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REACTIONS OF MOLECULES WITH TWO EQUIVALENT FUNCTIONAL GROUPS. 2. ACETYLATION OF THE ISOMERS OF BIS(HYDROXYMETHYL)BENZENE

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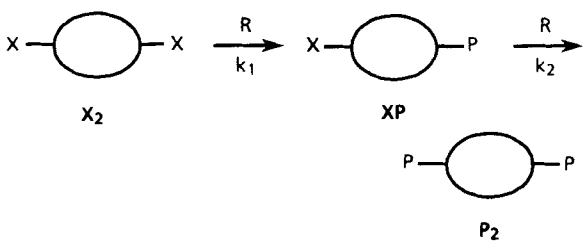
The acetylation (with acetic anhydride–pyridine in tetrahydrofuran) of the *ortho*, *meta* and *para* isomers of bis(hydroxymethyl)benzene (1) was studied. Third-order rate constants k_1 (formation of monoacetate 2 from 1) and k_2 (formation of diacetate 3 from 2) for all three isomers were determined, as were the rate constants for acetylation of benzyl alcohol and its *ortho*- and *para*-ethyl derivatives under the same conditions. The compositions of the final product mixtures (comprising 1, 2 and 3) were ascertained as a function of the initial ratio of acetic anhydride to 1. Comparisons were made with predictions based on a previously published independent functional groups model, which assumes that $k_2/k_1 = 0{\cdot}50$. All three isomers gave product mixtures whose compositions were in generally good agreement with predictions based on the model. For the *para* and *meta* isomers the ratios k_2/k_1 were determined experimentally to be 0·548 and 0·521, respectively. The k_2/k_1 ratio for the *ortho* isomer was found to be 0·605, and its k_1 and k_2 values were lower than those for the *para* and *meta* isomers. Possible explanations for the anomalous behavior of the *ortho* isomer are discussed.

INTRODUCTION

A problem frequently encountered in organic synthesis is to carry out a reaction at just one of two (or more) similar functional groups in a substrate molecule. Under most conditions, a mixture is obtained of products from reaction at either functional group, or both.[1] Chemists have developed several ingenious strategies to 'protect' (i.e. deactivate) one of the functional groups, or to isolate the initial product before it can react further. For example, in the esterification of dicarboxylic acids with diazomethane, adsorption of the starting material on alumina successfully inhibited methylation of the second carboxyl group.[2] Monoketalization of cyclohexane-1,4-dione and similar reactions can be effected by selective extraction of the 'monoadduct' prior to reaction at the second functional group.[3a–d] Recently, diols have been monoprotected by esterification on sulfate salt surfaces,[3e] or under phase-transfer conditions.[3f]

It is clear in many cases that two functional groups which might be expected *a priori* to be independent exhibit anomalous behavior instead. We recently reported[4] that, under most conditions, attempted nucleophilic addition to just one of the carbonyl groups of cyclooctadecane-1,10-dione instead gave predominantly the diadduct (and unreacted starting material), even when the mole ratio of reagent to substrate was less than 1 : 1 (theoretical, 2 : 1). This seemed to indicate that some sort of mutually protective 'cooperativity' existed when both carbonyls were present, causing the first addition to be significantly slower than expected (or the second faster). Conversely, in the epoxidation of 2,5-di-*tert*-butyl-1,4-benzoquinone,[5] the first epoxidation is 3·5 times faster than the second.[6a,6b]

In the first paper of this series,[7] we derived the equations which predict product ratios from the reaction of a molecule (X_2) with two *equivalent* but *independent* functional groups, as a function of the amount of reagent R in which converts group X to P. There it was shown that the fractions of 'monoadduct' (XP) 'diadduct' (P_2) and starting material (X_2) in the



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reaction mixture are described by the following relationships:

$$f_{X_2} = (1 - r/2)^2 \quad (1)$$

$$f_{XP} = r(1 - r/2) \quad (2)$$

$$f_{P_2} = r^2/4 \quad (3)$$

where r is the mole ratio of reagent (R) to starting material (X_2) and $0 \leqslant r \leqslant 2$. The derivation of these equations presumes that (i) X functional groups operate completely independently of other X or P groups in the molecule, (ii) X_2 is exactly twice as reactive as XP (i.e. $k_2/k_1 = 0{\cdot}5$) and (iii) the reaction between reagent and functional group is specific, rapid, and irreversible.

Armed with these theoretical predictions, we have begun to study several prototype difunctional molecules in order to test how well this model correlates with observed product ratios in molecular systems where the two functional groups *are* constrained to operate independently. If this model proves to be valid, we shall in the future examine systems where the significant deviations from the model will provide quantitative insights into intramolecular interactions between the functional groups present in X_2, XP and P_2.

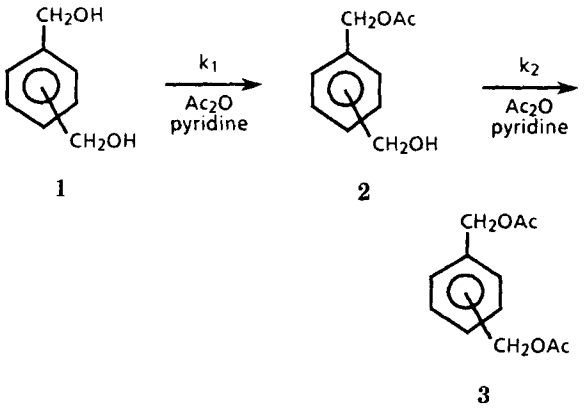
RESULTS

For this experimental study it was important for the substrate (X_2) to have two symmetry-equivalent functional groups (X) which are held rigidly apart from one another, insulating them in so far as possible from any steric or electronic interactions with each other or with the product functional groups P. Further, the relative concentrations of substrate X_2 and products XP and P_2 should be directly determinable by some analytical technique. The reaction to convert X to P should have a mechanism that has been well studied. In addition, the reaction should be clean, irreversible and homogeneous in order to permit accurate kinetic analysis.

