Tetrahedron Vol. 40, No 4, pp. 785 to 791, 1984
Printed in Great Britain

0040-4020/84 $3.00 + 00

SELECTIVE FUNCTIONALISATION—7

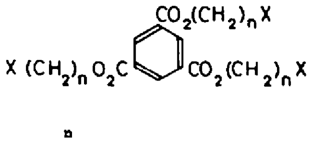
CHLORINATION OF AROMATIC COMPOUNDS IN THE PRESENCE OF TENTACLE MOLECULES WITH PYRIDINIUM HEAD GROUPS

D. I. ROBINSON, D. C. SHERRINGTON and C. J. SUCKLING*
Department of Pure and Applied Chemistry, University of Strathclyde, 295, Cathedral Street, Glasgow G1 1XL, Scotland

(*Received in the UK* 21 *April* 1983)

Abstract—tris-Pyridiniumalkyl triesters of benzene-1, 3, 5-tricarboxylic acid with 3, 6 and 11 carbon atoms in the alkyl chain interact with aromatic substrates, phenol, anisole, diphenyl ether and naphthalene in a manner dependent upon the structure of the substrate. Thus all three tentacle molecules interact with phenol through the pyridinium head group as shown by ^{1}H NMR (250 MHz) and confirmed by inhibition of chlorination of the bound phenol. The remaining substrates interact but away from the head group; chlorination is also inhibited. In these cases, a contributor to the low reactivity of the substrates to chlorination in the presence of the tentacle molecules is shown to be the unexpected inactivation of the chlorinating agent, t-butyl hypochlorite, by the tentacle molecules.

In recent years, considerable effort has been expended in the development of chemical systems capable of mimicking the selectivity of enzymes.[1-3] Our first investigations in this field led to the discovery that iron complexes of N-alkyl-2-hydroxybenzylamines caused selective hydroxylation of some aromatic compounds; the origin of the selectivity was considered to be the binding of the substrate into a pocket made up of the two phenyl and two alkyl arms.[4] The amphiphilic nature of these control agents led us to investigate the behaviour of simple detergents in controlling substitution reactions and in some cases, we noted that the change in selectivity with detergent concentration levelled off at a detergent; substrate ratio of about 3 : 1.[5,6] Together, these observations suggested that it might be possible to achieve enzyme-like binding with molecules bearing as few as three "arms" and that such compounds might form the basis of useful selective functionalisation systems. Similar considerations of limiting molecular motion in micelles led Menger to synthesise the first reported example of a tentacle molecule, hexapus.[7] Tentacle molecules can be defined as a group of detergent molecules whose motion is restricted by attachment to a central framework. There are clearly many ways in which such molecules can be constructed and our studies to date have concentrated upon triesters of benzene - 1,3,5 - tricarboxylic acid bearing pyridinium head groups.[8] In this paper, we describe some chemical and spectroscopic properties of these molecules relating to their interactions with four simple aromatic substrates, phenol, anisole, diphenyl ether and naphthalene.



	X	n
1a	Cl	3
1b	py$^+$Cl$^-$	3
2a	Cl	6
2b	py$^+$Cl$^-$	6
3a	Br	61
3b	py$^+$Cl$^-$	11

RESULTS AND DISCUSSION

An advantage of the choice of trimesic acid as the central building block for tentacle molecules was the ease of synthesis of a series of structural variants. Thus treatment of trimesyl trichloride with the appropriate haloalcohol in the presence of triethylamine led to the triesters (**1a**–**3a**) which were converted into the required tentacle molecules (**1b**–**3b**) by heating with excess pyridine. Purification of the products was not simple and it was particularly important for chlorination studies that any bromide in the product was enchanged for chloride. Exchange with dilute hydrochloric acid was modestly successful for the C-11 compound **3b** but it is best to proceed via the alkyl chlorides.

Chlorination of phenol. The chlorination of phenol by *t*-butyl hypochlorite has proved useful in our studies of selective functionalisation because of the lack of complicating side reactions.[5,6] The first study of this reaction in the presence of tentacle molecules was carried out using the C-11 compound 3b.[8] It was found that in acetonitrile solution, the tentacle molecule caused a marked change in the chlorination pattern. In free solution, an ortho:para ratio of about 0.23 was obtained without appreciable polychlorination but in the presence of the tentacle molecule **3b**, the major product under these conditions was 2,4,6-trichlorophenol. Since an excess of phenol was used in these experiments, polychlorination suggested that some of the substrate was no longer accessible to the chlorinating agent.

