Fig. 5.25. Structures of amphiphilic polymers **A** ester of carboxymethylated poly(ethylene glycol) with pullulan acetate and **B** bile acid ester of dextran prepared by esterification via in situ activation with DCC/DMAP

An alternative to DCC is 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, which is used for the hydrophobic modification of pullulan [226], and diisopropyl-carbodiimide, which can be utilised to introduce betaine moieties into starch [227].

5.2.3 *N,N'*-Carbonyldiimidazole

A method with an enormous potential for polysaccharide modification is the homogeneous one-pot synthesis after in situ activation of the carboxylic acids with CDI, which is rather well known from organic chemistry literature published
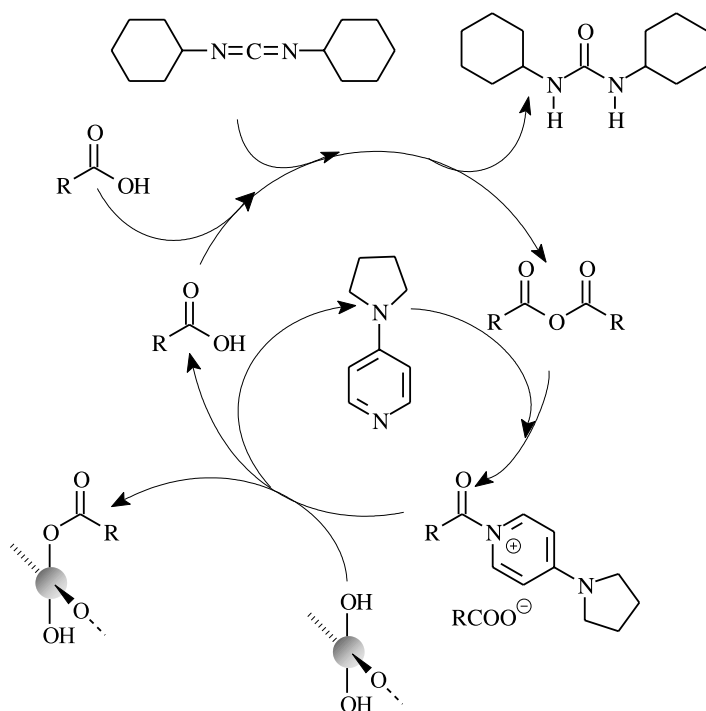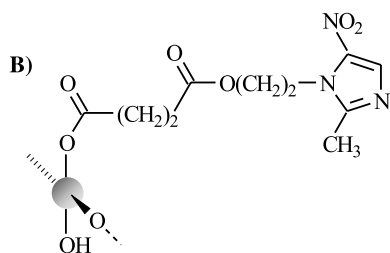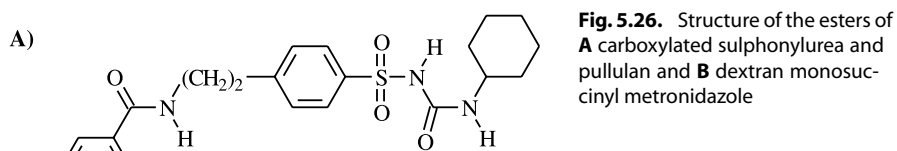
A)

Fig. 5.26. Structure of the esters of **A** carboxylated sulphonylurea and pullulan and **B** dextran monosuccinyl metronidazole

B)