After a considerable search for a system which met these criteria, we eventually focused on the acetylation of the *para* isomer of bis(hydroxymethyl)benzene (***p*-1**) with acetic anhydride–pyridine. Not only did this isomer provide two isolated equivalent hydroxyl groups, but it would also permit later comparisons with the *meta* and *ortho* isomers of **1** to see if their hydroxyl groups also function independently.

Preliminary product ratios

The target reaction, with acetic anhydride as limiting reagent and acetone-d_6 as solvent, was first monitored by 300 MHz ^{1}H NMR spectroscopy. Relevant spectral data for all three isomers of **1**, their monoacetates **2** and diacetates **3** are listed in Table 1. All three isomers of **1** required 3–4 days at room temperature for complete exhaustion of the acetic anhydride at the initial concentrations given in Table 2. Control experiments demonstrated that, once formed, the product mixture was stable toward the reaction conditions. There was no evidence for disproportionation of **2** to **1** and **3**, or the reverse reaction.



1 **2** **3**

The *para* isomer of **1** was expected to exhibit the least significant intramolecular interactions between the two hydroxyl groups. As is shown in Table 2, the observed fractions of ***p*-1**, ***p*-2**, ***p*-3** in the product mixture agree very closely (average deviations 3–12%) with values

Table 1. ^{1}H NMR spectral parameters for isomers of **1**, **2**, **3**[a]

Compound	Aromatic C—H	CH_2	OH	O ‖ C—CH_3
***p*-1**	7·319	4·618	3·122	—
***p*-2**	7·38(AA′BB′m)	4·640, 5·073	5·35(br)	2·035
***p*-3**	7·385	5·093	—	2·045
***m*-1**	7·233(m); 7·348(s)	4·644	4·45	—
***m*-2**	—[b]	4·659, 5·087	—[b]	2·041
***m*-3**	7·352(m); 7·396(s)	5·101	—	2·050
***o*-1**	7·323(AA′BB′)	4·739	4·365	—
***o*-2**	—[b]	4·756, 5·207	—[b]	2·040
***o*-3**	7·405(AA′BB′)	5·213	—	2·054
CH_3COCCH_3 (O O ‖ ‖)	—	—	—	2·201
$CH_3C{-}OH$[c] (O ‖)	—	—	—	1·967

[a] Spectra were recorded on acetone-d_6 solutions (internal TMS) at 300 MHz. All signals were singlets unless noted otherwise, with chemical shifts reproducible to ±0·005 ppm.
[b] Impossible to resolve from **1** and **3**.
[c] Pyridinium salt.

Table 2. Acetylation products from the isomers of **1** as determined by ^{1}H NMR

Diol	Amount (mmol)[c]	Ac_2O (mmol)[c]	r	Pyridine (mmol)[c]	Observed product mixture[a] (Predicted[b]) f_1	f_2	f_3	Av. deviation (%)
p-**1**	0·207	0·231	1·12	0·220	0·18 (0·195)	0·45 (0·493)	0·37 (0·311)	12
p-**1**	0·216	0·235	1·09	0·260	0·22 (0·208)	0·48 (0·496)	0·30 (0·296)	3
m-**1**	0·172	0·161	0·94	0·354	0·22 (0·283)	0·50 (0·498)	0·28 (0·219)	17
m-**1**	0·220	0·257	1·17	0·375	0·16 (0·174)	0·44 (0·486)	0·40 (0·340)	12
m-**1**	0·219	0·266	1·22	0·405	0·16 (0·154)	0·46 (0·477)	0·38 (0·369)	4
o-**1**	0·230	0·245	1·06	0·417	0·37 (0·221)	0·55 (0·498)	0·07 (0·281)	51
o-**1**	0·261	0·307	1·18	0·570	0·35 (0·168)	0·52 (0·484)	0·12 (0·348)	60
o-**1**	0·248	0·269	1·09	0·422	0·30 (0·208)	0·55 (0·496)	0·15 (0·296)	35
o-**1**	0·120	0·176	1·47	0·344	0·37 (0·070)	0·46 (0·390)	0·16 (0·540)	172

[a] From peak heights and integrals of the CH_2 signals (Table 1) at 300 MHz; precision ±0·02.
[b] Calculated with equations (1)–(3).
[c] Total volume *ca* 0·5 ml, with acetone-d_6 as solvent.
[d] Average absolute deviation as a percentage of predicted value.

predicted from equations (1)–(3) and the value of r. Not only is this consistent with the expectation that the two hydroxyl groups in *p*-**1** *are* independent, but it also affords confidence in the validity of equations (1)–(3) and the assumptions leading to them.

The behavior of *m*-**1** was equally well predicted by the independent groups model, exhibiting average deviations of 4–17% in three runs. However, *o*-**1** gave different results. The data in Table 2 demonstrate a greater average deviation between predicted and observed product fractions, viz. 35–172% in four runs. There was consistently more *o*-**1**, less *o*-**3** and more *o*-**2** present in the reaction mixture than predicted by the independent groups model. The reasons for this are discussed below.

Kinetics

The product ratio results for *p*-**1** and *m*-**1** support the validity of the independent functional groups model, and provide semi-quantitative information about the ratio k_2/k_1. However, direct determination of the values of k_1 and k_2 was essential in order to determine whether a k_2/k_1 ratio other than 0·5 was due to a change in k_2, k_1 or both.