In view of the electron deficient nature of the pyrindinium head group and the electron donating ability of phenol, it was probable that a contributor to the interaction of phenol with the tentacle molecule involved charge transfer in addition to the possibility of a binding pocket being formed by association of the long alkyl chains. In order to assess the contributions of the two

Table 1. Chlorination of phenol in the presence of tentacle molecules in acetonitrile solution

Compound	[Tentacle]	[PhOH]	[tBuOCl]	%Cl	2	4	2,4	2,6	2,4b
Chain length	mM	mM	mM	yield[a]	normalised %[b]				
1b 3	0	1.67	1.67	74	17	75	3	1	4
"	1.67	1.67	1.67	79	8	14	4	4	69
"	1.67	3.3	1.67	90	17	34	3	3	42
2b 6	3.15	3.15	3.15	64	16	50	7	3	24
"	3.15	6.30	3.15	62	18	47	7	2	26
3b 11	0	3.3	1.65	100	25	65	-	-	-
"	3.3	3.3	1.65	86	-	-	-	-	100
"	3.3	6.6	1.65	100	10	46	-	-	43

a based upon chlorinating agent consumed

b normalised % of total chlorinated products.

factors, we studied the effect of shorter chain analogues containing 6 (**2b**) and 3 (**1b**) carbon atoms. The results are reported in Table 1. It is apparent that the general pattern of behaviour of all three tentacle molecules was similar, that is, substantial polychlorination intruded especially at low substrate to tentacle molecule ratios. These observations suggest that the major interaction with phenol is with the head groups.

Support for the above conclusion comes from ^{1}H NMR studies at 250 MHz. As we have previously reported, the interaction of phenol with the tentacle molecule **3b** leads to a substantial change in the NMR spectrum.[8] The net result of the interaction was that the spectrum of phenol was transformed to appear very much as it does in micellar solution[5] that is, with the para triplet to higher field than the ortho doublet. However it is important to note that in the case of the tentacle molecules, the modified spectrum was produced not by a large upfield shift of the para proton resonance as in micellar solution, but by a substantial downfield shift of the ortho protons' resonance (Table 2). All three tentacle molecules showed interactions but the C-3 compound **1b** was significantly less effective than the others. In view of this result and the generally small shifts observed for micellar solutions of phenol in organic solvents,[5,6] it is most probable that the charge transfer interaction between phenol and the pyridinium head group is the cause of the alterations in the spectrum. Support for this conclusion comes from the NMR observation that phenol competed with iodide ion, which is well known to associate with pyridinium rings (Fig. 1). The deactivation of phenol to chlorination in the presence of tentacle molecules can thus be attributed to charge transfer interaction with the pyridinium ring: electron donation by phenol will clearly reduce its reactivity towards electrophilic reagents. The chlorination of phenol and its spectroscopic behaviour in acetonitrile solution therefore provide no evidence for the ability or otherwise of these tentacle molecules to

Table 2. Chemical shift changes (Hz) of protons of phenol in the presence of tentacle molecules in acetonitrile solution. Spectra measured at 250 MHz

Compound	[Tentacle]	[Phenol]	2,6	3,5	4
Chain length	mM	mM			
1b 3	3.3	33	5.2	4.3	5.4
"	3.3	3.3	5.2	4.3	3.0
2b 6	3.3	33	2.8	3.4	5.8
"	3.3	3.3	-3.0	5.2	8.5
3b 11	3.3	33	2.6	3.4	5.6
"	3.3	3.3	-3.0	6.5	7.4
"	26.6	26.6	-30.9	15.6	20.1

Over the concentration range 3-66 mM, the resonances of phenol alone were constant within ± 1 Hz.

