and **4** are well separated (see spectroscopic data). ^1H NMR spectra were recorded on a Varian A-90 with Me_4Si as an internal standard.

General Procedures. Reactions of Table I. To a rapidly stirred solution of **1** (5 mmol) in 10 mL of solvent (or in 10 mL of a binary mixture of solvents) the $TiCl_3$ solution (5 mL; 6 mmol) was added at once: reaction time, 30 min.

Reactions of Figures 1–3. The $TiCl_3$ solution (5 mL; 6 mmol) was added at once to a well-stirred solution of **1** (5 mmol) dissolved in 5, 10, 15, 20, or 25 mL of solvent (or binary mixture of solvents): reaction time, 30 min.

Reactions of Table II. The $TiCl_3$ solution (5 mL; 6 mmol) was added dropwise (flow rate 30, 10, or 5 mL/h) to a well-stirred solution of **1** (5 mmol) in CH_3COOH (10 mL): reaction time, 1 h.

Reactions of Table III. In all experiments the same amount of **1** (5 mmol) was used. The $TiCl_3$ solution was added at once to **1** dissolved in CH_3COOH or in $CH_3COOH–H_2O$ (70:30) (runs 10–12). The volumes of both CH_3COOH (or aqueous CH_3COOH) and $TiCl_3$ solutions were increased in such a way that the volume ratios $CH_3COOH/TiCl_3$ were constant in a set of three reactions (equal to 1, 3, and 5), whereas the molar ratio $TiCl_3/1$ was constantly increased in each set of reactions: reaction time, 30 min.

Reactions of Table IV. The $TiCl_3$ solution (5 mL; 6 mmol) was added at once to variable amount of **1** (5, 10, 15, or 20 mmol) dissolved in CH_3COOH (15 mL); reaction time, 30 min.

Reactions of Table V. In all experiments the same amount of **1** (5 mmol) and the same amount of *i*-PrOH (10 mL) were used. Only in runs 13–15 was a mixture (10 mL) of *i*-PrOH–37% HCl (70:30) used instead. A variable amount of 1.2 N $TiCl_3$ solution (2, 3, 4, or 5 mL) was added either at once or at different flow rate (1 or 0.1 mL/min) to the solution of **1** in *i*-PrOH (or in *i*-PrOH–37% HCl).

Spectroscopic Data. Methyl *meso*-diphenyltartrate 3: mp 153 °C (from ether) (lit.[30] mp 151–153 °C); ^1H NMR ($CDCl_3$) δ 3.88 (6 H, 2OCH_3, s), 5.0 (2 H, 2OH, s, D_2O exchange), 7.0–7.2 (10 H, Ph H, m).

Methyl *dl*-diphenyltartrate 3: mp 120–121 °C (from methanol) (lit.[30] mp 119–121 °C); ^1H NMR δ 3.8 (6 H, 2OCH_3, s), 5.5 (2 H, 2OH, br, D_2O exchange), 7.0–7.2 (10 H, Ph H, m).

Methyl *dl*-mandelate 4: mp 54–56 °C; ^1H NMR ($CDCl_3$) δ 3.75 (3 H, OCH_3, s), 5.2 (1 H, s), 6.0 (1 H, OH, br, D_2O exchange), 7.3–7.5 (5 H, Ph H, m).

Methyl phenylglyoxalate 1: ^1H NMR ($CDCl_3$) δ 4.0 (3 H, OCH_3, s), 7.4–7.6 (3 H, Ph H, m), 8.0–8.2 (2 H, Ph H, m).

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[29] Notwithstanding that in acetic acid an excess of **1** may shift the disproportionation equilibrium to the left, the "dilution effect" prevails (Table II) in determining the decrease of the dimer/alcohol ratio when the $TiCl_3$ solution is added dropwise to **1**.

[30] Juday, R. E. *J. Org. Chem.* **1958**, *23*, 1010.