

Kinetics and mechanism of the formation of mono- and di-phthalate esters catalysed by titanium and tin alkoxides

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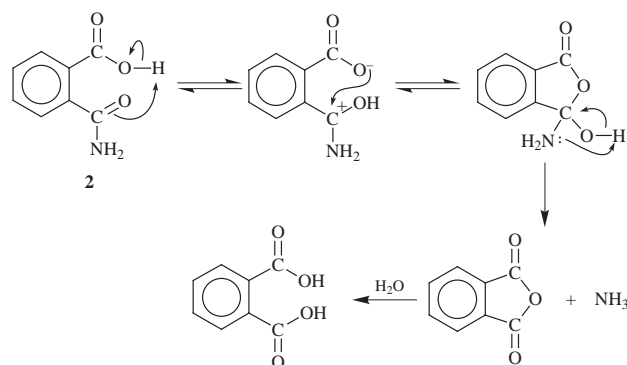
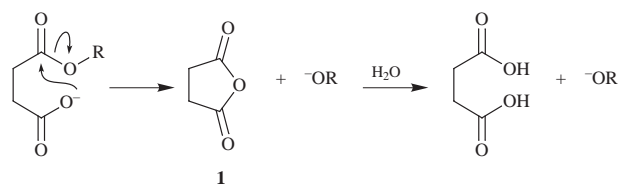
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The kinetics and mechanism of the formation of phthalate mono-esters and phthalate di-esters from phthalic anhydride and a variety of mono- and di-hyric alcohols are reported and discussed. The kinetic work is extended to a mechanistic study of the same reactions using titanium tetra-*n*-butoxide and tri-*n*-butyltin ethoxide as catalysts. The results support a mechanism involving alkoxy ligand exchange at the metal as a crucial step in the catalysis.

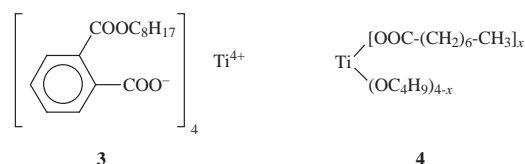
Introduction

The formation of phthalate esters has received considerable attention over the last 20 years due to the great importance of the compounds in both the polymer and plasticizer industries. The formation of phthalate esters involves sequential cyclic anhydride alcoholysis followed by esterification, both reactions which are seemingly well understood. Esterification reactions certainly fall into this category but many groups have failed to recognise the importance of the equilibrium which must exist in the alcoholysis of cyclic anhydrides. Two workers who have addressed this subject, however, are Hu and Lindt¹ who studied the formation of half-esters of maleic anhydride residues in a styrene-maleic anhydride copolymer in ethylbenzene. They surmised that such a reaction must be in equilibrium and that therefore the position of equilibrium should be temperature dependent. This was proved by their results which showed that a greater proportion of half-ester was formed at lower temperatures than at higher temperatures (*i.e.* the formation of the half-ester is exothermic). Cyclic anhydrides have also been recognised as important intermediates in the hydrolysis of half-esters² (**1**) and of phthalamic acid³ (**2**) both of which react *via*

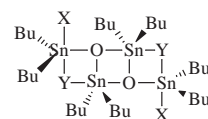


mechanisms involving intramolecular catalysis by the neighbouring acid function while aspirin has been shown to form an anhydride intermediate in an intramolecular step during hydrolysis.⁴

The organometallic catalysis of esterification reactions has also been widely studied while catalysis of the cyclic anhydride alcoholysis reactions has not.⁵ Leverd *et al.*⁶ and Otton *et al.*⁷ studied titanium tetraalkoxide catalysed esterification reactions in some detail and both groups suggested that the titanium is able to exchange alkoxy ligands readily with the alcoholic solvent molecules so that the active catalyst contains the reagent alcohol as a ligand. Similarly, it has been suggested that a possible mechanism involves titanium exchanging an alkoxy ligand for a molecule of acid⁸ and this has been shown to be plausible by Novrocík *et al.*⁹ who isolated and characterised the organotitanium compound **3** from mixtures of the half-ester and titanium tetra-*n*-butoxide and by Bulai *et al.*¹⁰ who have observed the species **4** from mixtures of titanium tetra-*n*-butoxide and octanoic acid.



A similar mechanism has also been proposed for the catalytic esterification of benzoic acid by polymeric dimethyltin oxide.¹¹ The catalyst binds an alcohol molecule followed by an acid molecule whereupon the alcohol is passed intramolecularly to the acid to form the ester which is then released to reform the catalyst. A similar intramolecular pathway occurs in both the esterification and transesterification reactions catalysed by the tetrameric species **5**.¹² The ligands Y can be either



5 X = NCS, Cl; Y = OH, OR¹, OCOR²

alcohol or acid depending on which is in excess. It is believed that the tetramer remains intact during the catalytic process and that two metal centres are involved during the catalytic cycle.

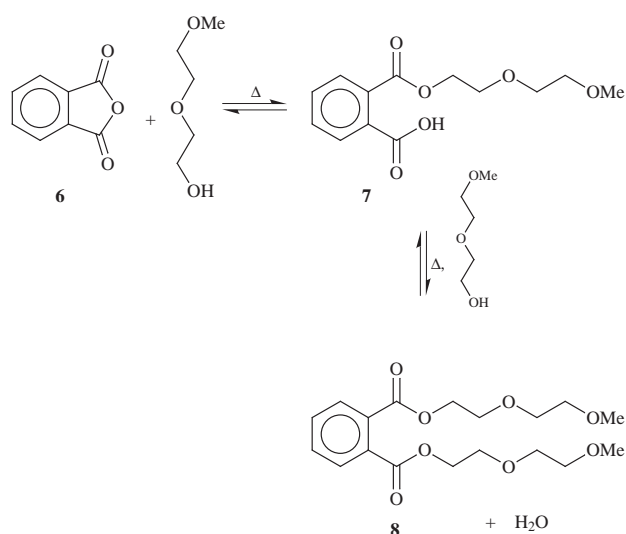
The current research was undertaken, therefore, with the intention of improving the understanding of anhydride reactions, especially with regard to the equilibria involved and catalysis of the reactions. The inclusion of a number of alcohols allows more secure mechanistic conclusions to be drawn.

Table 1 Rate data for the formation of **7** and **8** and the decomposition of **7**

Formation of 7		Formation of 8		Decomposition of 7	
<i>T</i> /K	<i>k</i> _{obs} /10 ⁻⁴ s ⁻¹	<i>T</i> /K	<i>k</i> _{obs} /10 ⁻⁵ s ⁻¹	<i>T</i> /K	<i>k</i> _{obs} /10 ⁻⁴ s ⁻¹
386.0	2.50	425.0	2.98	401.0	1.78
388.0	2.85	427.0	3.28	411.0	2.85
391.0	2.83	431.0	8.04	417.0	4.18
395.0	3.28	437.0	11.1	426.0	5.63
396.0	3.31	440.0	16.7	436.0	11.2
399.0	3.30	442.0	20.0	441.0	12.7
403.0	3.38	444.0	28.6	443.0	18.0
406.0	3.63	446.0	34.5		
409.0	3.95				
417.0	4.52				
419.0	5.43				
420.0	5.86				

Results and discussion

The system chosen for study was that of phthalic anhydride (**6**) with 2-(2-methoxyethoxy)ethanol [2-(2-ME)E] (Scheme 1) since

**Scheme 1**

this avoided the possibility of polymer formation. The rates of formation of **7** and **8** were studied alone and in the presence of titanium tetra-*n*-butoxide or tri-*n*-butyltin ethoxide as catalysts and the rate of decomposition of **7** was studied alone.