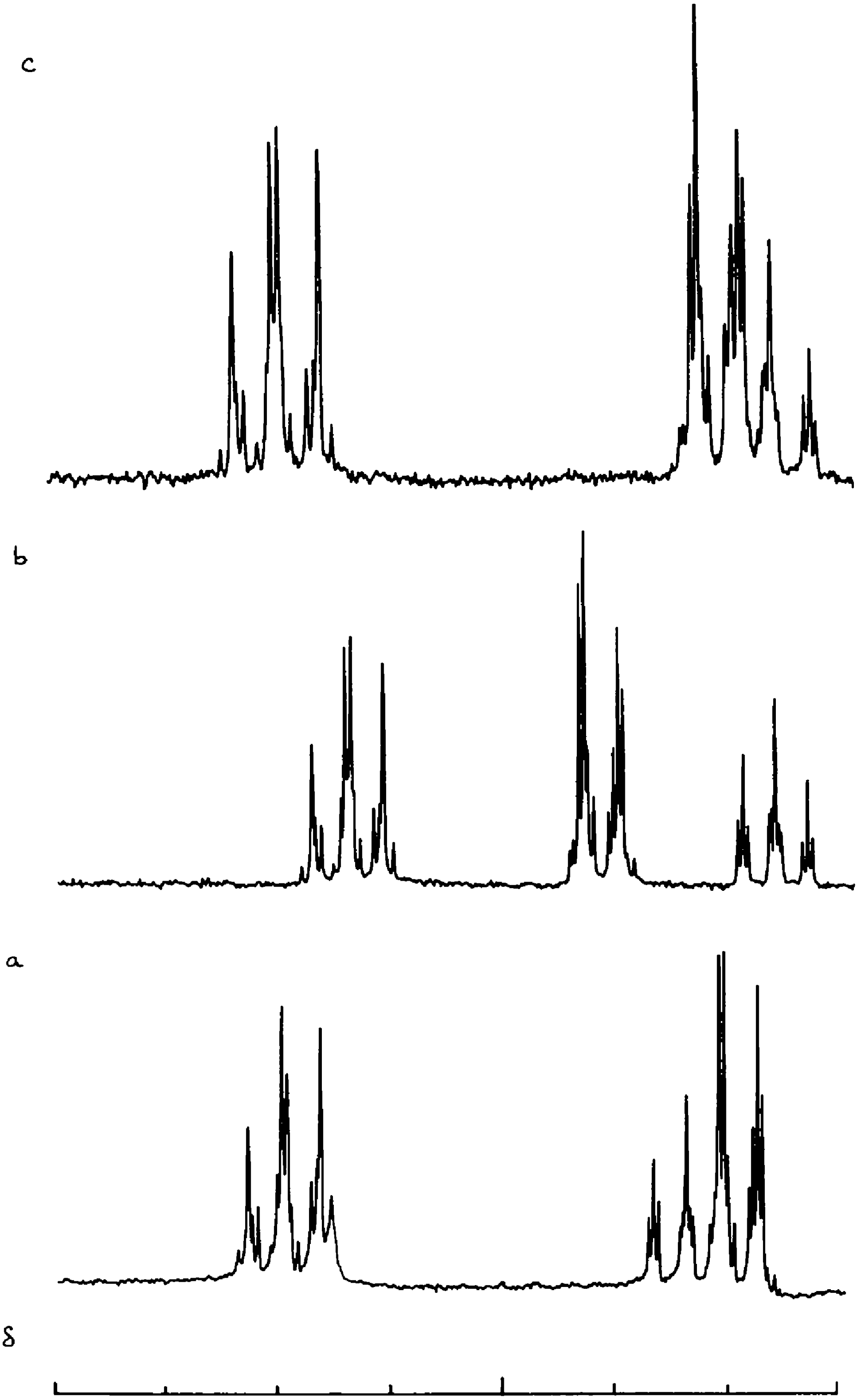


Fig. 1. 250 MHz spectra in CD$_3$CN of (a) phenol 26.6 mM, (b) phenol 26.6 mM + (**3b**) 26.6 mM and (c) phenol 24.8 mM + (**3b**) 24.8 mM + LiI 74.4 mM.

form binding pockets analogous to those of the iron complexes studied previously.[4] To investigate this matter, we turned to other substrates.

Chlorination of anisole. NMR experiments showed that only very small changes in the spectrum of anisole were produced in solutions of tentacle molecules (Table 3), and that anisole did not compete effectively with phenol for the electron deficient head groups. Anisole is less reactive than phenol to chlorination by *t*-butyl hypochlorite; under the conditions used, reactions with phenol were complete within 10 min but up to 16 h with anisole depending upon concentration of hypochlorite.