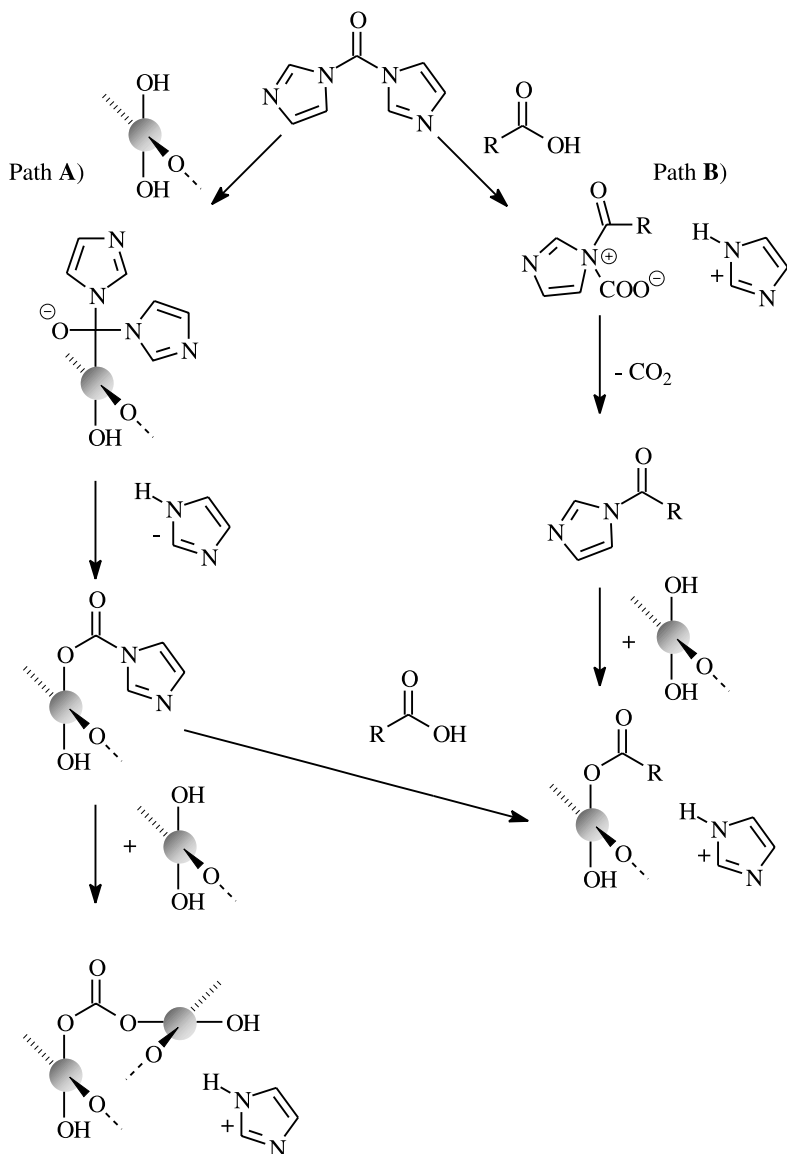**Fig. 5.27.** Scheme of the esterification of cellulose using PP/DCC (adapted from [223])

Fig. 5.28. Reaction paths leading exclusively to esterification (path **B**) or cross-linking (path **A**) if the polysaccharide is treated with CDI in the first step (adapted from [212])

in 1962 [228]. It is particularly suitable for the functionalisation of the biopolymers because, during the conversion, the reactive imidazolide of the acid is generated and the by-products formed are only CO_2 and imidazole (Fig. 5.28). The reagents and by-products are non-toxic. The imidazole is freely soluble in a broad variety of solvents including water, alcohol, ether, chloroform and Py, and can be easily

removed. In addition, the pH is not strongly changed during the conversion, resulting in negligible chain degradation.

In comparison to DCC, the application of CDI is much more efficient, avoids most of the side reactions, and allows the use of DMSO (good solvent for most of the complex carboxylic acids) as solvent. In the case of CDI, no oxidation is observed and no decomposition of DMSO occurs (cf. no odour of dimethylsulphide).

The conversion is generally carried out as a one-pot reaction in two stages. To start with, the acid is transformed with the CDI to give the imidazolide. The conversion of the alcohol in this first step is also possible for the esterification but yields undesired cross-linking by carbonate formation in the case of a polyol (see Fig. 5.28). However, this process can be used for the defined cross-linking of starch [138].

The imidazolide of the carboxylic acid should always be firstly synthesised. Model reactions and NMR spectroscopy (Fig. 5.29) with acetic acid confirm that, during a treatment at room temperature, CDI is completely consumed within 6 h (compare Fig. 5.28). Thereby, the tendency of cross-linking of unreacted CDI leading to insoluble products is avoided.

Basic investigations towards conditions for coupling by the use of butyric acid and dextran confirm that the imidazolide is formed within 2 h and the reaction at RT for 17 h yields a butyrate containing 92% of the acid applied. Only 0.25% N is found in the ester. The solvent has a pronounced influence. In the case of dextran, the solvent of choice is the mixture formamide/DMF/CH$_2$Cl$_2$ [212]. PP is used as catalyst in this process.
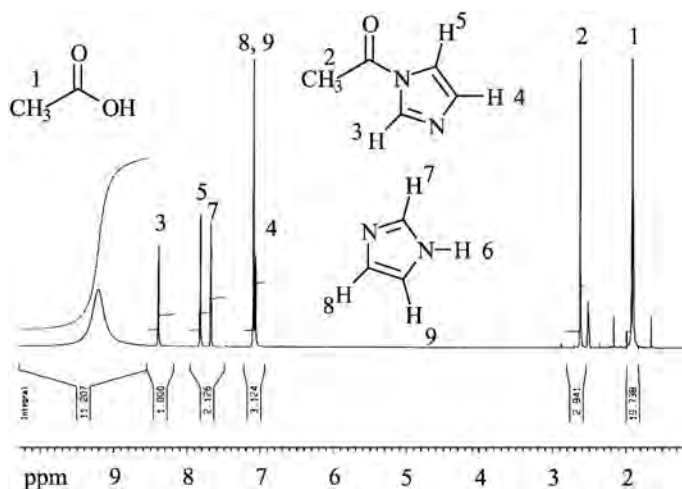