Kinetic data for the uncatalysed reactions

The rates of formation of **7** and **8** and the rate of decomposition of **7** were followed by UV-VIS spectroscopy under pseudo first-order conditions by observing the formation and decomposition of **7** at $\lambda_{\text{max}} = 292$ nm (for X = H) and the formation of **8** at $\lambda_{\text{max}} = 276$ nm (for X = H). Activation parameters were determined for each reaction and the values of *k*_{obs} at various temperatures are shown in Table 1 giving rise to the Arrhenius plots represented by eqns. (1)–(3), which allow the calculation of the activation parameters shown in Table 2.

Formation of **7**:

$$\ln k_{\text{obs}} = -3.40 \times 10^3 (1/T) + 0.54; r = 0.964 \quad (1)$$

Formation of **8**:

$$\ln k_{\text{obs}} = -2.19 \times 10^4 (1/T) + 41.0; r = 0.990 \quad (2)$$

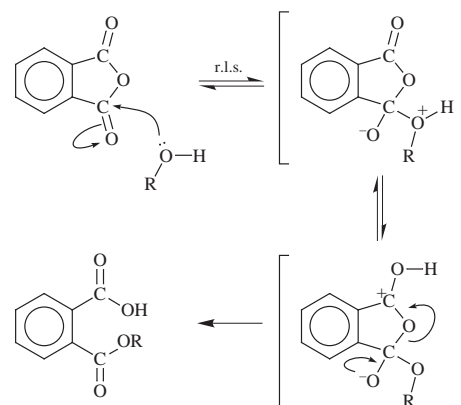
Decomposition of **7**:

$$\ln k_{\text{obs}} = -9.41 \times 10^3 (1/T) + 14.8; r = 0.993 \quad (3)$$

Table 2 Activation parameters at 298 K, with 95% confidence limits, for the formation of **7** and **8** and the decomposition of **7**

Reaction	<i>E</i> _A /kJ mol ⁻¹	ΔH^\ddagger /kJ mol ⁻¹	ΔG^\ddagger /kJ mol ⁻¹	ΔS^\ddagger /J K ⁻¹ mol ⁻¹
Formation of 7	28 ± 2	26 ± 2	100 ± 1	-249 ± 4
Formation of 8	182 ± 17	179 ± 17	153 ± 5	+88 ± 40
Decomposition of 7	78 ± 1	76 ± 1	115 ± 1	-131 ± 7

The low Arrhenius activation energy for the formation of **7** is in agreement with the findings of Ebersson on the neutral hydrolysis of anhydrides.¹³ The highly negative entropy of activation is indicative of a large decrease in translational energy characteristic of two separate species coming together to form the transition state, *i.e.* an A_{Ac}2-like mechanism is implied. Highly negative ΔS^\ddagger values are commonly seen for similar reactions such as the neutral hydrolysis of anhydrides,^{13,14} although the magnitude of the present value is surprising. The fact that the value is so highly negative indicates that the formation of the transition state requires an unusually high degree of organisation in the approach of the reactant molecules.¹⁵ This suggests that the rate-limiting step of the reaction is the formation of the addition intermediate as shown in Scheme 2.

**Scheme 2**

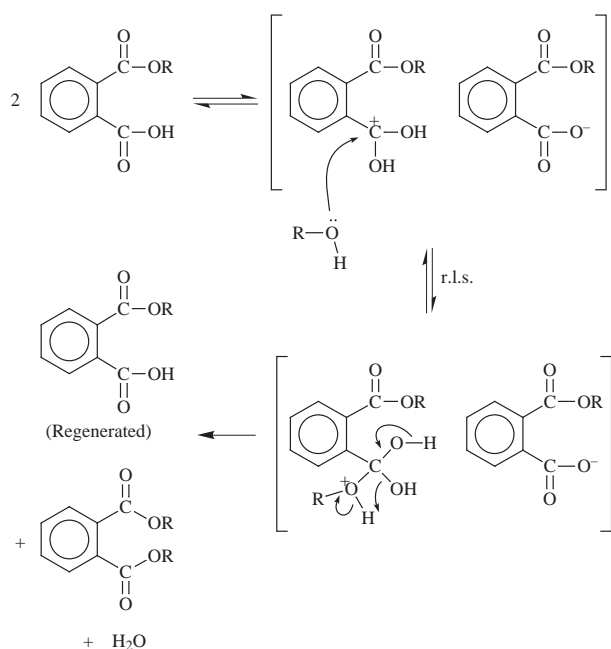
The value of *E*_A for the formation of **8** indicates a highly energetic reaction which is sensitive to small changes in temperature. Values of this magnitude have been found by Ueberreiter and Hager in their studies on the uncatalysed esterification of a number of di-acids with ethylene glycol.¹⁶ The positive value of ΔS^\ddagger is probably due to changes in the solvation shell resulting from the need to break the intermolecular hydrogen bonds between the acid functions of the half-ester dimer in order to allow attack on the carbonyl carbon by the alcohol nucleophile. The concept of a dimeric half-ester is substantiated by the X-ray crystal structure of 2-methoxyethyl hydrogen phthalate.¹⁷ The most likely mechanism for this reaction is therefore the A_{Ac}2 pathway involving rate-limiting attack of the nucleophile alcohol on the protonated acid carbonyl leading to formation of the tetrahedral intermediate (Scheme 3). The proton is supplied by the adjacent carboxylic acid function of the dimer but this in turn implies dissociation of the dimer either prior to or during the rate-limiting step.

The decomposition of **7** is promoted by intramolecular catalysis from the neighbouring carboxylic acid group and, consequently, the value found for the entropy of activation is of the same order as other reactions involving similar intramolecular catalysis steps, *e.g.* the neutral hydrolyses of methyl hydrogen phthalate² and aspirin.^{18,19} By the principle of microscopic reversibility, the mechanism may be assumed to be the reverse of that for the formation of **7** (Scheme 2).