The exact mechanism for acetylation of nucleophilic substrates with Ac_2O–pyridine or similar reagents (AcCl–DMAP[8a] or AcCl–tertiary amine[8b]) (Ac = CH_3CO) in aprotic media is not fully understood. There are three different mechanistic schemes which can occur competitively in some cases:[8c–e] (1) general base catalysis[8i,j]; (2) nucleophilic catalysis (via *N*-acetylpyridinium ion);[8f,g] and (3) merged mechanisms.[8b,h] For the Ac_2O–pyridine system in tetrahydrofuran (THF), it is unlikely that *N*-acetylpyridinium ion is formed[8c] and it is believed that general base catalysis is involved.[8c,j] However, in many of these studies the rate equation is found to be complex.[8k]

Initially, a kinetic study was performed with benzyl alcohol (**4**) to find the optimum conditions for the acetylation reaction. The solvent was changed to anhydrous THF, and the analytical technique used was gas chromatography (GC).

The acetylation of **4** in THF is extremely slow in the absence of pyridine, with a second-order rate constant of *ca* 1×10^{-4} l mol^{-1} min^{-1} at 35·5 °C (Table 3, run 1). For given initial concentrations of **4** and Ac_2O, the rate constant increases linearly with increase in pyridine concentration (see Table 3, runs 1–13, and Figure 1). At a given pyridine concentration, all kinetic runs exhibited cleanly linear pseudo-second-order kinetics (first order in both **4** and Ac_2O) to at least 80% reaction (with correlation coefficients of $\geqslant 0{\cdot}996$). This was true even when less than 1 equivalent of pyridine was initially present, demonstrating that the activity of pyridine was not significantly affected by the acetic acid generated during the reaction. These results indicate that the reaction is adequately described by the pseudo-second-order rate law $k_{obs}[\mathbf{4}][Ac_2O]$, where $k_{obs} = k[pyr]$, with [pyr] constant for a given run.

The value of k_{obs} was also sensitive to concentration and medium effects. For example, at a given pyridine concentration, doubling the concentration of either reactant caused a *ca* 5% increase in k_{obs} (compare runs 5–7 with runs 14 and 15). When the concentrations of both reactants were doubled, there was a 25% increase in k_{obs} (compare runs 5–7 with runs 20–24). Whether these rate increases simply reflect an increase in the net dielectric constant of the medium, or the ability of **4** to serve as a weak general base, is not yet known (see Discussion). However, a threefold increase was observed when the solvent was changed from THF to the slightly more polar chloroform (runs 27 and 28) (the E_T solvent polarity values of chloroform and THF are 39·1 and 37·4, respectively[9]).

It is clear from the above results that in order to

Table 3. Rate constants for acetylation of **4**, **5** and **6** at 35·5 °C

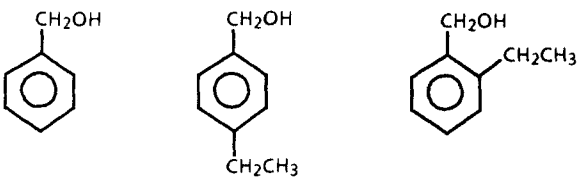
Compound	Run No.	Solvent	[**4**]$_0$(M)	[Ac_2O]$_0$(M)	[Py]$_0$(M)	k_{obs} (10^{-3} l mol^{-1} min^{-1})	k[a] (10^{-3} l^2 mol^{-2} min^{-1})
4	1	THF	0·544	0·736	0·00	0·1	—
	2	THF	0·344	0·450	1·20	11·1	9·3
	3	THF	0·270	0·297	1·76	17·8	10·1
	4	THF	0·317	0·436	3·24	29·9	9·2
	5	THF	0·252	0·302	3·50	31·4	8·97
	6	THF	0·285	0·302	3·51	31·0 $k_{obs} = 31·2 \pm 0·2$	8·83 $k = 8·91 \pm 0·07$
	7	THF	0·258	0·332	3·50	31·3	8·94
	8	THF	0·313	0·428	3·97	35·0	8·8
	9	THF	0·262	0·295	5·25	51·2	9·8
	10	THF	0·273	0·367	5·29	41·8	7·9
	11	THF	0·251	0·347	5·47	43·3	7·9
	12	THF	0·212	0·291	6·56	58·7	8·9
	13	THF	0·249	0·295	7·00	67·1	9·6
	14	THF	0·515	0·295	3·52	32·7	9·3
	15	THF	0·259	0·597	3·50	32·5	9·3
	16	THF	0·460	0·628	0·46	7·5	16·3
	17	THF	0·494	0·657	0·93	12·5	13·4
	18	THF	0·470	0·640	1·21	14·6	12·1
	19	THF	0·406	0·555	2·47	24·3	9·8
	20	THF	0·500	0·600	3·50	34·7	9·9
	21	THF	0·484	0·646	3·50	44·6	12·7
	22	THF	0·451	0·580	3·50	38·8 $k_{obs} = 38·9 \pm 3·7$	11·1 $k = 11·1 \pm 1·0$
	23	THF	0·481	0·607	3·50	37·0	10·6
	24	THF	0·484	0·606	3·50	39·6	11·3
	25	THF	0·924	1·053	3·50	46·3	13·2
	26	THF	0·764	0·999	2·67	34·6	13·0
	27	$CHCl_3$	0·189	0·290	1·26	34·5	27·4
	28	$CHCl_3$	0·153	0·238	2·07	52·1	25·2
5	1	THF	0·256	0·317	3·51	34·1	9·7
	2	THF	0·255	0·299	3·51	32·4 $k_{obs} = 33·1 \pm 0·9$	9·2 $k = 9·4 \pm 0·3$
	3	THF	0·252	0·301	3·51	32·8	9·3
6	1	THF	0·264	0·319	3·50	27·3	7·8
	2	THF	0·274	0·304	3·50	28·7 $k_{obs} = 27·9 \pm 0·7$	8·2 $k = 8·0 \pm 0·2$
	3	THF	0·254	0·301	3·50	27·8	7·9

[a] $k = k_{obs}/[pyr]$.

make meaningful comparisons between kinetic data for different substrates, it is necessary to keep the initial concentrations of substrate, acetic anhydride and pyridine within comparable ranges. With initial concentrations in the range of [4] ≈ 0·25 M, [Ac_2O] ≈ 0·30 M and [pyr] ≈ 3·5 M, the value of k is $(8·91 \pm 0·06) \times 10^{-3}$ l^2 mol^{-2} min^{-1} at 35·5 °C. Insofar as is possible, these same concentration ranges were used for all subsequent kinetic determinations.