Table 3. Chemical shift changes (Hz) of protons of anisole in the presence of tentacle molecules in acetonitrile

Compound Chain length	[Tentacle]	[Anisole]	OMe	o	m	p
1b 3	3.8	3.8	0.6	0.6	2.6	1.8
2b 6	9.1	9.1	0.9	0.9	2.7	0.9
3b 11	26.3	26.3	2.0	2.6	2.9	2.4

The major product was 4-chloroanisole and the o:p-ratio was about 0.1 under the conditions used. In the presence of tentacle molecules (Table 4) chlorination was again inhibited, the most pronounced inhibition being produced by the C-11 compound **3b**. The rate of chlorination of anisole, being slower than that of phenol, was suitable for kinetic studies. However we found surprisingly that a substantial drop (*ca* 75%) in the concentration of chlorinating agent occurred within 4 min of adding t-butyl hypochlorite to a solution of the tentacle molecules, as shown by titration of samples with thiosulphate. The effect of this behaviour upon the chlorination reaction is indicated by the data in Table 4 which shows the product yields after only 3 min and after 16 hr. At low concentrations of chlorinating agent, little reaction occurred in the presence or absence of the tentacle molecules. However, higher concentrations of chlorinating agent, approximately equimolar with the substrate, led initially to enhanced chlorination in the presence of the tentacle molecules. Paradoxically it appears that the tentacle molecules exert an inhibiting effect upon the chlorination of phenol, but initially a catalytic one upon the chlorination of anisole.

The chlorination of diphenyl ether and naphthalene was inhibited by the presence of each of the tentacle molecules and NMR spectroscopy confirmed that these substrates did not compete with phenol for the pyridinium head groups. However, since these reactions were very slow and the tentacle molecules interact with the chlorinating agent, it is not possible to derive any useful information from the products formed in these reactions.

Interactions between reactants and tentacle molecules. The nature of the interaction of t-butyl hypochlorite with the tentacle molecules probably involves association of the hypochlorite with the electron deficient head group. Evidence consistent with this possibility comes from NMR measurements (Table 5a) which show that the protons of the pyridinium head groups moved upfield on the addition of t-butyl hypochlorite. No traces of acetone or other possible products of t-butyl hypochlorite decomposition were detected in the NMR experiment.

Under these conditions this interaction was quite unexpected and must be considered in any rationalisation of the behaviour of the tentacle molecules in these reactions. We suggest that the dominant interaction is between electron donors such as phenols and t-butyl hypochlorite and the pyridinium head group. Thus with phenol as substrate, the inhibition of chlorination is a consequence of the charge transfer interaction between phenol and pyridinium head group, a conclusion con-

Table 4. Chlorination of anisole in the presence of tentacle molecules in acetonitrile solution

Compound	[Tentacle]	[Anisole]	[tBuOCl]	% chlorination	
Chain length	mM	mM	mM	at 3 min.	16 h
-	-	5.0	2.5	8.6	29.4
-	-	5.0	5.0	35.2	100
1b (3)	4.4	5.0	2.5	-	14.1
"	4.4	5.0	5.0	-	84.6
"	2.8	5.0	2.5	1.4	-
"	2.8	5.0	5.0	46.6	-
2b (6)	6.1	5.0	2.5	-	20.3
"	6.1	5.0	5.0	-	84.6
"	5.4	5.0	2.5	11.0	-
"	5.4	5.0	5.0	59.8	-
3b (11)	6.2	5.0	2.5	-	4.1
"	6.2	5.0	5.0	60.4	63.2

Table 5. The interactions of molecules other than phenol with tentacle molecules (3b) in acetonitrile solution

a tBuOCl

[tBuOCl] mM	[3b] mM	time min	Chemical Shift Change (Hz) 2,4	3,5	4	Ar
78	26	10	54.8	-0.5	3.3	-5.8
78	26	210	56.5	-0.2	9.2	-6.0

b Chlorophenols

[Chlorophenol]	mM	[3b] mM			
2-	3.3	3.3	H^4 12.6	H^5 6.5	H^6 7.8
4-	3.3	3.3	$H^{2,6}$ -26.4	$H^{3,5}$ 9.5	
2,6-	20.3	22.9	$H^{3,5}$ 6.6	H^4 6.1	
2,4-	2.4	2.5	H^3 4.2	H^5 4.2	H^6 -27.1
2,4,6-	3.3	3.3	$H^{3,5}$ -2.4		

sistent with NMR observations. Such an interaction could leave some molecules of phenol unassociated and hence susceptible to chlorination. Polychlorination giving high proportions of 2,4,6-trichlorophenol was observed as has been described. NMR observations (Table 5b) indicate that mono- and dichlorophenols also interact with the pyridinium head group. Of the chlorophenols, the interaction of 2,4,6-trichlorophenol and 2,6-dichlorophenol are the weakest. With anisole as substrate, the head groups are comparatively free for association with a large proportion of the available t-butyl hypochlorite, and consequently, little chlorination was observed until the hypochlorite concentration was raised to 5 mM. Evidently at this concentration, rapid chlorination proceeds within 3 min, all three tentacle molecules' providing a favourable environment for the chlorination reaction.