An analysis of the Arrhenius equations, (1) and (3), for the formation and decomposition of **7** indicates that there is an

Table 3 Activation parameters at 298 K, with 95% confidence limits, for the formation of hydroxyalkyl hydrogen phthalates from phthalic anhydride and EG, 1,2-PG, DEG and TEG

Alcohol	$E_A/\text{kJ mol}^{-1}$	$\Delta H^\ddagger/\text{kJ mol}^{-1}$	$\Delta G^\ddagger/\text{kJ mol}^{-1}$	$\Delta S^\ddagger/\text{J K}^{-1} \text{mol}^{-1}$
EG	51 ± 9	48 ± 9	94 ± 2	-155 ± 23
1,2-PG	32 ± 1	29 ± 1	94 ± 1	-219 ± 2
DEG	70 ± 12	67 ± 12	102 ± 4	-116 ± 28
TEG	35 ± 2	32 ± 2	$96 \pm <1$	-215 ± 7



isokinetic temperature associated with the reactions. At this temperature the rate of each reaction is the same while decomposition of **7** is the faster reaction above this temperature and the slower reaction below it. Solving the two Arrhenius equations as simultaneous equations reveals that the isokinetic temperature is 422 K ($1/T = 2.368 \times 10^{-3} \text{ K}^{-1}$). This means that if the forward reaction was carried out in the absence of a sufficient quantity of alcohol at a temperature approaching or above 422 K the decomposition reaction would have a significant effect on the product composition.

In a similar manner an analysis of the Arrhenius equations, (2) and (3), for the formation of **8** and decomposition of **7** indicates that the isokinetic temperature for this pair of reactions is 474 K ($1/T = 2.109 \times 10^{-3} \text{ K}^{-1}$) with di-ester formation being the faster reaction above this temperature. Again this means that when forming the di-ester, the decomposition reaction must be taken into account if the esterification reaction is carried out in the absence of a sufficient quantity of alcohol at a temperature around or below 474 K.

It is apparent from the data presented above that the ring-opening reaction and the esterification reaction have distinct thermodynamic parameters and can therefore be studied independently. Consequently the study of the ring-opening reaction was developed to include a number of dihydric alcohols. Under pseudo first-order conditions these reactions were found to behave in an analogous manner to the initial system with the protected alcohol. Therefore the rates of formation of hydroxyalkyl hydrogen phthalates from phthalic anhydride and ethylene glycol (EG), 1,2-propylene glycol (1,2-PG), diethylene glycol (DEG) and triethylene glycol (TEG) were followed by UV-VIS spectroscopy. The values of k_{obs} over a range of temperatures are given in Supplementary Table A† giving rise to the Arrhenius plots represented by eqns. (4)–(7),

Table 4 Rate data for the formation of 2-hydroxyethyl hydrogen phthalate with varying ethylene glycol concentration carried out at 395 K

[EG]/mol dm ⁻³	$k_{\text{obs}}/10^{-4} \text{ s}^{-1}$
2.0	2.80
3.0	5.11
4.0	7.65

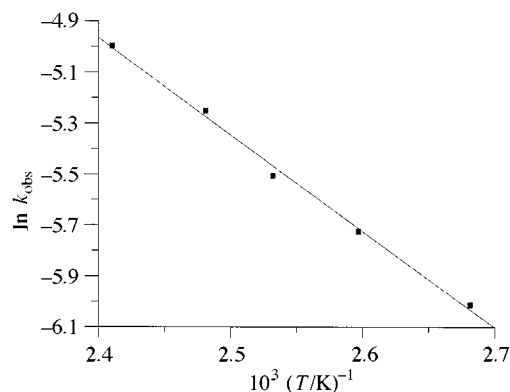


Fig. 1 Arrhenius plot for the formation of 2-hydroxypropyl hydrogen phthalate

$$\text{EG } \ln k_{\text{obs}} = -6.12 \times 10^3 (1/T) + 11.9; r = 0.999 \quad (4)$$

$$1,2\text{-PG } \ln k_{\text{obs}} = -3.79 \times 10^3 (1/T) + 4.13; r = 0.998 \quad (5)$$

$$\text{DEG } \ln k_{\text{obs}} = -8.30 \times 10^3 (1/T) + 16.3; r = 0.989 \quad (6)$$

$$\text{TEG } \ln k_{\text{obs}} = -4.15 \times 10^3 (1/T) + 4.50; r = 0.990 \quad (7)$$

which allow the calculation of the activation parameters shown in Table 3. As an example, one of the Arrhenius plots (for 1,2-propylene glycol) is given in Fig. 1. These data indicate an order of reactivity which can be explained in terms of the relative steric bulk of the alcohols. As expected, the longer chain alcohols react more slowly as do those with only one primary alcohol group.

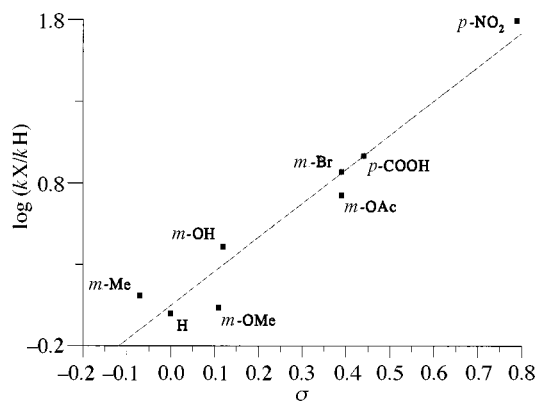
The order of reaction in alcohol was determined for the ring-opening reaction between phthalic anhydride and ethylene glycol at 395 K. The k_{obs} data are given in Table 4 and, as expected, the reaction was found to be first-order in alcohol. This observation reinforces the proposal that the reaction proceeds *via* an A-2 mechanism as shown in Scheme 2. The second-order rate constant, k_2 , obtained from the gradient of the plot of k_{obs} vs. [EG] is given by: $k_2 = 2.43 \times 10^{-4} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at 395 K ($r = 1.000$).

The rates of formation of 2-hydroxyethyl hydrogen phthalate were also investigated by variations of the substituents, X, in position 4 of the aromatic ring of phthalic anhydride. Since phthalic anhydride is a symmetrical molecule it follows that either of the two carbonyl groups may be attacked by the alcohol nucleophile. Introducing a substituent into position 4 of the aromatic ring leads to the loss of the symmetry in the molecule resulting in the two carbonyl groups becoming non-identical. Whether the alcohol attacks the carbonyl group *meta* or *para* to the substituent is dependent on the electronic demands of the reaction transition state (which are dependent on the substituent, X, and the structure of the alcohol nucleophile).

† Supplementary Tables A–H are available as supplementary material (SUPPL. NO. 57 361, 6 pp.). For details of the Supplementary Publications Scheme see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, available *via* the RSC Web page (<http://www.rsc.org/authors>).

Table 5 Hammett rate data for the formation of substituted 2-hydroxyethyl hydrogen phthalates carried out at 343 K

X	$k_x/10^{-3} \text{ s}^{-1}$
4-OMe (<i>m</i>)	1.86
4-Me (<i>m</i>)	2.20
H	3.43
4-OH (<i>m</i>)	4.42
4-OAc (<i>m</i>)	9.13
4-Br (<i>m</i>)	12.8
4-COOH (<i>p</i>)	16.0
4-NO ₂ (<i>p</i>)	108

**Fig. 2** Hammett σ plot for the formation of substituted 2-hydroxyethyl hydrogen phthalates at 343 K

A reaction following an A-1 mechanism would be favoured by electron-donating substituents which would stabilise the developing positive charge at the carbonyl carbon atom. On the other hand, a reaction following an A-2 mechanism would be favoured by electron-withdrawing substituents since these would reduce the electron density around the carbonyl carbon atom and make it more susceptible to nucleophilic attack by an alcohol molecule. It is widely accepted that most anhydrides, with the exception of sterically hindered species such as mesitoic anhydride, react with primary alcohols *via* an A-2 pathway.^{20–22} Thus, one may assume that the alcohol will attack that carbonyl carbon (*meta* or *para* to the substituent) at which the electron-withdrawing character of the substituent is greater, *i.e.* the more positive value of sigma (σ_m , or σ_p) for a given substituent may be used.