For the purpose of establishing the effects (both steric and perhaps electronic) of a simple remote alkyl group on the acetylation of benzyl alcohol, we also measured the rate for the *para*-ethyl (**5**) and *ortho*-ethyl (**6**) derivatives of **4**. The results are also given in Table 3.

The acetylation kinetics for the isomers of **1** were, of course, far more complicated than those with **4**, **5** and **6** because consecutive/competitive pseudo-second-order reactions are involved. Fortunately, there are algorithms[10a–d] for extracting the observed second-order rate constants for each step ($k_{1_{obs}}$ and $k_{2_{obs}}$), provided that the concentrations of **1**, **2** and **3** are all known as a function of time (see Experimental). The method we chose led directly to $k_{1_{obs}}$ and the ratio $k_{2_{obs}}/k_{1_{obs}}$ (hereafter labelled K), from which $k_{2_{obs}}$ can be calculated. To test the validity of this mathematical method, a direct determination of $k_{2_{obs}}$ for ***p*-1** was made starting with authentic ***p*-2**. This value agreed exactly with the value obtained independently from



4 **5** **6**

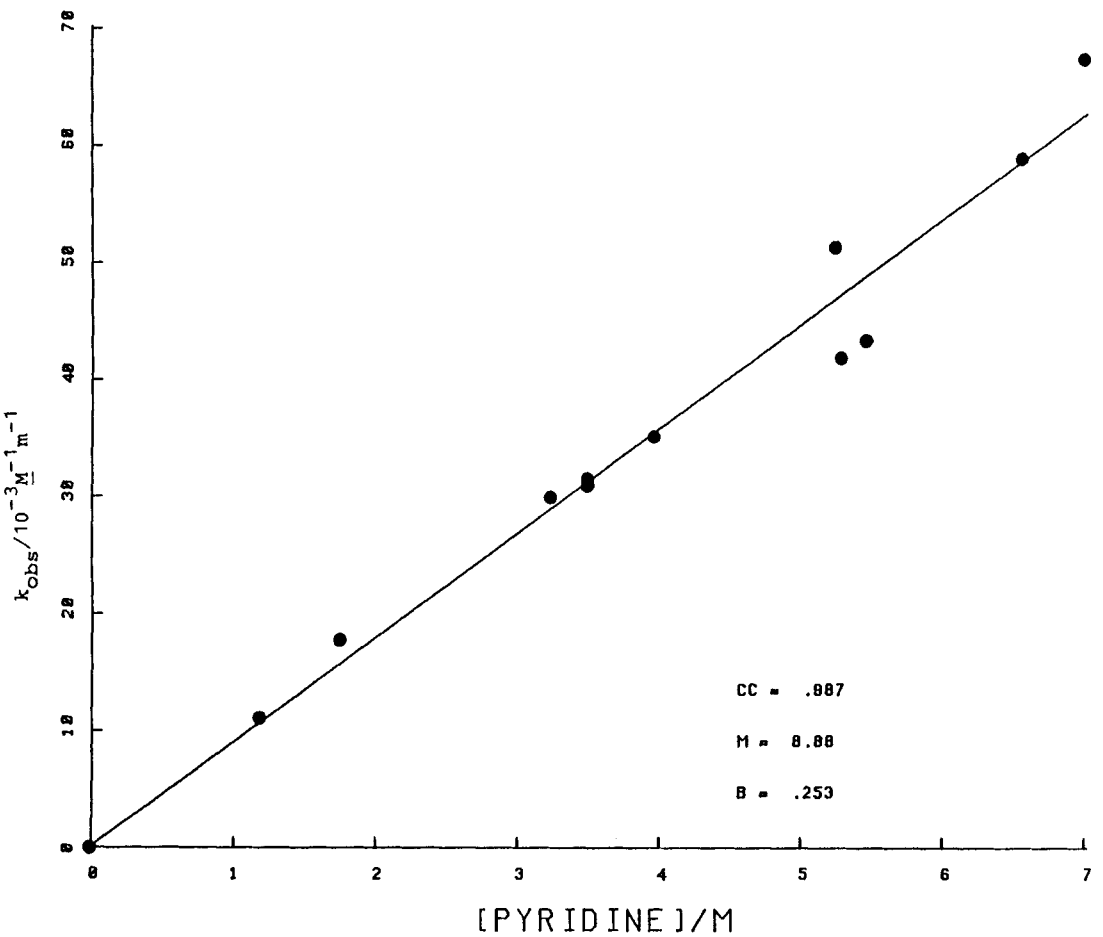
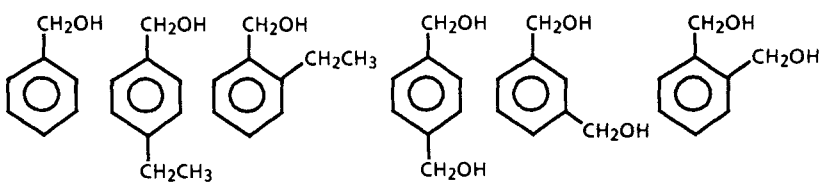


Figure 1. Effect of pyridine concentration on the pseudo-second-order rate constant for acetylation of **4**

$k_{1_{obs}}$ and K (Table 4). As with **4**, **5** and **6**, the values of the third-order rate constants k_1 and k_2 were generated by dividing each observed pseudo-second-order rate constant by the concentration of pyridine. The kinetic results for all three isomers of **1** are summarized in Table 4. For each kinetic run, the final product ratios were also determined by GC analysis at time = ∞, and were compared with predicted values from the independent groups model.

