41. *Reactions of Cellulose. Part I.*

By John Honeyman.

The course of tritylation, tosylation, and ethylation of cellulose has been followed by determining the relative positions of the substituents and the number of glycol groups present.*

The very rapid rate of tritylation in the primary position compared with the average rate of substitution of secondary hydroxyl groups markedly decreases as the degree of substitution increases. A pronounced steric effect is noticeable as the number of secondary trityl groups increases. A monotrityl cellulose with practically all the primary and very few secondary hydroxyl groups substituted has been prepared.

For tosylation, the relative speed of primary substitution varies less, and no steric effect enters during esterification of secondary hydroxyl groups.

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* The abbreviations trityl (for triphenylmethyl) and tosyl (for *p*-toluenesulphonyl) are used throughout.

The usual commercial process for ethyl cellulose manufacture is shown to be initially heterogeneous becoming homogeneous in the later stages. If the reaction is maintained heterogeneous throughout a product of somewhat different properties is obtained.

I. *Tritylation.*—Trityl cellulose was first prepared by Helferich and Koester (*Ber.*, 1924, **57**, 587) as a brown powder containing one trityl group for each anhydroglucose residue. At that time it was considered that trityl chloride reacted only with primary hydroxyl groups and hence this product was assumed to be 6-trityl cellulose. Later work, however, showed that trityl chloride was not specific for primary hydroxyl groups (*e.g.*, Oldham and Rutherford, *J. Amer. Chem. Soc.*, 1932, **54**, 366) and, in fact, could react with compounds such as α-methylxyloside and β-methylarabinoside which contain secondary hydroxyl groups only (Hockett and Hudson, *J. Amer. Chem. Soc.*, 1931, **53**, 4457). More recently it has been shown by McIlroy (*J.*, 1946, 100) that αβ-methylxylofuranosides can give a ditrityl derivative in which the primary and one secondary hydroxyl group have been substituted. The reaction of trityl chloride with cellulose was studied more systematically by Hearon, Hiatt, and Fordyce (*J. Amer. Chem. Soc.*, 1943, **65**, 2449) who showed that tritylation in pyridine took place with little or no reduction in chain-length of the molecule. Treatment with phenyl *iso*cyanate under conditions which these workers had previously found (*ibid.*, p. 829) to effect complete substitution, followed by detritylation, gave a product with free hydroxyl where trityl groups had originally been. The position of these free hydroxyl groups was then determined by Oldham's method (*loc. cit.*) of tosylation followed by treatment with sodium iodide–acetone which Purves and co-workers (*J. Amer. Chem. Soc.*, 1939, **61**, 3458; 1942, **64**, 9) have shown to be applicable to cellulose derivatives. The results showed that the primary hydroxyl groups were tritylated about 14 times as fast as the secondaries, 90% of the former and 6·5% of the latter being simultaneously substituted.

This reaction has now been more closely studied by following the same procedure as Hearon *et al.* together with the lead tetra-acetate method of estimating the number of glycol groups which Purves (*ibid.*, 1942 ref.) has shown to be applicable to cellulose derivatives. In this paper Purves shows that for a heterogeneous reaction the number of glycol groups will be $H/2$ (where H = number of free secondary hydroxyl groups), *i.e.*, along the anhydroglucose chain there will be zones of complete reaction and zones with all the hydroxyl groups free; for a homogeneous reaction the number of glycol groups will be $H^2/4$, *i.e.*, completely random reaction; while if the number of glycol groups approaches $H - 1$ it will indicate a pronounced steric effect so that, in the extreme case, *all* the glucose residues will have one trityl group on a secondary carbon before any *one* has both secondaries substituted.

In the first series of experiments (Ia), regenerated cellulose was treated in pyridine at 100° with 2·5 times the theoretical amount of trityl chloride required for one hydroxyl group. At first the primary hydroxyl was rapidly substituted (58 times the average rate of secondary tritylation in the first two hours) but the relative rate quickly fell away until, when the number of free primary groups was small, the rates were equal (16—20 hours: 1·10—1·15 trityl groups/glucose residue). Thereafter the phenomenon (noted by Hearon *et al.*) of apparent loss of trityl was observed. It was shown that trityl groups were being removed from C_6 while substitution was still taking place on C_2 and C_3. This is considered to be due to the easier removal of primary trityl groups with hydrogen chloride in pyridine. While the product remained undissolved the number of glycol groups was found to be close to $H/2$, but after it became soluble the value more nearly approached $H - 1$ or $H^2/4$. With the low degree of secondary tritylation achieved in this case the values of $H - 1$ and $H^2/4$ are very close together and so it is not possible to tell whether a steric effect is operative.