This hypothesis was tested for the reaction between 4-hydroxyphthalic anhydride (which has widely different σ_m and σ_p values) and 2-methoxyethanol. Selective ¹H decoupled ¹³C NMR studies on the reaction product indicated that the alcohol reacted only at the position *meta* to the 4-hydroxy substituent thus recognising the electron-withdrawing effect of the OH group *meta* to the carbonyl.

The observed rate coefficients for the various substituents (with the respective relative reaction positions) are given in Table 5 and the resultant Hammett plot against σ in Fig. 2. The ρ value of +2.1 indicates that the rates of reaction are increased by electron-withdrawing substituents on the aryl ring and suggests that there is a greater degree of bond formation than bond cleavage in forming the transition state. This is consistent with the accepted view that anhydrides react with alcohols *via* an A-2 pathway forming a tetrahedral species in the transition state (Scheme 2).

Anhydride/half-ester equilibrium data

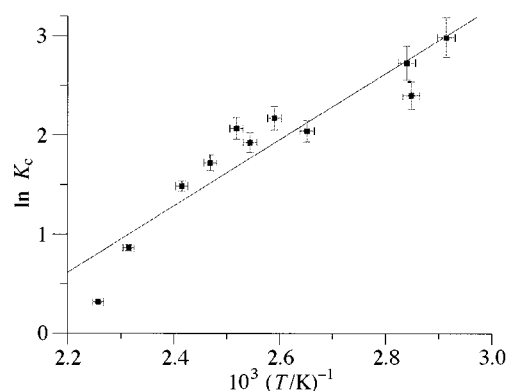
The reaction for the formation of **7** was found to be an equilibrium process (Scheme 1) and in order to establish the equilibrium-temperature profile the reaction was followed by

Table 6 Thermodynamic parameters for the equilibrium between **7** and phthalic anhydride/2-(2-methoxyethoxy)ethanol

$\Delta G^\ominus/\text{kJ mol}^{-1}$	$\Delta H^\ominus/\text{kJ mol}^{-1}$	$\Delta S^\ominus/\text{J K}^{-1} \text{ mol}^{-1}$
$-11 \pm <1$	-28 ± 1	-56 ± 2

Table 7 Activation parameters at 298 K, with 95% confidence limits, for the formation of half-esters, from a variety of alcohols, catalysed by titanium tetra-*n*-butoxide

Alcohol	$E_A/\text{kJ mol}^{-1}$	$\Delta H^\ddagger/\text{kJ mol}^{-1}$	$\Delta G^\ddagger/\text{kJ mol}^{-1}$	$\Delta S^\ddagger/\text{J K}^{-1} \text{ mol}^{-1}$
2-(2-ME)E	105 ± 4	103 ± 4	113 ± 1	-35 ± 13
EG	51 ± 1	48 ± 1	92 ± 1	-148 ± 1
1,2-PG	57 ± 4	54 ± 4	97 ± 1	-144 ± 7
DEG	73 ± 4	70 ± 4	99 ± 2	-98 ± 10
TEG	75 ± 10	72 ± 10	103 ± 1	-105 ± 26

**Fig. 3** Plot of $\ln K_c$ vs. $1/T$ (with error bars) for the equilibrium of the formation of **7**

¹H NMR spectroscopy over a wide temperature range (70–170 °C) with a 1:1 molar ratio of reactants. The equilibrium data are given in Supplementary Table B and, using eqn. (8), a

$$\ln K_c = -\Delta H^\ominus/RT + \Delta S^\ominus/R \quad (8)$$

plot of $\ln K_c$ vs. $1/T$ (Fig. 3) represented by eqn. (9) allows

$$\ln K_c = 3.31 \times 10^3 (1/T) - 6.649; r = 0.939 \quad (9)$$

calculation of the thermal parameters (Table 6) with the positive slope indicating an exothermic reaction.

Kinetic data for the catalysed reactions

Titanium tetra-*n*-butoxide catalysed formation of the half-esters. The values of k_{obs} are given in Supplementary Table C giving rise to the Arrhenius plots represented by eqns. (10)–(14),

$$2-(2\text{-ME})\text{E} \ln k_{\text{obs}} = -1.26 \times 10^4 (1/T) + 26.2; r = 0.996 \quad (10)$$

$$\text{EG} \ln k_{\text{obs}} = -6.10 \times 10^3 (1/T) + 12.7; r = 0.995 \quad (11)$$

$$1,2\text{-PG} \ln k_{\text{obs}} = -6.82 \times 10^3 (1/T) + 13.1; r = 0.999 \quad (12)$$

$$\text{DEG} \ln k_{\text{obs}} = -8.55 \times 10^3 (1/T) + 18.1; r = 0.991 \quad (13)$$

$$\text{TEG} \ln k_{\text{obs}} = -8.93 \times 10^3 (1/T) + 17.8; r = 0.995 \quad (14)$$

which allow the calculation of the activation parameters shown in Table 7. As an example, one of the Arrhenius plots (for ethylene glycol) is given in Fig. 4.

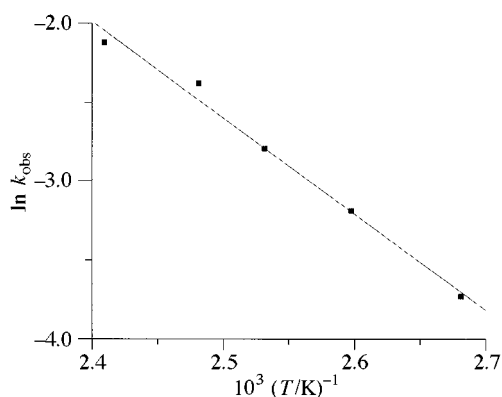


Fig. 4 Arrhenius plot for the titanium tetra-*n*-butoxide catalysed formation of 2-hydroxyethyl hydrogen phthalate

There is a similar order of reactivity to the uncatalysed reactions which can be explained in terms of the relative steric bulk of the alcohols. As expected the longer chain alcohols react more slowly as also do those with only one primary alcohol group. However, at lower temperatures the rate of reaction for 1,2-propylene glycol overtakes that for diethylene glycol. This is due to the fact that the catalyst exchanges its alkoxide ligands with the alcohols and therefore the less sterically bulky 1,2-propylene glycol is more reactive than the larger diethylene glycol unit, particularly at lower temperatures where diethylene glycol is fairly viscous. The alkoxide ligand exchange reaction has been proposed previously by a number of workers⁶⁻⁸ and was found, in this work, to proceed readily even at ambient temperature to give a quantitative yield of the corresponding titanium alkoxide (*vide supra*). Therefore the active catalyst in each reaction is the titanium tetraalkoxide corresponding to the alcohol reactant and solvent.