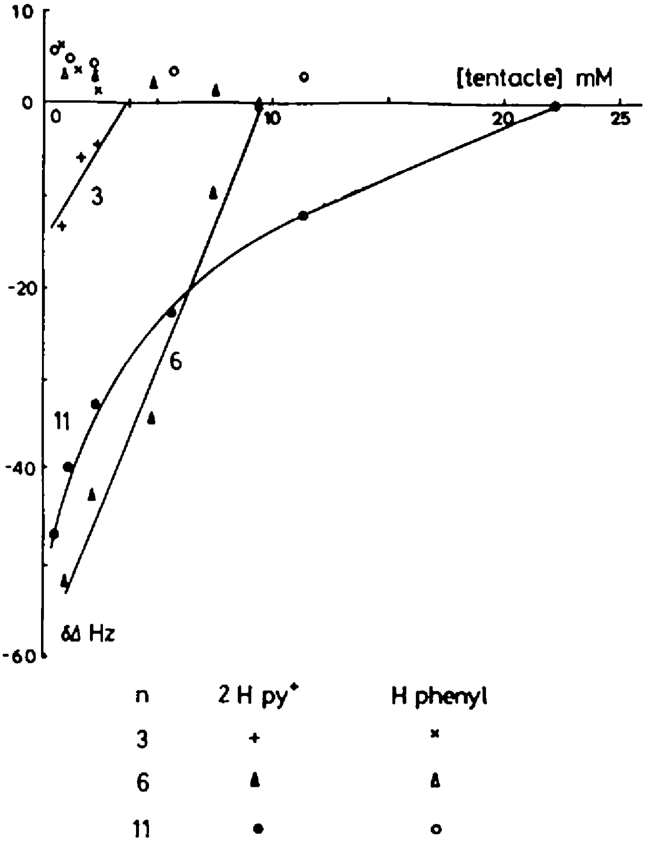


Fig. 2. Chemical shift changes of protons in tentacle molecules (1-3b) as a function of concentration.

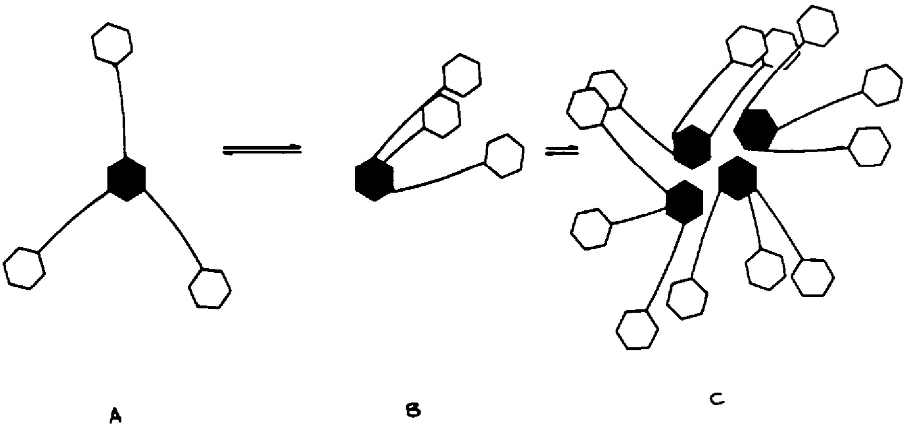


Fig. 3. Possible conformational behaviour of tentacle molecules. Only (**3b**) can evidently exist in form *C* but form *A* and *B* are possible for (**1b**) and (**2b**) also.