Fig. 5.29. ^{1}H NMR spectroscopic investigation of the in situ activation of acetic acid with CDI, confirming complete consumption of the CDI to the acetyl imidazolide

To ensure complete consumption of the CDI for all types of acids, the reaction towards the imidazolide is carried out most commonly for 16 h at 60 °C with equimolar ratios of acid/CDI. The intermediately formed imidazolide is unified with the polysaccharide solution to give the ester. The reaction is possible without catalysis or by applying PP, DMAP or alcoholates (e.g. potassium methanolate) in catalytic amounts. The utilisation of a catalyst may cause problems during the product isolation. Usually, precipitation and washing with ethanol is sufficient to obtain white, highly soluble, pure products.

Although CDI was applied as early as 1972 as reagent for the esterification of starch and dextran, it has only rarely been used up to now. Its renaissance during the last few years may be due to the fact that it became an affordable, commercially available product.

Among the first attempts for the esterification of polysaccharides via CDI is the introduction of amino acids into dextran. In addition to CDI, N,N'-(thiocarbonyl)diimidazole can be utilised to obtain the corresponding imidazolide [229]. The amino acids utilised are glycine, L-leucine, L-phenylalanine, L-histidine, and L-alanyl-L-histidine. They are protected with N-trifluoroacetyl-, N-benzyloxycarbonyl and 2,4-dinitrophenyl moieties. The protecting groups can be removed after the esterification of the polysaccharide by hydrolysis or hydrogenation over Pd catalyst [215].
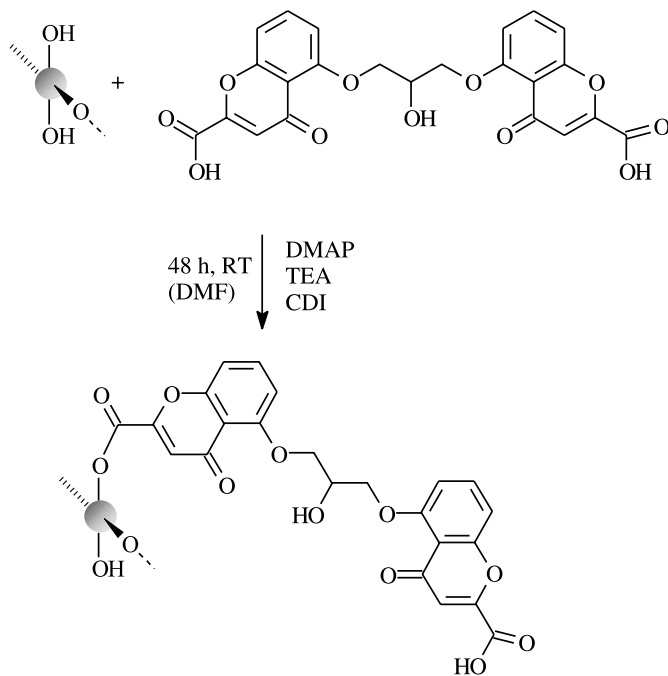

Fig. 5.30. Esterification of dextran with cromoglycic acid using in situ activation with CDI (adapted from [230])

The cromoglycic acid antiasthmatic drug (see Chap. 10) is covalently bound to dextran (Fig. 5.30). The acid is transferred into the imidazolide with CDI in DMF in the presence of TEA and DMAP within 5 h at RT. The conversion with dextran dissolved in DMF is achieved within 48 h at RT. The procedure gives high yields (up to 50%), with derivatives containing between 0.8 and 40% (w/w) of the acid (DS can not be calculated because there is no structural information, excluding the intermolecular esterification of the acid). Comparison with a route involving chlorination of the free acid in a first step, followed by reaction with dextran in formamide, results in low yields (1.5%) of an ester containing only 2.5% (w/w) cromoglycic acid [230].