The values found for E_A are mostly larger than those of the uncatalysed reactions indicating that the catalyst increases the temperature sensitivity of the reactions. More important, however, are the less negative values for the entropies of activation for each reaction which are probably responsible for the observed rate increases.

The order of reaction in catalyst was determined for the reactions with 2-(2-methoxyethoxy)ethanol at 415 K and ethylene glycol at 395 K. The k_{obs} data are given in Supplementary Table D and the reactions were found to be first-order in catalyst in both cases. The second-order rate constants, k_{cat} , obtained from the gradients of the plots of k_{obs} vs. [catalyst] are given by eqns. (15) and (16).

$$\text{2-(2-ME)E } k_{\text{cat}} = 2.51 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1} \text{ at } 415 \text{ K}; r = 0.992 \quad (15)$$

$$\text{EG } k_{\text{cat}} = 6.48 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1} \text{ at } 395 \text{ K}; r = 0.985 \quad (16)$$

Tri-*n*-butyltin ethoxide catalysed formation of the half-esters.

The values of k_{obs} are shown in Supplementary Table E giving rise to the Arrhenius eqns. (17)–(21), and shown in Fig. 5 for

$$\text{2-(2-ME)E } \ln k_{\text{obs}} = -1.05 \times 10^4 (1/T) + 23.3; r = 0.976 \quad (17)$$

$$\text{EG } \ln k_{\text{obs}} = -3.67 \times 10^3 (1/T) + 7.04; r = 0.951 \quad (18)$$

$$\text{1,2-PG } \ln k_{\text{obs}} = -5.75 \times 10^3 (1/T) + 11.0; r = 0.979 \quad (19)$$

$$\text{DEG } \ln k_{\text{obs}} = -6.04 \times 10^3 (1/T) + 11.1; r = 0.990 \quad (20)$$

$$\text{TEG } \ln k_{\text{obs}} = -7.80 \times 10^3 (1/T) + 16.2; r = 0.978 \quad (21)$$

diethylene glycol, which allows the calculation of the activation

Table 8 Activation parameters at 298 K, with 95% confidence limits, for the formation of half-esters, from a variety of alcohols, catalysed by tri-*n*-butyltin ethoxide

Alcohol	$E_A/\text{kJ mol}^{-1}$	$\Delta H^\ddagger/\text{kJ mol}^{-1}$	$\Delta G^\ddagger/\text{kJ mol}^{-1}$	$\Delta S^\ddagger/\text{J K}^{-1} \text{ mol}^{-1}$
2-(2-ME)E	87 ± 2	85 ± 2	$102 \pm <1$	-59 ± 8
EG	30 ± 2	28 ± 1	$86 \pm <1$	-195 ± 5
1,2-PG	48 ± 1	45 ± 1	$93 \pm <1$	-162 ± 4
DEG	50 ± 5	48 ± 5	$96 \pm <1$	-161 ± 17
TEG	48 ± 11	45 ± 11	94 ± 3	-163 ± 25

Table 9 Rate data for the formation of 2-hydroxyethyl hydrogen phthalate with varying Bu_3SnOEt concentration

$[\text{Bu}_3\text{SnOEt}]/10^{-3} \text{ mol dm}^{-3}$	$k_{\text{obs}}/10^{-2} \text{ s}^{-1}$
0.0	2.55
2.50	5.06
4.00	7.44
5.00	8.70

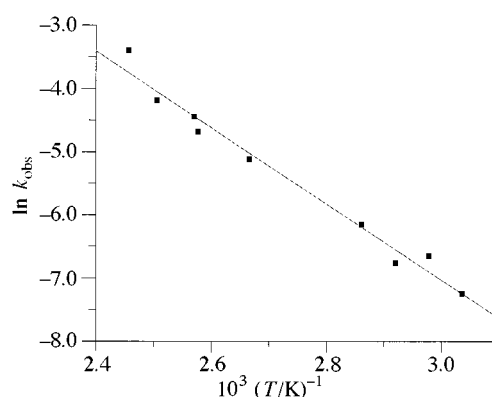
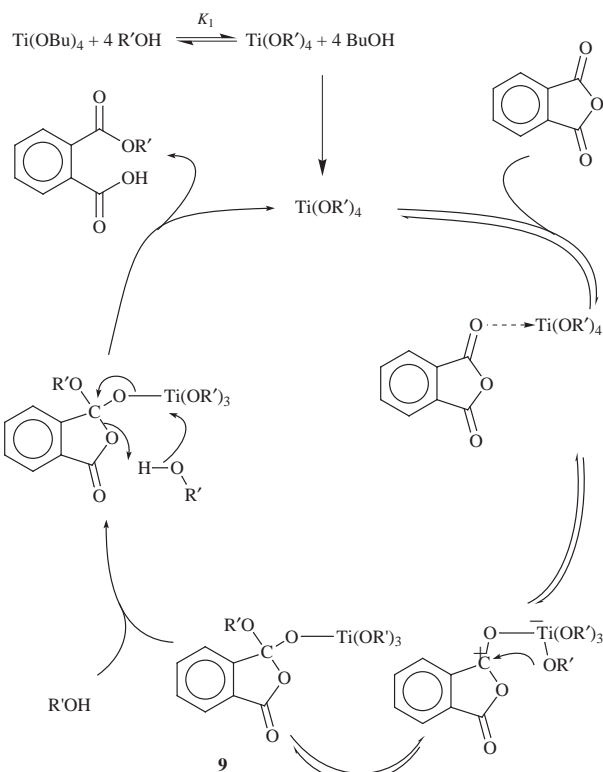


Fig. 5 Arrhenius plot for the tri-*n*-butyltin ethoxide catalysed formation of 2-(2-hydroxyethoxy)ethyl hydrogen phthalate

parameters shown in Table 8. The pattern of reactivity, as shown by the Arrhenius activation parameters, is not as simple for these reactions. The reactions carried out with 2-(2-methoxyethoxy)ethanol, 1,2-propylene glycol and triethylene glycol follow the same trend as the analogous reactions catalysed by titanium tetra-*n*-butoxide, *i.e.* they exhibit a higher E_A value and a less negative entropy of activation when compared to the uncatalysed reactions. Thus it is likely that the entropies of activation are responsible for the observed rate increases. However, for the reactions with ethylene glycol and diethylene glycol the reverse trend is observed, *i.e.* they exhibit a slightly lower E_A and correspondingly a slightly more negative entropy of activation in comparison with the uncatalysed reactions.

The order of reaction in catalyst was determined for the reaction with ethylene glycol at 395 K. The k_{obs} data are given in Table 9 and the reaction was again found to be first order in catalyst with $k_{\text{cat}} = 12.4 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at 395 K ($r = 0.995$).