However, it is impossible to infer from these data how such a catalytic effect might arise, especially since it is a property of all three tentacle species. Some indication that intermolecular association of the tentacle molecules is significant under these reaction conditions was obtained from an NMR study of the concentration dependence of the chemical shifts of the pyridinium protons (Fig. 2). The most substantial shifts were observed for the 2-protons of the pyridinium ring and in each case, the resonance moved upfield as the concentration of the tentacle molecule was increased to saturation. For the 3 and 6 carbon chain compounds **1b** and **2b**, the change was linear but a pronounced curve was obtained for the C-11 tentacle molecule **3b**. The curved plot is reminiscent of the evidence for micelle-like agglomeration and suggests that the C-11 compound can become associated in a manner expected from the original design. This association is illustrated schematically in Fig. 3. Such an agglomerate would have a capacity for several molecules of substrates and a Scatchard analysis of the NMR data for the association of phenol with **3b** indicates that four molecules of phenol may be easily accommodated per tentacle molecule. In contrast, the other tentacle molecules are evidently unable to attain such an agglomerated form although they may clearly fold; their association probably involves intermolecular ion pairing (Fig. 4). All three molecules, when associated, may thus have structures with loci in which enhanced concentrations of anisole and t-butyl hypochlorite can arise leading to an initial promotion of chlorination. It is also possible that trichlorination of phenol results from a similarly enhanced concentration of reactants.

The behaviour of this system reveals some unexpectedly significant interactions and complicates the evaluation of the usefulness of tentacle molecules of this type as the basis for the design of selective functionalisation systems. It will be necessary, therefore, to synthesise a further series of similar molecules with anionic head groups to avoid the offending interaction of t-butyl hypochlorite with the pyridinium head group; we are currently pursuing this goal.

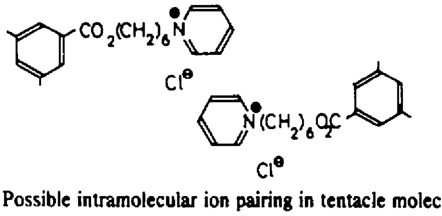


Fig. 4. Possible intramolecular ion pairing in tentacle molecules.

EXPERIMENTAL

^{1}H NMR spectra for characterisation purposes were recorded on a Perkin–Elmer instrument at 90 MHz. GLC analyses were carried out as described previously[5,6] on a 5% FFAP on Chromosorb G column at 210°.

Tris(3-Chloro-1-propyl)benzene-1,3,5-tricarboxylate (**1a**)

To a solution of 3-chloropropanol (5.7 g, 0.06 mol.) and trimesic chloride (5.3 g, 0.02 mol) in dry ether (100 ml), a solution of trimethylamine (6.2 g, 0.06 mol) in dry ether (50 ml) was added dropwise with stirring. The solution was heated under reflux for 3 hr and a white precipitate formed. The precipitate was filtered off and the solution evaporated to dryness *in vacuo*. The residue was triturated with methanol and the product obtained as a brown waxy solid. The required triester was purified with difficulty and considerable losses by recrystallisation from ethyl acetate and petroleum ether (b.p. 60–80°), 3.25 g, 13%, mp 43–46°. Found: C, 49.1; H, 4.9; Cl, 23.7. $C_{18}H_{25}Cl_3O_6$ requires C, 49.2; H, 4.81; Cl, 24.2%. ^{1}H NMR ($CDCl_3$) 2.30, 6H, q; 3.72, 6H, t; 458, 6H, t; 8.84, 3H, s.

Tris(6 - chloro - 1 - hexyl)benzene - 1,3,5 - tricarboxylate **2a**

This compound was prepared in an analogous manner to the above from 6-chlorohexanol in 27% yield. The product was a viscous liquid that failed to crystallise. ^{1}H NMR ($CDCl_3$) 1.3–2.0, 12H, broad m, peaks at 1.55 and 1.85; 3.67, 6H, t; 4.51, 6H, t; 8.82, 3H, s.

Tris(11 - bromo - 1 - undecyl)benzene - 1,3,4 - tricarboxylate **3a**

This compound was obtained from 11-bromoundecanol in the same manner as the foregoing compounds in 40% yield. The prodict as a viscous oil insoluble in methanol and was not distilled. Found: C, 56.0; H, 7.7; Br, 26.4. $C_{42}H_{69}Br_3O_6$ requires C, 55.5; H, 7.65; Br, 26.35%. ^{1}H NMR ($CDCl_3$) 1.31, 42H, bds; 1.65–2.05, 6H, m; 3.49, 6H, t; 4.38, 6H, t; 8.82, 3H, s.