CDI can also be utilised for the introduction of ester-containing substituents by coupling OH groups of the ester moiety with OH groups of the polysaccharide via a carbonate function. The route is shown in Fig. 5.31. By means of this method, a new class of polymerisable dextrans with hydrolysable groups becomes accessible [231].
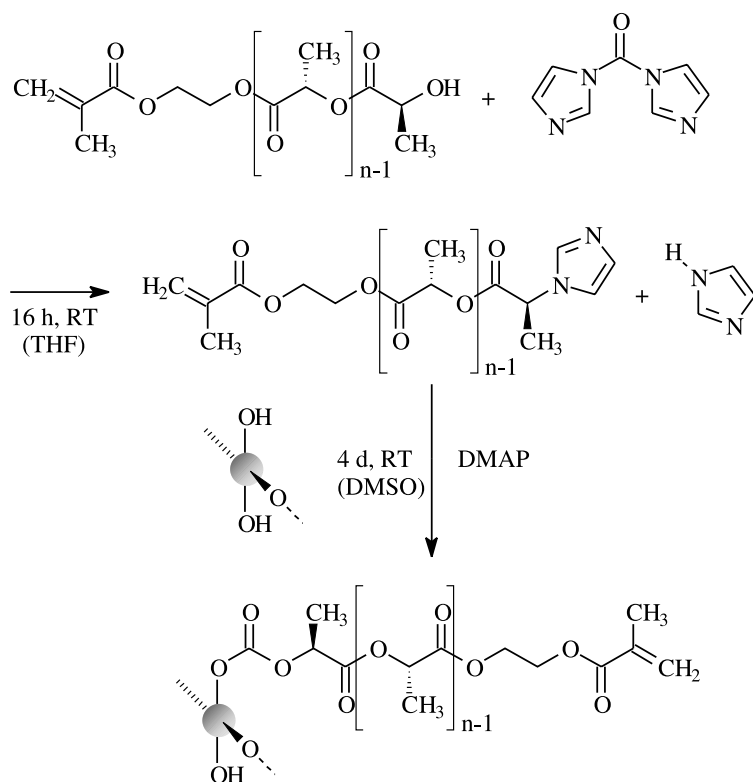

Fig. 5.31. Conversion of dextran with hydroxyethylmethacrylate lactate using CDI, yielding a carbonate-bound ester moiety (adapted from [231])

In the case of starch, the esterification applying CDI is used for the introduction of long-chain aliphatic esters. It is possible both in aqueous media and in suspension, e.g. halogenated hydrocarbons [138]. Introduction of aliphatic acids (acetate to stearate) and of di- and tricarboxylic acids is achieved but with low DS in the range of 0.01 to 0.15 (see Table 5.3).

Comparison of results of the esterification of starch with fatty acids (C_{14}–C_{18}) in DMAc/LiCl applying carboxylic acid chloride, in situ activation of the fatty acid with TosCl, and with CDI is given in Table 5.22. In situ activation with CDI leads to much less chain degradation and side reactions [168].

Table 5.22. Esterification of starch with long-chain aliphatic carboxylic acids using the corresponding chlorides and in situ activation with TosCl and CDI (adapted from [168])

Conditions Reagent	Molar ratio		Coupling agent		Py	Time (h)	Temp. (°C)	Product DS
	AGU	Reagent	Type	Equivalent				
Myristoyl chloride	1	4.5	–		5.4	6	100	2.69
Palmitoyl chloride	1	4.5	–		5.4	6	100	2.70
Stearoyl chloride	1	4.5	–		5.4	6	100	2.17
Myristic acid	1	6.0	TosCl	6	12.0	24	50	1.87
Palmitic acid	1	6.0	TosCl	6	12.0	24	50	1.18
Stearic acid	1	6.0	TosCl	6	12.0	24	50	2.17
Myristic acid	1	3.0	CDI	3	–	24	80	1.78
Palmitic acid	1	3.0	CDI	3	–	24	80	1.52
Stearic acid	1	3.0	CDI	3	–	24	80	1.65

It is noteworthy that esterification of starch with long-chain aliphatic acids using the imidazolide is also accomplished if the corresponding acid chlorides are converted with imidazole. The derivatisation is a homogeneous process in DMSO applying potassium methanolate as catalyst. The imidazole can be recovered. A summary of conditions and results for this path is given in Table 5.23 [232].

Table 5.23. Esterification of starch with long-chain aliphatic carboxylic acid imidazolides formed from the acid chloride and imidazole (adapted from [232])

Conditions Imidazolide	Molar ratio		Time (h)	Temp. (°C)	Product DS
	AGU	Reagent			
Octanoyl	1	2	3	90	1.55
Dodecanoyl	1	2	3	90	1.90
Hexadecanoyl	1	2	3	90	1.66

Table 5.24. DS values for starch cinnamates, furan-2-carboxylic acid esters, and 3-(2-furyl)-acrylic acid esters prepared homogeneously with CDI activation (molar ratio AGU:carboxylic acid:CDI = 1:3:3, adapted from [232])

| Conditions | | | Product |
Acid	Solvent	Temp. (°C)	DS
Cinnamic	DMAc/LiCl	50	0.89
Furan-2-carboxylic	DMSO	50	0.98
3-(2-Furyl)-acrylic	DMAc/LiCl	40	0.58
3-(2-Furyl)-acrylic	DMAc/LiCl	50	0.79
3-(2-Furyl)-acrylic	DMAc/LiCl	80	1.07

CDI can be used for the mild introduction of reactive unsaturated moieties into the starch backbone. Cinnamates, furan-2-carboxylic acid esters, and 3-(2-furyl)-acrylic acid esters of starch can be obtained in DMAc/LiCl and DMSO (Table 5.24, [233]).