Mechanism of catalysis. Titanium tetra-*n*-butoxide undergoes a pre-catalytic exchange reaction with the solvent so that the active catalyst is the titanium tetraalkoxide corresponding to the reactant alcohol. An initial Lewis acid interaction between the titanium atom of one catalyst molecule and the oxygen atom of one carbonyl function of the anhydride leads to a more formal bond (the negative sign on titanium is only present for descriptive purposes) as an alkoxide ligand is passed intramolecularly from the titanium to the carbon atom of the bound carbonyl function to form the tetrahedral species **9**, which is essentially an *ortho*-ester (Scheme 4). The next step in the cycle is another ligand exchange reaction at the titanium.



Scheme 4

An alcohol molecule from the solvent attacks titanium to release the half-ester product and re-form the catalyst which then re-enters the catalytic cycle.

The catalytic mechanism for the action of tri-*n*-butyltin ethoxide can be assumed to be identical to that of titanium tetra-*n*-butoxide since it is known that alkyltin alkoxides are capable of alkoxide ligand exchange in a similar manner to that seen with titanium tetraalkoxides and that tin is able to expand its coordination shell beyond four.^{11,12}

Titanium tetra-*n*-butoxide catalysed formation of di-ester 8.

The values of k_{obs} are shown in Supplementary Table F giving rise to the Arrhenius plot represented by eqn. (22) which allows

$$\ln k_{\text{obs}} = -2.24 \times 10^4 (1/T) + 43.81; r = 0.998 \quad (22)$$

the calculation of the activation parameters shown in Table 10. As with the uncatalysed di-ester formation reaction, the catalysed reaction exhibits a high E_A value which indicates a temperature sensitive reaction. The unusually high positive value of ΔS^\ddagger is again probably due to changes in the solvation shell resulting from the need to break the intermolecular hydrogen bonds between two acid functions of the half-ester dimer in order to achieve complexation with the titanium atom.

The order of reaction in catalyst was determined at 441 K. The k_{obs} data are given in Supplementary Table G and the reaction was found to be first-order in catalyst with $k_{\text{cat}} = 0.326 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at 441 K ($r = 0.996$).

It is proposed that the mechanism of catalysis for di-ester formation is analogous to that for half-ester formation. The acid carbonyl bond is activated by the metal and an alcohol ligand is transferred in an intramolecular fashion to form the ester function.

Table 10 Activation parameters at 298 K, with 95% confidence limits, for the titanium tetra-*n*-butoxide catalysed formation of 8

$E_A/\text{kJ mol}^{-1}$	$\Delta H^\ddagger/\text{kJ mol}^{-1}$	$\Delta G^\ddagger/\text{kJ mol}^{-1}$	$\Delta S^\ddagger/\text{J K}^{-1} \text{ mol}^{-1}$
186 ± 10	184 ± 10	150 ± 2	$+111 \pm 24$

Conclusions

The conclusions of the work may be summarised as follows:

The uncatalysed formation of the half-esters occurs through an A-2 mechanism *via* rate-determining attack of the alcohol on a carbonyl carbon of the anhydride (Scheme 2). This is evidenced by the observations that the reaction is first-order in both anhydride and alcohol, the ΔS^\ddagger values are highly negative indicating an associative process and the Hammett ρ value is +2.1 which implies that the reaction is promoted by electron-withdrawing groups in the anhydride ring.

The ring-closing reaction for the decomposition of 7 is catalysed intramolecularly by the neighbouring carboxylic acid group. The alcohols show the order of reactivity expected, in both uncatalysed and catalysed reactions, with the more sterically hindered alcohols and those with only one primary alcohol group reacting more slowly.

The catalysed reactions for the formation of the half-esters were found to be first-order in anhydride, alcohol and catalyst. These reactions occur *via* the intramolecular transfer of an alkoxide ligand to the activated carbonyl carbon of the anhydride with both catalysts operating *via* the same mechanism (Scheme 4). The formation of the di-ester occurs in an analogous manner. Tri-*n*-butyltin ethoxide is a marginally more effective catalyst than titanium tetra-*n*-butoxide as seen by a comparison of the respective ΔG^\ddagger values and the second-order rate coefficients.

Experimental

General

^1H NMR spectra were recorded at 360.1 MHz on a Bruker AM360 instrument or at 400.13 MHz on a Bruker AMX400 instrument and referenced to TMS as internal standard in CDCl_3 or CD_3CN , unless otherwise stated. ^{13}C NMR spectra were recorded at 90.6 MHz on a Bruker AM360 instrument or at 100.61 MHz on a Bruker AMX400 instrument and were referenced to the CDCl_3 signal at 77 ppm in CDCl_3 and to the CD_3CN signal at 1.3 ppm in CD_3CN , unless otherwise stated. The decoupled proton, ^1H COSY 45, heteronuclear $^1\text{H}/^{13}\text{C}$ correlation and $^{13}\text{C}/^1\text{H}$ long-range coupling spectra were obtained using standard Bruker pulse sequences on the Bruker AM360 instrument.

Mass spectra were obtained at the ULIRS Mass Spectrometry Service, King's College, London. The FAB mass spectra were obtained from a thioglycerol matrix on a KRATOS MS890MS spectrometer and the high resolution EI mass spectra using a JEOL JMS-AX505W or a KRATOS MS890MS instrument.

Infrared spectra were obtained using a Perkin-Elmer Paragon 1000 FT-IR spectrometer in the range 4400–450 cm^{-1} . The spectra of liquid compounds were obtained from the neat sample on NaCl plates while solid compounds were run as Nujol mulls on NaCl plates.

Kinetic measurements

High temperature UV–VIS spectroscopy rate measurements ($>100^\circ\text{C}$) were carried out on a Hewlett-Packard system incorporating a HP8452A Diode Array spectrophotometer connected to a Vectra QS/165 data processing computer and a HP500 Deskjet printer. The apparatus was thermostatted to $\pm 1^\circ\text{C}$ using an electrically heated aluminium cell holder. All other UV–VIS spectroscopy rate measurements were carried out on a Hewlett-Packard system incorporating a HP8453 Diode Array spectrophotometer fitted with an automatic cell changer linked to a P75 Windows based data processing computer and a HP540 Deskjet printer. The apparatus was thermostatted to $\pm 0.2^\circ\text{C}$ by a Grant water thermostat bath and a Grant refrigeration unit.