When cotton cellulose was used (Ib and Ic) the product remained insoluble throughout although the degree of tritylation achieved was just as great as for regenerated cellulose. The number of glycol groups was approximately $H/2$ throughout, showing that with the small amount of secondary tritylation obtained (0·29 trityl/gluc.), there is no apparent steric effect. The rate of overall tritylation was less than for regenerated cellulose, but the same gradual fall in the relative rate of primary to secondary tritylation was observed.

More rapid and complete reaction was obtained by using a tenfold excess of trityl chloride (Id and Ie), but the reduction in rates already observed still obtained. Regenerated cellulose reacted more rapidly and gave a soluble product, but the derivative obtained from cotton cellulose remained undissolved. In both cases, however, the number of glycol groups present showed that, as the degree of secondary tritylation increased, a pronounced steric effect was operating, making it difficult to substitute both secondary hydroxyl groups in any glucose residue. The product obtained from regenerated cellulose after three hours' reaction is interesting, as practically all the primary but only 3·5% of the secondary hydroxyl groups are substituted. This derivative is more nearly a true 6-trityl cellulose than any yet characterised, and it is intended to use it as an intermediate for preparing other cellulose derivatives with the substituents occupying chosen positions. Already a 2 : 3-diacetyl 6-propionyl cellulose has been prepared and found to differ from a commercial product made by random substitution.

II. *Tosylation.*—The reaction of tosyl chloride with cellulose in the presence of alkali has been investigated in a general way by Sakurada and Nakashima (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1927, **6**, 214) who found it difficult to raise the degree of esterification above that of a mono-ester even when using pyridine. Chippindale (*J. Soc. Dyers and Col.*, 1934, **50**, 144) suggested that incomplete reaction was due to an outer layer of ester preventing access of the reagents to unreacted cellulose. A very low degree of substitution was obtained by Karrer (*Helv. Chim. Acta*, 1926, **9**, 597).

The reaction has now been examined more closely by the methods described for studying tritylation. In no case was a soluble product obtained, but no difficulty was experienced in obtaining a degree of substitution corresponding to two tosyl groups/glucose residue. The results (IIa, IIb, and IIc) show that the reaction is fundamentally distinct from tritylation. The relative speed with which primary tosylation occurred did not vary so greatly when the number of free primary hydroxyl groups became small, while the glycol content approximated throughout to H/2; *i.e.*, the reaction is heterogeneous without any noticeable steric effect.

III. *Ethylation.*—The study of ethyl cellulose of different composition prepared by different methods has been described by Mahoney and Purves (*loc. cit.*), but no record has yet been made of an attempt to follow the course of ethylation.

This has now been done using the methods already described. The standard commercial method for preparing high-grade ethyl cellulose was used. Cotton cellulose was heated with sodium hydroxide solution and ethyl chloride in an autoclave. It was found that when the ethoxyl content of the product was still low it remained undissolved in the reaction mixture, but when the degree of substitution approached two ethoxyl groups/glucose residue the derivative dissolved in the reaction mixture which contained, in addition to excess ethyl chloride, ether and alcohol produced from the interaction of aqueous alkali and ethyl chloride. Examination of the glycol content of a range of products confirmed that the original heterogeneous reaction became homogeneous in the later stages. In a special preparation a very high sodium hydroxide concentration was used so that by-product formation was a minimum. The number of glycol groups, even in highly ethylated material, corresponded to H/2 showing that the reaction remained heterogeneous throughout. The properties of products obtained by this method differed in certain respects from those of the same degree of substituton obtained by the more standard method, *e.g.*, the water absorption of the heterogeneous product was lower.

EXPERIMENTAL.

I. *Tritylation.*—The regenerated cellulose used was prepared from a commercial cellulose acetate by treatment with aqueous ammonia. The low- and high-viscosity cellulose used were high grade commercial α-cellulose supplied by the Holden Vale Manufacturing Co. Ltd. as Bleached Cotton Linters (samples A and F).