Results of investigations concerning the potential of the in situ activation with CDI for a wide variety of carboxylic acids with chiral, (−)-menthyloxyacetic acid, unsaturated, 3-(2-furyl)-acrylcarboxylic acid, heterocyclic, furan-2-carboxylic acid, crown ether, 4′-carboxybenzo-18-crown-6, and cyclodextrin, carboxymethyl-β-cyclodextrin containing moieties are available by the conversion of cellulose, and will be discussed in detail (Fig. 5.32, [234]).

A reaction with (−)-menthyloxyacetic acid in situ activated with CDI can be carried out simply by mixing the solution of the imidazolide prepared in DMAc and the cellulose in DMAc/LiCl, and increasing the temperature to 60 °C. Pure (−)-menthyloxyacetic acid esters of cellulose with DS as high as 2.53 are obtained by precipitation in methanol and filtration (Table 5.25). The cellulose esters are characterised in terms of structure and DS by means of FTIR spectroscopy, elemental analysis, ^{1}H- and ^{13}C NMR spectroscopy, and additionally by ^{1}H NMR spectroscopy after peracylation. Cellulose (−)-menthyloxyacetate yields well-resolved NMR spectra.

Table 5.25. Esterification of cellulose with (−)-menthyloxyacetic acid via in situ activation with CDI (adapted from [234])

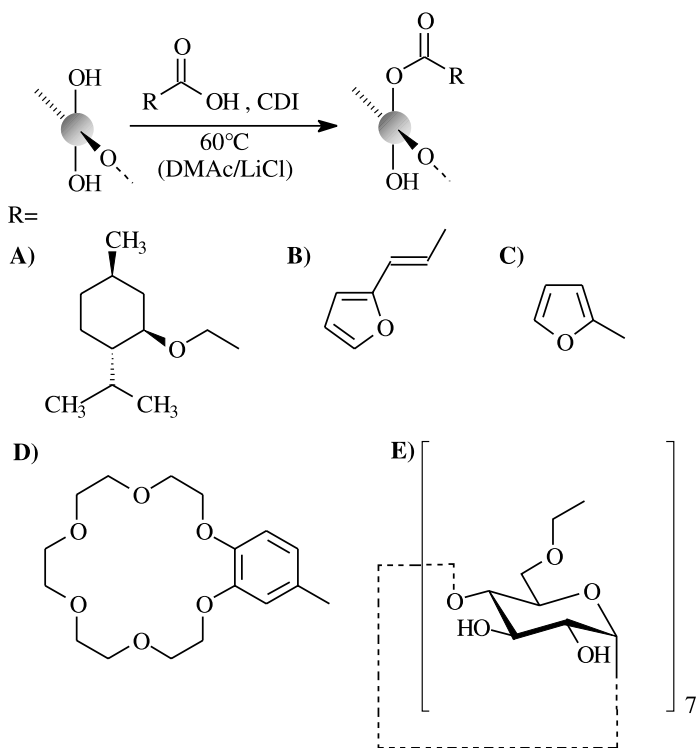| Reaction conditions | | | Product | | | | |
| Molar ratio | | | DS | Solubility | | | |
AGU	Acid	CDI		DMSO	DMF	Acetone	CHCl$_3$
1	2.5	2.5	0.20	+	+	−	−
1	5.0	5.0	1.66	−	+	+	+
1	7.5	7.5	2.53	−	+	+	+

Fig. 5.32. Conversion of cellulose with carboxylic acids applying in situ activation with CDI yielding the esters of **A** (−)-menthyloxyacetic acid; **B** 3-(2-furyl)-acrylcarboxylic acid; **C** furan-2-carboxylic acid; **D** 4′-carboxybenzo-18-crown-6; **E** carboxymethyl-β-cyclodextrin (adapted from [234])

Figure 5.33 shows the ^{13}C NMR spectrum of cellulose (−)-menthyloxyacetate (DS 1.66) recorded in CDCl$_3$. The highly functionalised product is even soluble in easily evaporable solvents including THF and chloroform, which is desired for the transformation into membranes or beads.

Signal assignment was achieved by comparison with simulated spectra and by measuring DEPT135 NMR spectra (Fig. 5.33). Besides signals for the carbons of the AGU (103.7–60.1 ppm), resonances assigned to the carbon atoms of the menthyloxyacetate moieties are visible between 81.0 (C-9) and 16.9 ppm (C-16) (for complete assignment, see Chap. 12). The carbon atoms C-16 and C-17 are not chemically equivalent because of the chirality of the substituent, and give two separate signals at 16.9 and 21.3 ppm.