Half-ester formation reactions. Stock solutions of the

phthalic anhydrides were prepared in bis(2-methoxyethyl) ether (diglyme) at 0.1 M. In the cases of 4-nitrophthalic anhydride and 4-hydroxyphthalic anhydride the stock solutions were prepared at 0.02 and 0.025 M respectively in order to accommodate the larger extinction coefficients. For high temperature measurements ($>100\text{ }^{\circ}\text{C}$) reactions were initiated by the addition of 25 μl of a stock solution to pre-equilibrated 1 mm cuvettes containing 0.5 ml of the alcohol being studied. Final concentrations of the substrates were 5×10^{-3} M. For lower temperature measurements ($<100\text{ }^{\circ}\text{C}$) reactions were initiated by the addition of 25 μl of a stock solution to pre-equilibrated 10 mm cuvettes containing 2.5 ml of the alcohol being studied. Final concentrations of the substrates were 1×10^{-3} M (2×10^{-4} M for 4-nitrophthalic anhydride and 2.5×10^{-4} M for 4-hydroxyphthalic anhydride). Reactions were monitored by following the decrease in absorbance at wavelengths ranging from 230 to 330 nm (Supplementary Table H). Wavelengths employed for the uncatalysed and tri-*n*-butyltin ethoxide catalysed reactions are λ_{max} values while those employed for the titanium tetra-*n*-butoxide catalysed reactions are $\lambda_{\text{off,max}}$ due to an overlap in the absorption spectrum with that of the catalyst.

Di-ester formation reactions. A stock solution of the half-ester, (2-methoxyethoxy)ethyl hydrogen phthalate, was prepared in bis(2-methoxyethyl) ether at 0.1 M. Reactions were initiated by the addition of 25 μl of the stock solution to pre-equilibrated 1 mm cuvettes containing 0.5 ml of the alcohol. The final concentration of the substrate was 5×10^{-3} M. Reactions were monitored by following the increase in absorbance at $\lambda_{\text{max}} = 276$ nm. At higher catalyst concentrations it was necessary to monitor the reactions at $\lambda = 300$ nm since the absorption of the catalyst interfered with the absorption of the substrate at $\lambda_{\text{max}} = 276$ nm.

Half-ester decomposition reactions. The reactions were carried out in the inert solvent 1,2-bis(2-methoxyethoxy)ethane. A stock solution of the half-ester, (2-methoxyethoxy)ethyl hydrogen phthalate, was prepared in 1,2-bis(2-methoxyethoxy)ethane at 0.1 M. Reactions were initiated by the addition of 25 μl of the stock solution to pre-equilibrated 1 mm cuvettes containing 0.5 ml of 1,2-bis(2-methoxyethoxy)ethane. The final concentration of the substrate was 5×10^{-3} M. Reactions were monitored by following the increase in absorbance at $\lambda_{\text{max}} = 292$ nm.

The order in alcohol was determined by carrying out the reactions in the alcohol diluted with the inert solvent bis(2-methoxyethyl) ether to achieve the required alcohol concentration. For reactions involving the use of catalysts, stock solutions of the catalysts were prepared daily in the alcohols at 5×10^{-3} M. For reactions to determine the order in catalyst these were diluted to obtain the required catalyst concentration.

Spectra of the products at the end of any given kinetic run matched those of the independently formed and measured reaction products under the same solvent and concentration conditions. Pseudo first-order rate constants were calculated by a computer program which fitted the data to exponential curves or from plots of $\ln|A_{\infty} - A_t|$ vs. time. The two procedures yielded identical rate constants, within experimental error, when applied to the same set of data. In the case of the reaction for the formation of the di-ester, use of the Guggenheim method ($\ln|A_{t+\Delta} - A_t|$ vs. time) to evaluate the rate constants was necessary since accurate evaluation of A_{∞} was not possible. The logarithmic plots were linear over several (≥ 3) half-lives. All rate constants were the average of at least three kinetic runs. All Arrhenius activation parameters are presented with 95% confidence intervals calculated using two standard deviations of the observed rate data.

Preparation of 2-(2-methoxyethoxy)ethyl hydrogen phthalate

A mixture of phthalic anhydride (18.35 g, 0.124 mol) and 2-(2-methoxyethoxy)ethanol (15.2 ml, 0.128 mol) was heated at $105\text{ }^{\circ}\text{C}$ with stirring for 6 h. After cooling the mixture was taken up in water (60 ml) and 5 M NaOH (30 ml) added. The aqueous

solution was washed with dichloromethane (2 \times 75 ml) and then acidified to *ca.* pH 3 with concentrated HCl (12 ml). The precipitate was dissolved in dichloromethane (50 ml) and the aqueous layer washed further with dichloromethane (2 \times 50 ml). The organic extracts were combined, dried with MgSO_4 and filtered. The solvent was evaporated to give 31.3 g (94%) of a colourless viscous liquid. $\nu_{\text{max}}/\text{cm}^{-1}$ 3434 (OH), 2635 (COOH overtone), 1728 (C=O), 1602, 1581 (*ortho*-di-subst aromatic), 1285 (COOH), 1267, 1129 [C(O)OR]; $\delta_{\text{H}}(\text{CDCl}_3)$ 3.52 (3 H, s, OCH₃), 3.71 (4 H, s, CH₂CH₂OCH₃), 3.77 (2 H, m, CH₂OCH₂), 4.47 [2 H, m, C(O)OCH₂], 7.54 (2 H, m, Ar), 7.69 (1 H, m, Ar), 7.80 (1 H, m, Ar), 9.35 [1 H, br s, C(O)OH]; $\delta_{\text{C}}(\text{CDCl}_3)$ 58.7 (OCH₃), 64.7, 68.7, 69.5, 72.1 (4 \times OCH₂), 128.4, 129.4, 130.6, 131.6 (Ar, 4 \times C), 129.6, 130.8 [Ar, 2 \times C(qt)], 167.5, 170.0 (2 \times C=O). *m/z* (HRMS, EI) (M + 1)⁺ = 269.1025. Calc. (M)⁺ = 268.0947, corresponding to a molecular formula of C₁₃H₁₆O₆.

Equilibria studies by NMR

Phthalic anhydride (1.25 g, 8.4 mmol) and 2-(2-methoxyethoxy)ethanol (1 ml, 8.4 mmol) were stirred and heated in a sealed Microvial[®] at a constant temperature for at least 6 h to ensure that the equilibrium was properly established. The reaction was quenched by rapid cooling and the ¹H NMR spectrum of the mixture recorded. Integration of the peaks in the aromatic region of the spectrum allowed calculation of the relative quantities of reactants and products in the reaction mixture. The experiment was repeated over a wide temperature range (70–170 $^{\circ}\text{C}$) to give an equilibrium-temperature profile. As a check, a number of experiments were carried out in a similar manner but approaching the equilibrium from the side of the product, 2-(2-methoxyethoxy)ethyl hydrogen phthalate. Identical results were obtained.

Preparation of 4-acetoxypthalic anhydride

4-Hydroxyphthalic acid (2.0 g, 11 mmol) was dissolved in acetic anhydride (5.2 ml, 55 mmol) and heated at $120\text{ }^{\circ}\text{C}$ for 1 h. The mixture was heated under reflux for a further 1.5 h and after cooling, the acetic acid and excess acetic anhydride were distilled off under vacuum. The residual solid was dissolved in dichloromethane (25 ml) and washed with 0.5 M Na₂CO₃ (2 \times 10 ml). The organic layer was dried with MgSO_4 , filtered and the solvent evaporated to yield 1.42 g (63%) of an off-white crystalline solid, mp 127–130 $^{\circ}\text{C}$. $\delta_{\text{H}}(\text{CDCl}_3)$ 2.40 [3 H, s, CH₃C(O)O], 7.62 (1 H, d of d, Ar), 7.79 (1 H, d, Ar), 8.04 (1 H, d, Ar); $\delta_{\text{C}}(\text{CDCl}_3)$ 21.0 [CH₃C(O)O], 119.1, 127.1, 129.6 (Ar, 3 \times C), 128.1, 133.1 [Ar, 2 \times C(qt)], 156.6, 161.8, 168.1 (3 \times C=O). *m/z* (EI) (M)⁺ = 206 (C₁₀H₆O₅).