Below, the average rate constants for each compound



	4	5	6	p-1	m-1	o-1
$k_{(1)rel}$	1.00	1.05	0.90	2.40	2.45	1.78
k_{2rel}	---	---	---	1.31	1.27	1.08
$K = k_2/k_1$	---	---	---	0.55	0.52	0.61

Table 4. Kinetic and product ratio data for the isomers of **1**[a]

Compound	Run No.	k_1 [b]	K	k_2 [b]	r	f_{X_2} [c]	f_{XP} [c]	f_{P_2} [c]	Av. deviation (%)
p-**1**	1	20·9	0·529	11·1	1·197	0·155 (0·161)	0·456 (0·481)	0·389 (0·358)	5·9
	2	23·0	0·541	12·4	1·200	0·164 (0·160)	0·449 (0·480)	0·387 (0·360)	5·5
	3	20·9	0·545	11·4	1·532	0·044 (0·055)	0·330 (0·359)	0·626 (0·586)	11·6
	4	20·7	0·578	12·0	1·213	0·162 (0·155)	0·439 (0·477)	0·399 (0·368)	7·0
	Av.	21·4 ± 1·1	0·548 ± 0·021	11·7 ± 0·6[d]					
	5[e]	28·1	0·554	15·6	0·598	0·483 (0·491)	0·413 (0·419)	0·104 (0·0894)	6·6
	6[e]	27·4	0·553	15·2	0·598	0·491 (0·491)	0·410 (0·419)	0·0989 (0·0894)	4·2
	Av.	27·8 ± 0·5	0·554 ± 0·001	15·4 ± 0·3					
	7[f]	22·8	0·560	12·8	2·42				
	8[f]	20·6	0·560	11·5	2·38				
	Av.	21·7 ± 1·6	0·560	12·2 ± 0·9					
m-**1**	1	21·3	0·513	10·9	1·210	0·144 (0·156)	0·455 (0·478)	0·401 (0·366)	7·4
	2	21·7	0·531	11·5	1·342	0·0911 (0·108)	0·423 (0·442)	0·486 (0·450)	9·3
	3	22·4	0·520	11·6	1·214	0·150 (0·155)	0·457 (0·477)	0·393 (0·368)	4·7
	Av.	21·8 ± 0·6	0·521 ± 0·009	11·3 ± 0·4					
o-**1**	1	16·1	0·600	9·66	1·388	0·0915 (0·0936)	0·354 (0·425)	0·554 (0·482)	11·2
	2	15·9	0·607	9·65	1·140	0·200 (0·185)	0·447 (0·490)	0·353 (0·325)	8·5
	3	15·8	0·609	9·62	1·223	0·155 (0·151)	0·428 (0·475)	0·417 (0·374)	8·0
	Av.	15·9 ± 0·2	0·605 ± 0·005	9·64 ± 0·02					

[a] $[\mathbf{1}]_0 \approx 0{\cdot}25$ M; $[Ac_2O]_0 \approx 0{\cdot}30$ M; $[pyr] \approx 3{\cdot}5$ M.
[b] Rate constants k ($= k_{obs}/[pyr]$) are in units of 10^{-3} l^{2}mol^{-2}min^{-1} at $T = 35{\cdot}5 \pm 0{\cdot}1$ °C. $K = k_2/k_1$. Error limits are standard deviations.
[c] Product fractions in parentheses are calculated from equations (1)–(3). See Table 2.
[d] Acetylation of pure *p*-**2** exhibited an identical k_2 value of $1{\cdot}17 \times 10^{-2}$ l^{2}mol^{-2}min^{-1}.
[e] $[\mathbf{1}]_0 \approx 0{\cdot}50$ M; $[Ac_2O]_0 \approx 0{\cdot}30$ M; $[pyr]_0 \approx 3{\cdot}5$ M.
[f] $[\mathbf{1}]_0 \approx 0{\cdot}25$ M; $[Ac_2O]_0 \approx 0{\cdot}60$ M; $[pyr]_0 \approx 3{\cdot}5$ M.

are expressed relative to the rate for benzyl alcohol. Note that **5** undergoes acetylation only 5% (just outside the experimental error limits) faster than **4**, suggesting a very modest increase in the nucleophilicity of the hydroxyl group in **5** by the remote electron-releasing ethyl group. More significantly, an *ortho*-ethyl group causes only a modest 10% *decrease* in the acetylation rate, an effect which is probably steric in nature.

With *p*-**1**, the final product ratios were once again in good agreement with predictions. Further, the experimentally determined ratio k_2/k_1 is 0·548, in reasonable agreement with the value of 0·5 assumed by the independent functional groups model. However, k_2 for *p*-**1** is 25% greater than the k value for **5**. Similarly, k_1 is 2·29 times greater than the k value for **5**. Hence both k_2 and k_1 are accelerated relative to the monofunctional model compound, with k_2 accelerated more. Like the reaction of **4**, the acetylation of *p*-**1** was subject to medium effects. Doubling the concentration of acetic anhydride led to a slight increase in k_1, and doubling the concentration of *p*-**1** increased both k_1 and k_2 by *ca* 30% (Table 4).

The *meta* isomer behaved almost identically with the *para* isomer, with $k_2/k_1 = 0{\cdot}521$ and values of k_1 and k_2 within 3% of those for *p*-**1**. Additionally, the final product ratios were well correlated with the independent groups model.