The peak for C-6, influenced by esterification in O-6, appears at 62.4 ppm (C-6$_s$). In addition, the spectrum shows a signal at 101.6 ppm, corresponding to C-1 adjacent to the C-2 atom bearing a menthyloxyacetate unit. Comparison of the intensities of signals related to substituted and unsubstituted C-2 and C-6 reveals that substitution with the bulky menthyloxyacetate moiety proceeds faster at the primary OH.
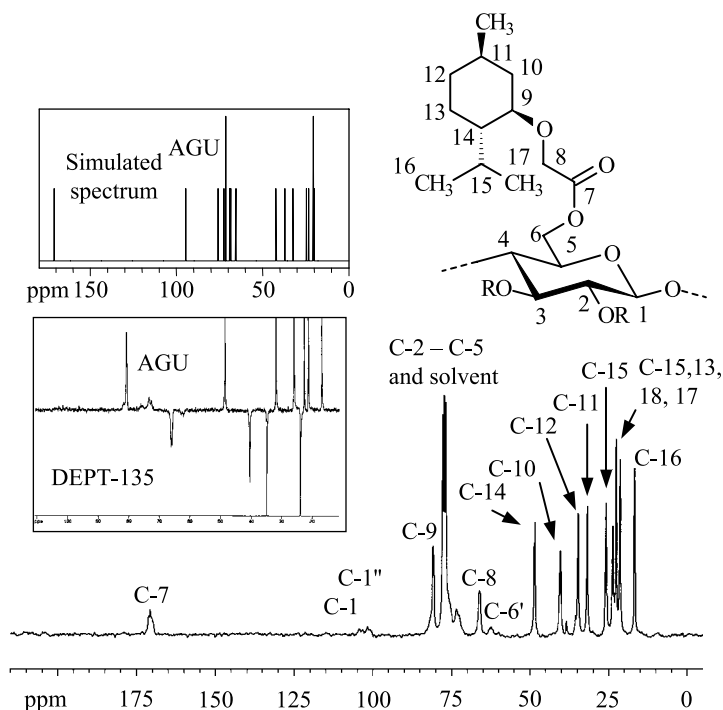
Fig. 5.33. ^{13}C NMR spectrum of cellulose (−)-menthyloxyacetate (DS 1.66, in CDCl$_3$), compared with its simulated spectrum and a DEPT135 NMR spectrum (adapted from [234])

For complete assignment of the ^{1}H NMR spectrum of this complex polysaccharide ester, simulation and a variety of two-dimensional techniques including ^{1}H,^{1}H-COSY-DQF-, HSQC-DEPT- and HSQC-TOCSY-NMR spectra (Fig. 5.34) are necessary.

The protons of the menthyloxyacetate moiety are visible in the range from 0.82 to 3.19 and at 4.13 ppm (for complete assignment, see experimental section of this book). The two sets of protons of the methyl moieties of C-16 and C-17 have different chemical environments and therefore show two separate signals at 0.82 and 0.92 ppm. The presence of chiral carbon atoms results in splitting of the signals of the protons in position 10, 12 and 13. Therefore, peaks at 0.87 and 1.67 (H-12 and H-12*), at 0.93 and 2.08 (H-10 and H-10*), and at 0.99 and 1.64 ppm (H-13 and H-13*) can be found. Signals of the AGU are observed at 3.42–4.98 ppm. The NMR spectroscopy confirms the structural homogeneity of the ester. There are no hints for side reactions or impurities.