Preparation of 4-hydroxyphthalic anhydride²³

4-Hydroxyphthalic acid (0.5 g, 2.7 mmol) was heated at $210\text{ }^{\circ}\text{C}$ at atmospheric pressure for 1 h and then under reduced pressure for 1 h. The white crystalline solid product (0.45 g) with mp 164–166 $^{\circ}\text{C}$ (lit. mp 165–166 $^{\circ}\text{C}$ ²⁴) was formed in quantitative yield. $\delta_{\text{H}}(\text{CDCl}_3)$ 7.29 (2 H, m, Ar), 7.91 (1 H, d, Ar), 11.48 (1 H, br s, OH); $\delta_{\text{C}}(\text{CDCl}_3)$ 111.0, 123.0, 127.6 (Ar, 3 \times C), 120.7, 133.9, 164.7 [Ar, 3 \times C(qt)], 162.7, 163.2 (2 \times C=O). *m/z* (HRMS, EI) (M)⁺ = 164.0109, corresponding to a molecular formula of C₈H₄O₄.

Preparation of 4-methoxyphthalic anhydride²³

Diazomethane was prepared *in situ* as follows and used without further purification.²⁵ DIAZALD[®] (*N*-methyl-*N*-nitrosotoluene-*p*-sulfonamide, 2.44 g), dissolved in diethyl ether (15 ml), was added dropwise to a cooled solution of potassium hydroxide (1 g, 18 mmol) in water (2 ml) and ethanol (8 ml). The mixture was allowed to reach room temperature and the diazomethane distilled at 55–60 $^{\circ}\text{C}$ into a cooled flask containing diethyl ether (10 ml). The remaining reactants were deactivated with glacial acetic acid.

The solution of diazomethane in diethyl ether was added dropwise to a cooled solution of 4-hydroxyphthalic anhydride (0.5 g, 3.0 mmol) in diethyl ether (10 ml). The diethyl ether was evaporated and the remaining solid was recrystallised from toluene–petroleum spirit (50:50, v/v) to yield 0.31 g (57%) of an off-white crystalline solid with mp 95–97 °C (lit. mp 98–99 °C²³). δ_{H} (CDCl₃) 3.96 (3 H, s, OCH₃), 7.42 (1 H, d of d, Ar), 7.47 (1 H, d, Ar), 7.92 (1 H, d, Ar); δ_{C} (CDCl₃) 57.5 (OCH₃), 110.3, 123.9, 128.2 (Ar, 3 × C), 124.0, 135.3, 167.3 [Ar, 3 × C(qt)], 163.9, 164.4 (2 × C=O). m/z (HRMS, EI) found (M)⁺ = 178.0262; calc. for C₉H₆O₄ = 178.0266.

Preparation of 4-bromophthalic anhydride

A mixture of 4-bromophthalic acid (1 g, 4.1 mmol) and acetic anhydride (5 ml, 53 mmol) was heated under reflux for 2 h. After cooling, the acetic acid and excess acetic anhydride were distilled off and the solid was dissolved in dichloromethane (25 ml) and washed with 0.5 M Na₂CO₃ (2 × 5 ml). The organic layer was dried (MgSO₄), filtered and the solvent evaporated off to yield 0.9 g (97%) of a white crystalline solid, mp 106–109 °C (lit. mp 108–110 °C²⁶). δ_{H} (CDCl₃) 7.90 (1 H, d of d, Ar), 8.06 (1 H, d of d, Ar), 8.17 (1 H, d, Ar); δ_{C} (CDCl₃) 126.9, 128.9, 139.3 (Ar, 3 × C), 129.8, 131.5, 132.9 [Ar, 3 × C(qt)], 161.4, 161.9 (2 × C=O). m/z (EI) (M)⁺ = 226 (⁷⁹Br), 228 (⁸¹Br) (C₈H₃O₃Br).

Preparation of 2-methoxyethyl hydrogen 4-hydroxyphthalate

A mixture of 4-hydroxyphthalic anhydride (0.5 g, 3.0 mmol) and 2-methoxyethanol (0.25 ml, 3.2 mmol) was heated at 108 °C for 1.5 h with stirring. After cooling, dichloromethane (50 ml) was added when a white product precipitated from the solution. The solid was filtered, washed with dichloromethane (2 × 10 ml) and dried under vacuum to give 0.39 g (54%) of a white crystalline solid. δ_{H} (CDCl₃) 3.26 (3 H, s, OCH₃), 3.59 (2 H, q, CH₂OCH₃), 4.29 [2 H, m, C(O)OCH₂O], 6.84 (1 H, d, Ar), 6.92 (1 H, d of d, Ar), 7.72 (1 H, d, Ar), 10.55 [1 H, br s, C(O)OH]; δ_{C} (CDCl₃) 58.0 (OCH₃), 64.0, 69.4 (2 × OCH₂), 114.2, 116.6, 131.8 (Ar, 3 × C), 120.3, 136.3, 160.4 [Ar, 3 × C(qt)], 166.8, 168.1 (2 × C=O).

Assignment of the *meta* orientation of the hydroxy group to the ester function was achieved by the use of the ¹H coupled ¹³C spectrum and a number of selective ¹H decoupled ¹³C spectra of the product in the region 165–170 ppm.

Titanium tetraalkoxide ligand exchange

A mixture of titanium tetra-*n*-butoxide (5 g, 14.7 mmol) and 2-(2-methoxyethoxy)ethanol (28 ml, 0.235 mol) was stirred at ambient temperature. On mixing the titanium tetra-*n*-butoxide appeared to dissolve but after a delay of ca. 30 s the appearance of a milky white emulsion was observed. After a further delay of ca. 20 s the emulsion disappeared and the mixture was stirred for a further 10 min. *o*-Xylene (3 ml) was added to the mixture as an azeotrope for the displaced *n*-butanol. The *o*-xylene-*n*-butanol mixture was distilled under reduced pressure (0.06 mmHg) at ambient temperature and then the remaining 2-(2-methoxyethoxy)ethanol was distilled off under reduced pressure (bp 66–68 °C/0.06 mmHg) to leave the product as a yellow liquid in quantitative yield (7.7 g). δ_{H} (CDCl₃) 3.35 (12 H,

s, OCH₃), 3.52–3.67 (32 H, m, OCH₂). m/z (HRMS, EI) found 405.1604; calc. for (C₂₀H₄₄O₁₂Ti)⁺ = 524.2312; calc. for (C₁₅H₃₃O₉Ti)⁺ = 405.1604 (M⁺ – C₅H₁₁O₃).

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