Tris(3 - pyridiniumprop - 1 - yl)benzene - 1,3,5 - tricarboxylatetrichloride **1b**

A solution of the trischloroester (1 g) in pyridine (5 ml) was heated under reflux for 16 hr in the presence of a catalytic quantity of tetra - n - butylammonium chloride. The product separated as a gum. The supernatant pyridine was decanted, the residue washed with ether and dried *in vacuo*. The residue was dissolved in methanol and the product reprecipitated with ether. The required pyridinium salt was obtained as a hygroscopic brown resinous solid on freeze drying the filtered precipitate. Found: C, 51.1; H, 5.60; N, 5.4; Cl, 13.5. $C_{33}H_{36}Cl_3N_3N_3O_6$ 5.5 H_2O requires C, 51.02; H, 6.10; N, 5.40; Cl, 13.7%. λ_{max} (MeOH) nm (ϵ) 259 (13200). ^1H NMR (CD_3OD): 2.7, 6H, q; 4.65, 6H, t; 5.0, 6H, t; 8.2, 6H, t; 8.5, 3H, s; 8.65, 3H, t; 9.25, 6H, d.

Tris(6 - pyridiniumhex - 1 - yl)benzene - 1,3,5 - tricarboxylatetrichloride **2b**

This compound was obtained as a fluffy hygroscopic crystalline solid from the triester (2a) by the above procedure. Found: C, 60.9; H, 6.79; N, 5.2; Cl, 13.2. $C_{42}H_{54}Cl_3N_3O_6$ H_2O requires C, 61.4, H, 6.87; N, 5.1; Cl, 12.9%. λ_{max} (MeOH) nm (ϵ) 259 (12500). ^1H NMR (CD_3OD): 1.6, 12H, m; 1.9, 6H, m; 2.15, 6H, m; 4.4, 6H, m; 4.8, 6H, t; 8.2, 6H, t; 8.7, 6H, m; 9.2, 6H, d.

Tris(11 - pyridiniumundec - 1 - yl)benzene - 1,3,5 - tricarboxylatetrichliride **3b**

This compound was prepared by the same procedures from the bromotriester **3a**. The trichloride was obtained from the tribromide by shaking a solution of the former in methanol–chloroform, 1:9 v/v with 6M hydrochloric acid. The required pyridinium salt separated as an oily layer between aqueous and organic phases. It was separated and dried thoroughly *in vacuo* affording a hygroscopic wax. Found:C, 67.4; H, 8.7; N, 4.5; Cl, 10.3. $C_{57}H_{86}Cl_3N_30_6$ requires C, 67.4; H, 8.53; N, 4.14; Cl, 10.47%. ^1H NMR ($(CD_3)_2SO$) 1.26, bds, 42H; 1.6–2.1, 6H, m; 4.32, 6H, t; 4.69, 6H, t; 8.18, 6H, t; 8.62, 3H, s; 9.24, 6H, d.

Chlorination reactions were carried out as described previously[5,6] by adding solutions of t-butyl hypochlorite to the reaction mixture to give the concentrations stated in the tables. NMR observations were made on a Bruker 250 MHz instrument using CD_3CN as lock and the residual protons (1.93 ppm downfield from TMS) as internal standard.

Acknowledgements—Financial support from the Nuffield Foundation (D.I.R.) is acknowledged. This was carried out during the tenure of the Royal Society Smith and Nephew Senior Research Fellowship (C.J.S.).

REFERENCES

[1] R. Breslow, *Science* **218**, 532 (1982).
[2] I. Tabushi, *Accts. Chem. Res.* **15**, 66 (1982).
[3] C. J. Suckling, *Ind. Eng. Chem. Prod. Res. Dev.* **20**, 434 (1981).
[4] C. A. Dewar, C. J. Suckling and R. Higgins, *J. Chem. Res.* (*S*) 336, (M) 3812 (1979).
[5] C. J. Suckling and A. A. Wilson, *J. Chem. Soc.*, *Perkin Trans.* 2 1616 (1981).
[6] S. Onyiriuka and C. J. Suckling, *Ibid.* in press.
[7] F. M. Menger, M. Takeshita and J. F. Chow, *J. Am. Chem. Soc.* **103**, 5938 (1981).
[8] C. J. Suckling, *J. Chem. Soc.*, Chem. Commun. 661 (1982).