The conversion of cellulose with camphor-10-sulphonic acid via in situ activation with CDI can not be used to obtain a chiral sulphonic acid ester of cellulose. Only very small amounts of sulphonic acid ester functions can be introduced, in agreement with results of the chemistry of low-molecular mass alcohols showing a much lower efficiency of CDI for the preparation of sulphonic acid esters [228].
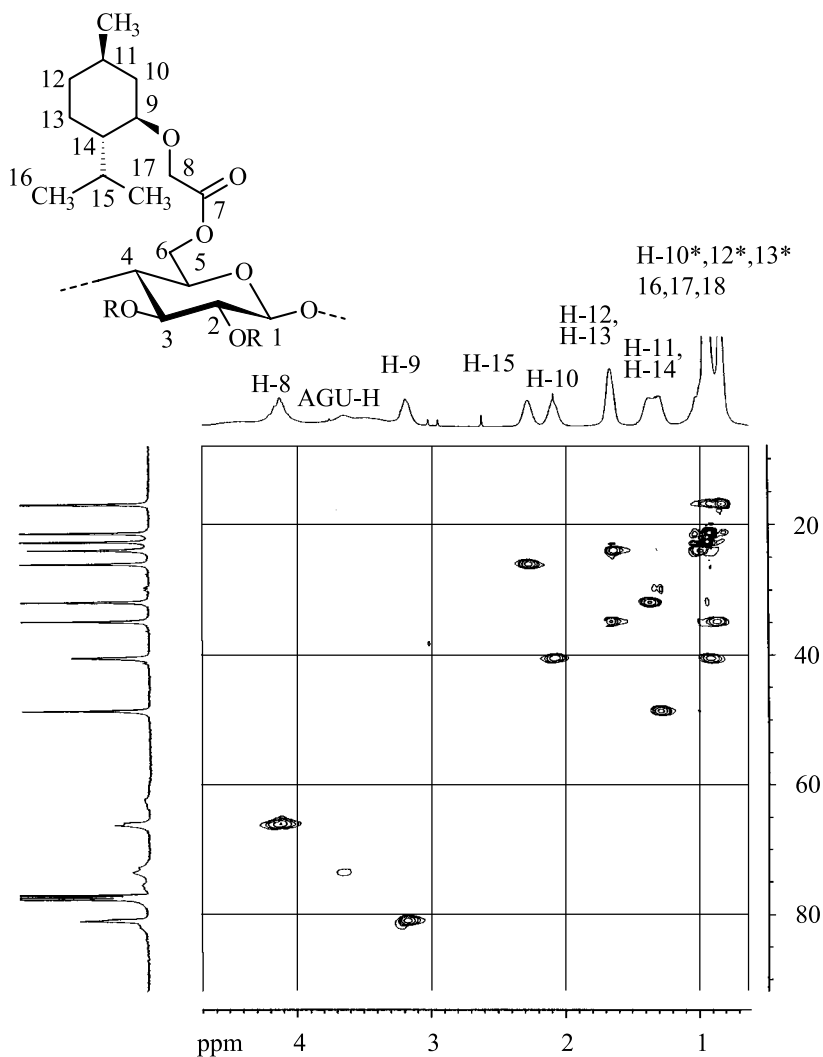
Fig. 5.34. HSQC NMR spectrum of cellulose (−)-menthyloxyacetate (DS 1.66, in CDCl$_3$). R = H or the ester moiety, according to the DS and the distribution of the functional groups (adapted from [234])

In the case of unsaturated esters, the double bonds can be exploited for subsequent cross-linking or for grafting reactions. Nevertheless, these reactions need to be suppressed during the esterification with the polysaccharide to obtain soluble products. Therefore, mild reaction conditions are indispensable for reactive unsaturated acids. In this regard, CDI is very helpful, although the preparation of esters with terminal double bonds may be combined with the introduction of covalently bound imidazole units, which is shown for the conversion with acrylic acid in Fig. 5.35.
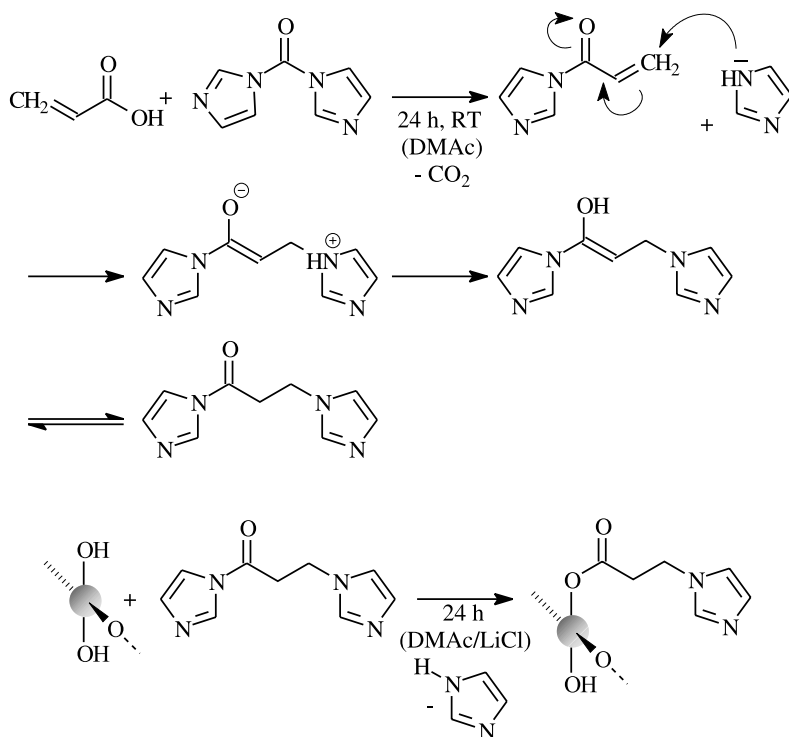
Fig. 5.35. Mechanistic considerations for the binding of imidazole containing esters via reaction of polysaccharides with acrylic acid (adapted from [233])