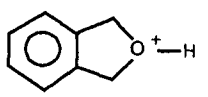
Our initial work with the *ortho* isomer provided a complication not observed with the other two isomers, viz. an inadequate mass balance; that is, although a known amount of acetic anhydride has been completely consumed, there was appreciably less of products *o*-**2** and *o*-**3** than should have been formed. Eventually it was found that, unlike the *para* and *meta* isomers, crystalline *o*-**1** was hydrated, and the water consumed an equivalent amount of the anhydride. This problem, which also accounted for the behavior of *o*-**1** in the NMR experiments (see above), was solved by careful sublimation of the substrate.

Anhydrous *o*-**1** was kinetically well behaved and its final product ratios showed good agreement with predictions. However, both its rate constants were lower than those of the *para* and *meta* isomers, and the ratio k_2/k_1 was 0·605. Interestingly, the value of k_2 was 20% greater than the k value for **6** whereas k_1 was exactly twice the k value for **6**. Hence the *ortho* isomer shows a modest anomaly.

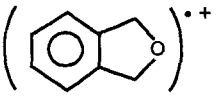
Mass spectral analyses of 1 and 3

In an attempt to correlate the esterification results with other properties of the isomers of **1**, we examined the electron impact mass spectra of the isomers of **1** and **3** under comparable conditions. The three isomers of diester **3** all gave similar spectra (Table 5, see experimental section), dominated by absent molecular

ions, and fragments from loss of acetate, acetic acid, acetic acid + acetyl and formation of acetyl. By contrast, the three isomers of diol **1** gave different spectra (Table 6, see experimental section). For example, whereas the *para* and *meta* isomers of **1** exhibited either molecular ions or $(M-H)^+$ ions, the *ortho* isomer showed neither. Instead, the *ortho* isomer's most significant fragments resulted from loss of OH and water, to which we assign structures **7-H** and **7**, respectively. Such structures are impossible with the *para* and *meta* isomers. Similarly, whereas the *para* and *meta* isomers showed fragments involving loss of CH_2OH, the *ortho* isomer did not.



7-H



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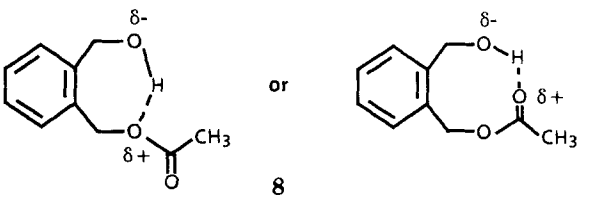
DISCUSSION

The good correlation of the final acetylation product ratios from the three isomers of **1** with predictions based on the independent functional groups model [equations (1)–(3)] implies that the model is valid and can indeed be used to confirm the absence of dramatic intramolecular interactions between equivalent functional groups. Specifically, the present results show that the hydroxyl groups in each isomer of **1** and **2** function essentially independently of other functional groups in the molecule. It is nonetheless clear that the model is not highly sensitive to modest departures of K $(= k_2/k_1)$ away from 0·5; these must be determined by direct measurement of the actual rate constants. Armed with these rate constants, it is possible to detect even relatively small departures from independent behavior which are not obvious from product ratio data alone.

A comparison between the rate constants in Tables 3 and 4 reveals only modest departures from expectations based on the independent groups model. The rate constants k_1 and k_2 for the *para* and *meta* isomers of **1** and **2** are nearly identical, and 14–25% greater than expectations based on the ethyl-substituted model **5** under comparable conditions. Because this modest increase is unlikely to be steric or electronic in nature, we attribute it to the same type of concentration-dependent medium effect exhibited by **4**. That is, **1** and **2** (each with two oxygenated groups) should be expected to have a greater effect on the net dielectric constant and general basicity of the medium than an equal concentration of **5** (with just one oxygenated group).

The *ortho* isomer, where some degree of intramolecular interaction was expected, exhibited the smallest rate constants and the largest k_2/k_1 ratio of the three isomers. Steric effects certainly play some role in this, as evidenced by the 14% rate *decrease* on changing from **5** to **6**. Nonetheless, steric effects alone cannot be entirely responsible for the modest anomaly presented by the *ortho* system, since ***o*-2** is 20% *more* reactive than **6**. Part of this increase may be due to the fact that a methyl group is slightly more sterically demanding than an acetoxy group (which is comparable to a hydroxyl group).[11] However, the acetoxymethyl group in ***o*-2** must present at least some steric hindrance to the reaction, yet ***o*-2** reacts even *faster* than **4** and **5**, where there is no *ortho* substituent. It might seem tempting to attribute this increase in reactivity of ***o*-2** to intramolecular hydrogen bonding as in **8**. However, structures



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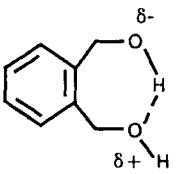
such as these are probably not important because of the low basicity of the ester group [the pK_a of $RC(=\dot{O}H)OR$ is $-6{\cdot}5$ whereas that of $RCH_2\dot{O}H_2$ is -2],[12] and the fact that such bridging hydrogens would be less available to pyridine during the rate-limiting step of acylation. Instead, we attribute the increased reactivity of ***o*-2** to the fact that its effect on the polarity of the medium should be greater than those for **4**, **6**, ***p*-1** or ***m*-1** because the rotationally averageed polar moments of the two functional groups are more nearly aligned, making for a larger net dipole moment.

By contrast, the reactivity of ***o*-1** at first glance seems perfectly in line with expectations, since it is exactly twice as reactive as **6**. However, it can be argued that ***o*-1** should be *more* than twice as reactive as **6**, because the second hydroxyl group in ***o*-1** is smaller than methyl in **6**, and because ***o*-1** should exhibit the same increased dipole moment as ***o*-2**. However, since a hydroxyl group is *ca* $10^{2{\cdot}5}$ more basic than an ester group,[12] hydrogen-bonded structures such as **9** or **10** are likely to be more important than hydrogen-bonded structures were for ***o*-2**. As stated above, such structures should reduce the reactivity of ***o*-1** relative to twice the value for ***o*-2**, and this is observed.