The samples which were taken during the reactions described were purified for examination by washing free from pyridine and trityl chloride. In the case of insoluble products this was done by squeezing out as much liquid as possible, then washing with pyridine followed by dry methanol. When solution had taken place the syrup was filtered, diluted with dry methanol almost to precipitation point, and then poured in a thin stream with steady, gentle stirring into a large excess of methanol. The derivative was obtained by this method as a fine thread which was readily handled and purified by further washing. Before analysis all samples were dried to constant weight at 60°/40 mm. over calcium chloride. The trityl content and the number of free primary hydroxyl groups were determined by the methods described by Hearon *et al.* (*loc. cit.*). The number of glycol groups was found by titration with lead tetra-acetate solution under the conditions used by Mahoney and Purves (*loc. cit.*) for ethyl cellulose. Although this method was designed for products soluble in glacial acetic acid it was found to be satisfactory for insoluble products provided vigorous agitation was used, although the time required to reach the end-point was greater.

In the tables which follow the abbreviations used are :

I = insoluble.
S = soluble.
$R = \frac{\text{rate of primary tritylation}}{\text{rate of secondary tritylation}}$.
H = number of free secondary hydroxyl groups.
N = number of glycol groups found.

All the values of substituents and of free hydroxyl groups are for each anhydroglucose unit.

I(a). Regenerated cellulose (100 g.) which had been pretreated according to the method of Hearon *et al.* was added to trityl chloride (430 g., 150% excess for one hydroxyl group) in dry pyridine (1500 ml.) at 100° and the reaction mixture mechanically stirred.

Reaction time (hrs.).	Sol. or insol.	No. of trityl groups. Primary.	Secondary.	R. Period.	Average.	H.	H − 1.	$H^2/4$.	H/2.	N.
1	I	0·16	0·00	∞	∞	2·00	1·00	1·00	1·00	0·99
2	I	0·29	0·01	26	58	1·99	0·99	0·99	1·00	0·99
3	I	0·40	0·02	22	40	1·98	0·98	0·98	0·99	0·98
4	I	0·48	0·03	16	32	1·97	0·97	0·97	0·99	0·98
6	I	0·63	0·05	15	25	1·95	0·95	0·95	0·98	0·97
8	I	0·76	0·07	13	22	1·93	0·93	0·93	0·97	0·97
12	I/S	0·86	0·09	10	19	1·91	0·91	0·91	0·96	0·93
16	S	0·94	0·16	2	12	1·84	0·84	0·85	0·92	0·85
20	S	0·95	0·20	1	10	1·80	0·80	0·81	0·90	0·81
24	S	0·94	0·21	− 2	9	1·79	0·79	0·80	0·90	0·80
36	S	0·92	0·22	− 4	8	1·78	0·78	0·79	0·89	0·78
48	S	0·85	0·24	− 7	7	1·76	0·76	0·77	0·88	0·76
96	S	0·70	0·26	−15	6	1·74	0·74	0·76	0·87	0·76

Note.—After 12 hours' reaction time the product had partly dissolved. No difference was detected in the distribution of the free hydroxyl groups in the two fractions.

I(b). Low-viscosity cellulose was used but quantities and conditions were as for I(a). The derivative remained insoluble in the reaction mixture throughout.

Reaction time (hrs.).	No. of trityl groups. Primary.	Secondary.	R (average).	H.	H/2.	$H^2/4$.	N.
1	0·10	0·00	∞	2·00	1·00	1·00	0·99
2	0·18	0·01	36	1·99	1·00	0·99	0·99
4	0·29	0·02	29	1·98	0·99	0·98	0·99
8	0·48	0·04	24	1·96	0·98	0·96	0·97
16	0·76	0·09	17	1·91	0·96	0·91	0·96
32	0·96	0·16	12	1·84	0·92	0·85	0·92
64	0·98	0·25	8	1·75	0·88	0·77	0·86
140	0·98	0·27	7	1·73	0·87	0·75	0·87
260	0·98	0·29	7	1·71	0·86	0·73	0·85

I(c). High-viscosity cellulose was used under the conditions for I(a). The product remained insoluble throughout.