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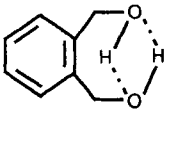

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CONCLUSIONS

We have demonstrated that the acetylations of ***p*-**, ***m*-** and ***o*-1** proceed in a manner essentially consistent with

the independent group model. In all cases K ($=k_2/k_1$) is in the range 0·5–0·6, with the largest value exhibited by the *ortho* isomer. The individual rate constants k_2 and k_1 for the *para* and *meta* isomers are significantly greater than k and $2k$ for monofunctional model compound **5**. Those for the *ortho* isomer are the least of the three isomers, but equal to $2k$ for model compound **6**. The lower reactivity of the *ortho* isomer can be attributed to a combination of steric effects and intramolecular hydrogen bonding in the diol, which decreases the reactivity of its OH group.

EXPERIMENTAL

General. The instruments used included the following spectrometers: IBM NR-80, Bruker AC250 and General Electric (formerly Nicolet) NT-300 (NMR); Hewlett Packard Model 5995 (MS) and Perkin-Elmer 1600 FT-IR (IR). A Hewlett Packard Model 700 gas chromatograph with disk integrator and thermal conductivity detector was used. The GC analyses were performed with a 6 ft × 1/8 in i.d. column packed with 10% UC W-98 on Chromosorb S, 80–100 mesh, except for the acetylation of **5**, where an 8 ft × 1/8 in i.d. column packed with 5% Carbowax 20M on Chromosorb W, 80–100 mesh, was used. The relative retention times were diol (or alcohol) < monoacetate (or acetate) < diacetate when the UC W-98 column was used, and acetate < alcohol when the Carbowax column was used. The GC response factor for each ester product (E) relative to the starting alcohol (A) was determined by GC analysis of standard solutions, and application of the equation: Rf_E = (moles of E/moles of A) (signal area for A/signal area for E). For the 5% Carbowax 20M column, the response factors were: benzyl acetate, 0·79; ***P*-2**, 0·78; ***P*-3**, 0·66; 4-ethylbenzyl acetate, 0·78 (0·71 for the UC W-98 column). Because thermal conductivity detection was used, it was assumed that the response factors of the *meta* and *ortho* isomers of **1** were the same as those of the *para* isomer.

Materials. The three isomers of **1** were supplied by Aldrich Chemical; ***P*-1** was recrystallized from chloroform and ***o*-1** was sublimed prior to use. The *ortho*,[13a] *meta*[13b] and *para*[13c] isomers of **3** were prepared directly from the diols by standard methods. Analytical-reagent grade pyridine was refluxed and distilled over KOH according to Ref. 14. THF was freshly distilled over potassium. All glassware was oven-dried. Compound **5** was supplied by Aldrich Chemical and was distilled under high vacuum prior to use.

Product mixture analysis by NMR. The desired diol (**1**) was weighed by difference into a dried NMR tube, then dissolved in 0·4 ml of dry acetone-d_6. Pyridine was added by syringe, and its mass determined by difference weighing. Finally, the desired amount of freshly distilled acetic anhydride was added via a syringe, its mass determined by difference weighing and the tube sealed with Parafilm. The resulting solution was shaken thoroughly and the time started. At intervals, the ^{1}H NMR spectrum of the reaction mixtures was recorded.

Kinetic method. To a 2 ml volumetric flask, containing *ca* 1 ml of THF and the desired exact amounts of the diol (or benzyl alcohol) and pyridine, was added dropwise the acetic anhydride, whose mass was determined by difference weighing. The volumetric flask was filled to the mark with THF and the solution was transferred into a 5-ml two-necked round-bottomed flask fitted with a septum and a condenser with a drying tube on top. The flask was inserted in an oil-bath maintained at 35·5 ± 0·1 °C. Aliquot portions (1–3 μl) of the reaction mixture were analyzed by GC every 10–20 min until the reaction was *ca* 85% completed, then also after 24 h ($t = \infty$). Absolute concentrations of starting alcohol and (mono- and di-) acetate were determined from GC integrations (corrected for response factors) and the known initial concentration of the alcohol. The concentration of acetic anhydride was calculated from its known initial concentration, less the total amount of acetate product(s) formed. Thus, in the reactions of benzyl alcohol, $[Ac_2O] = [Ac_2O]_0 - [\text{benzyl acetate}]$, and for the diols, $[Ac_2O] = [Ac_2O]_0 - [2] - 2[3]$.

In the case of benzyl alcohol, the rate constant k_{obs} was determined as the slope of a plot of

$$\frac{1}{[Ac_2O]_0 - [4]_0} \ln\left(\frac{[4]_0[Ac_2O]}{[4][Ac_2O]_0}\right)$$

versus time. The value of k was determined by dividing k_{obs} by [pyridine].

In the case of the isomers of **1**, the graphical integration method of Widequist[10b,c] was used. For each timed aliquot (data point) the concentrations [**1**], [**2**], [**3**] and $[Ac_2O]$ were determined as described above. For each data point the values of $\ln([1]_0/[1])$ and θ (defined below and determined by graphical integration[10b,c]) were determined:

$$\theta = \int_0^t [Ac_2O]\, dt$$

The value of $k_{1_{obs}}$ was found as the slope of a linear plot of $\ln([1]_0/[1])$ versus θ (as abscissa). Then, for each data point, the value of K ($=k_{2_{obs}}/k_{1_{obs}}$) was determined iteratively from the equation[10b,d]

$$\frac{1}{K-1}\left[1 - \left(\frac{[1]}{[1]_0}\right)^{K-1}\right] - \frac{[2]}{[1]} = 0$$

The K value for a given run was the mean of the point-by-point K values. Finally, $k_{2_{obs}}$ was found by multiplying $k_{1_{obs}}$ and $k_{2_{obs}}$ by [pyridine].

Synthesis of p-bis(hydroxymethyl)benzene monoacetate and diacetate (p-2 and p-3). To a solution of 1·382 g of *p*-bis(hydroxymethyl)benzene (***p*-1**, 10·00 mmol) in 30 ml of THF were added dropwise 1·023 g of acetic anhydride (10·02 mmol) and 1·0 ml of pyridine. After stirring for 48 h at 25 °C the solution was analyzed by GC, and found to contain the expected diol : monoacetate : diacetate ratio of 1 : 2 : 1. The colorless crystals that appeared after rotary and high-vacuum evaporation of the solvent were partitioned in 20 ml of $CHCl_3$ and 20 ml of H_2O to separate most of the water-soluble ***p*-1**. The aqueous layer (pH = 6) was extracted with an additional 20 ml of $CHCl_3$, the organic layers were combined and the solvent was evaporated. The remaining pale yellow liquid (1·389 g) was subjected to flash column chromatography[15] (17 cm × 0·30 cm i.d. column, 40% EtOAc–60% ligroin as eluent) to give pure ***p*-2** and ***p*-3** as colorless oils and a small amount of ***p*-1** as colorless crystals. The ***p*-2** was crystallized by adding a small piece of dry-ice, and then distilled/sublimed (40–45 °C, 0·1 mm Hg) to give 0·725 g (40·2%) of ***p*-2** as colorless crystals, m.p. 35–37·5 °C. ^{1}H NMR ($CDCl_3$/TMS): δ 2·085 (s, 3H), 4·676 (s, 2H), 5·088 (s, 2H), 7·347 (s, 4H). IR (CCl_4): 3615 (w), 3525 (br), 3467 (w), 2954 (w), 2876 (w), 1744 (vs), 1422 (w), 1379 (m), 1361 (m), 1227 (vs), 1029 (m), 1019 (m), 967 (w), 818 (w), 809 (w) cm^{-1}. MS: *m/z* 181 (M + H), 180 (M^+), 149, 138, 121, 120, 119, 108, 107, 93, 92, 91 (base), 89, 79, 78, 77, 65, 63, 51, 50, 43, 39.

The ***p*-3** was crystallized by adding a small piece of dry-ice and was recrystallized from EtOH–H_2O to give colorless crystals (0·385 g, 17·3%), m.p. 47·5–50 °C (lit: 47 °C,[16a] 45–49 °C,[13c] 49–50 °C[16b]). ^{1}H NMR ($CDCl_3$/TMS): δ 2·091 (s, 6H), 5·100 (s, 4H); 7·348 (s, 4H). MS: see Table 5.

Table 5. EI mass spectra of the three isomers of **3**[a]

	Relative abundance (%)			
m/z	*para*	*meta*	*ortho*	Assignment
163	12	30	6	M – OAc
162	20	39	35	M – HOAc
121	10	18	13	
120	100	100	100	M – (Ac + HOAc)
119	25	30	44	
103	7	13	5	
92	10	35	6	
91	48	59	29	
89	17	25	7	
78		11	5	
77	16	27	13	
65	9	20	12	
63	8	15	6	
57	7			
51	11	17	8	
45		17		
43	149	244	168	Ac
41		10		

[a] For comparison purposes, the peak at *m/z* = 120 was set at 100%; Ac = CH_3CO.

Table 6. EI mass spectra of the three isomers of **1**

m/z	*para*	*meta*	*ortho*	Assignment
138	—	39·5	—	$M^{+\cdot}$
137	49	—	—	M – H
136	90	—	—	M – H_2
121	—	—	58	M – OH
120	—	—	100	M – H_2O
119	—	—	92	
107	100	39	—	M – CH_2OH
105	35	—	—	
92	—	46	19	
91	—	71	99·5	*m/z* 107 – OH
90	—	—	9	
89	50	—	13	
79	59	—	19·5	
78	19	100	—	
77	91	74	35	Ph^+
65	—	—	25	
64	—	—	12·5	
63	—	38	—	
51	36	27	—	
50	—	18	—	

Synthesis of 2-ethylbenzyl alcohol (6). A mixture containing 0·415 g (17·1 mg-atom) of magnesium, 2·0 ml (14·5 mmol) of 1-bromo-2-ethylbenzene and 15 ml of diethyl ether was refluxed for 2 h. Formaldehyde vapor generated in another flask by heating 1·2 g of paraformaldehyde (previously dried over P_2O_5) at 180 °C was carried into this reaction flask by a slow stream of nitrogen through a glass tube terminating about 1 cm above the surface of the solution. The mixture was stirred for 30 min, then it was quenched with 10 g of ice and 10 ml of 50% H_2SO_4.[17] The layers were separated and the aqueous layer was saturated with NaCl and extracted with 20 ml of diethyl ether. The combined ether layers were dried with K_2CO_3, the solvent was evaporated and the resulting pale yellow oil was distilled twice under high vacuum to give 0·85 g (40% yield) of **6**.[18] ^{1}H NMR ($CDCl_3$/TMS): δ 1·24 (t, 3H), 1·67 (s, 1H), 2·70 (q, 2H), 4·73 (s, 2H), 7·15–7·50 (m, 4H).

Synthesis of 4-ethylbenzyl acetate. The reaction mixture from the three experiments for the determination of the rate of acetylation of **5** were combined and the volatile solvents were rotary evaporated. Distillation of the residue under reduced pressure (0·1 mm Hg) gave 0·112 g of 4-ethylbenzyl acetate (47% yield) as a colorless liquid whose ^{1}H NMR spectrum matched the previously reported one.[19]

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