Reaction time (hrs.).	No. of trityl groups. Primary.	Secondary.	R (average).	H.	H/2.	$H^2/4$.	N.
2	0·15	0·00	∞	2·00	1·00	1·00	1·00
24	0·63	0·07	18	1·93	0·97	0·93	0·96
98	0·86	0·12	14	1·88	0·94	0·88	0·94
218	0·99	0·20	10	1·80	0·90	0·81	0·90
338	0·99	0·24	· 8	1·76	0·88	0·77	0·85

I(d). Regenerated cellulose and ten times the quantity of trityl chloride theoretically required for one hydroxyl group were used under the conditions for I(a).

Reaction time (hrs.).	Sol. or insol.	No. of trityl groups. Primary.	Secondary.	R (average).	H.	$H^2/4$.	H/2.	H − 1.	N.
½	I	0·32	0·01	64	1·99	0·99	1·00	0·99	1·00
1	I	0·51	0·02	51	1·98	0·98	0·99	0·98	0·99
2	I	0·87	0·04	44	1·96	0·96	0·98	0·96	0·97
3	S	0·98	0·07	28	1·93	0·93	0·97	0·93	0·94
4	S	0·99	0·10	20	1·90	0·90	0·95	0·90	0·90
12	S	0·99	0·32	6	1·68	0·71	0·84	0·68	0·79
24	S	0·99	0·58	4	1·42	0·50	0·71	0·42	0·48
32	S	0·98	0·74	3	1·26	0·40	0·63	0·26	0·29
38	S	0·99	0·84	2	1·16	0·34	0·58	0·16	0·19
48	S	0·99	0·90	2	1·10	0·30	0·55	0·10	0·15

I(e). Conditions were as for I(d) : high-viscosity cellulose was used. Solution did not take place.

Reaction time (hrs.).	No. of trityl groups. Primary.	Secondary.	R (average).	H.	H/2.	$H^2/4$.	H − 1.	N.
1	0·35	0·01	70	1·99	1·00	0·99	0·99	0·98
2	0·59	0·02	59	1·98	0·99	0·98	0·98	0·98
4	0·74	0·04	37	1·96	0·98	0·96	0·96	0·96
8	0·95	0·12	16	1·88	0·94	0·88	0·88	0·87
20	0·99	0·35	6	1·65	0·83	0·68	0·65	0·74
32	0·99	0·57	3	1·43	0·72	0·52	0·43	0·44
48	0·98	0·77	3	1·23	0·62	0·38	0·23	0·25
60	0·99	0·84	2	1·16	0·58	0·34	0·16	0·19

II. *Tosylation*.—The same samples of cellulose were used as described under I.

The yellowish, fibrous, and insoluble products of this series were purified by washing with pyridine followed by water before drying as before. The degree of tosylation was estimated from the sulphur content as determined by micro-analysis and the amount of primary hydroxyl groups tosylated was determined by Oldham and Rutherford's method (*J. Amer. Chem. Soc.*, 1932, **54**, 366). The number of glycol groups was determined as in I.

II(a). Pretreated regenerated cellulose (100 g.) was added to a solution of tosyl chloride (353 g., 200% excess for one hydroxyl group) in dry pyridine (1500 ml.) at 100° and the mixture mechanically stirred.

Reaction time (hrs.).	No. of tosyl groups.		R (average).	H.	H/2.	$H^2/4$.	H − 1.	N.
	Primary.	Secondary.						
2	0·21	0·02	21	1·98	0·99	0·98	0·98	0·99
4	0·41	0·06	14	1·94	0·97	0·94	0·94	0·96
6	0·60	0·08	15	1·92	0·96	0·92	0·92	0·95
8	0·78	0·11	14	1·89	0·95	0·89	0·89	0·93
12	0·95	0·15	13	1·85	0·93	0·86	0·85	0·92
16	0·99	0·19	10	1·81	0·91	0·82	0·81	0·89
24	1·01	0·26	—	1·74	0·87	0·76	0·74	0·86
54	1·00	0·48	—	1·52	0·76	0·58	0·52	0·74
72	1·00	0·61	—	1·39	0·70	0·48	0·39	0·67

II(b). Low-viscosity cellulose was used under the conditions of II(a).

Reaction time (hrs.).	No. of tosyl groups.		R (average).	H.	H/2.	$H^2/4$.	H − 1.	N.
	Primary.	Secondary.						
½	0·21	0·03	14	1·97	0·99	0·97	0·97	0·98
1	0·40	0·06	13	1·94	0·97	0·94	0·94	0·97
2	0·59	0·08	15	1·92	0·96	0·92	0·92	0·96
4	0·79	0·12	13	1·88	0·94	0·88	0·88	0·94
6	0·97	0·15	13	1·85	0·93	0·86	0·85	0·93
8	0·99	0·18	—	1·82	0·91	0·83	0·82	0·91
12	0·99	0·24	—	1·76	0·88	0·77	0·76	0·87
16	1·01	0·29	—	1·71	0·86	0·73	0·71	0·86
24	0·99	0·39	—	1·61	0·81	0·65	0·61	0·80
36	1·00	0·51	—	1·49	0·75	0·56	0·49	0·73
48	1·00	0·61	—	1·39	0·70	0·48	0·39	0·69
72	1·00	0·79	—	1·21	0·61	0·37	0·21	0·58
96	1·00	0·94	—	1·06	0·53	0·28	0·06	0·49

II(c). As II(a) except that ten times the theoretical amount of tosyl chloride for one hydroxyl was used.

Reaction time (hrs.).	No. of tosyl groups.		R (average).	H.	H/2.	$H^2/4$.	H − 1.	N.
	Primary.	Secondary.						
4	0·22	0·02	22	1·98	0·99	0·98	0·98	0·99
8	0·42	0·04	21	1·96	0·98	0·96	0·96	0·98
16	0·72	0·10	14	1·90	0·95	0·90	0·90	0·95
24	0·99	0·15	13	1·85	0·93	0·86	0·85	0·92
36	0·99	0·21	—	1·79	0·90	0·80	0·79	0·90
48	1·01	0·26	—	1·74	0·87	0·76	0·74	0·86
72	1·00	0·32	—	1·68	0·84	0·71	0·68	0·85
96	1·00	0·38	—	1·62	0·81	0·66	0·62	0·82

III. *Ethylation*.—Low-viscosity cellulose was used in the preparation of ethyl cellulose. The reaction was carried out in a Monel-metal-lined, steam-jacketed, mechanically stirred autoclave at 120°. Cellulose and sodium hydroxide solution were added to the autoclave which was evacuated as quickly as possible as it had been found that little degradation took place in the absence of air. Ethyl chloride was then pumped in. Sufficient hydroxide was present to ensure that the reaction mixture remained alkaline throughout, since ethyl cellulose is rapidly hydrolysed by acid although exceptionally stable towards alkali. At the end of the specified time excess of ethyl chloride was released and the mixture rapidly cooled by circulating water through the jacket. The product was purified by washing with distilled water until ion-free.

The degree of ethylation was determined by Zeisel's method, and the number of free primary hydroxyl and glycol groups was determined by the methods described by Mahoney and Purves (*loc. cit.*).

In the tables the solubility refers to whether or not the product had dissolved in the reaction mixture.

III(a). In each experiment cellulose (2 lb.) and aqueous sodium hydroxide (45%, 10 lb.) were added to the autoclave, and ethyl chloride (6·5 lb.) pumped in.

Reaction time (hrs.).	Sol. or insol.	No. of ethoxyl groups.		H.	$H^2/4$.	H/2.	N.
		Primary.	Secondary.				
1	I	0·41	0·49	1·51	0·57	0·76	0·70
2	I	0·61	1·01	0·99	0·24	0·55	0·59
3	I	0·69	1·25	0·75	0·14	0·38	0·39
4	S	0·77	1·39	0·61	0·09	0·31	0·12
6	S	0·85	1·67	0·33	0·03	0·17	0·04

III(b). In this series the concentration of the sodium hydroxide solution was increased to 90%; very little by-product formation took place so that the product remained undissolved throughout.

Reaction time (hrs.).	Sol. or insol.	No. of ethoxyl groups.		H.	$H^2/4$.	H/2.	N.
		Primary.	Secondary.				
3	I	0·72	1·25	0·75	0·14	0·38	0·36
4	I	0·82	1·46	0·54	0·07	0·27	0·24
5	I	0·88	1·64	0·36	0·03	0·18	0·17
6	I	0·92	1·82	0·18	0·01	0·09	0·10

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