Nonetheless, via in situ activation with CDI, the preparation of 3-(2-furyl)-acrylcarboxylic acid esters of cellulose is possible. A maximum DS of 1.52 is obtained, and the sample is soluble in the freshly precipitated form. Isolation and drying gives an insoluble product, which is obviously due to a spontaneous cross-linking process. Structural analysis by means of ^{13}C NMR spectroscopy in DMSO-d_6 can be carried out for derivatives with lower DS showing characteristic signals, i.e. at 165.3 ppm for the carbonyl carbon atom of the ester, at 150.1 (C-10), 145.8 (C-13) 116.5 (C-12) and 112.5 ppm (C-11) for the furan ring, at 145.8, (C-9), 131.6 ppm (C-8) for the double bond, and from 60.2 to 102.9 ppm for the AGU. A preferred functionalisation of position 6 and no impurities (oxidation reactions, imidazole) are found. DS values calculated from ^{1}H NMR spectra of completely functionalised samples by subsequent perpropionylation of the remaining OH groups in CDCl$_3$ are summarised in Table 5.26. Both the pure 3-(2-furyl)-acrylcarboxylic acid esters of cellulose and the propionylated samples need to be stored in the dark. Otherwise, they become insoluble due to cross-linking.

Preparation of a furan-2-carboxylic acid ester of cellulose is achieved using CDI for the in situ activation. DS values up to 1.97 are obtainable (Table 5.26, entry **6**). Structural evidence is gained by ^{13}C NMR spectroscopy (Fig. 5.36). Signals at

Table 5.26. Esterification of cellulose with furan-2-carboxylic acid, 3-(2-furyl)-acrylcarboxylic acid, and 4′-carboxybenzo-18-crown-6 via in situ activation with CDI (adapted from [234])

Conditions					Product		
Entry	Carboxylic acid	Molar ratio			DS	Solubility	
		AGU	Acid	CDI		DMSO	DMF
1	3-(2-Furyl)-acryl-	1	2.5	2.5	0.52	+	–
2		1	5.0	5.0	1.14	+	+
3		1	7.5	7.5	1.52	+	–
4	Furan-2-	1	2.5	2.5	0.80	+	+
5		1	5.0	5.0	1.49	+	+
6		1	7.5	7.5	1.97	+	+
7	(Benzo-18-crown-6)-4′-	1	2.3	2.3	0.40	+	–
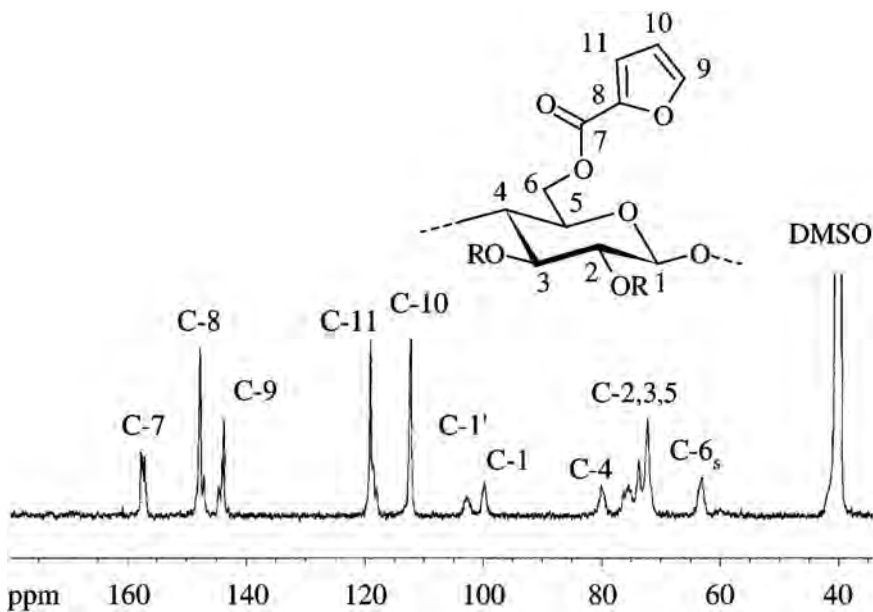
Fig. 5.36. ^{13}C NMR spectrum of a furan-2-carboxylic acid ester of cellulose (DS = 1.91, adapted from [234])

112.1, 118.8, 143.4 and 157.4 ppm show that the unsaturated system is stable under the reaction conditions applied. From the peak at 63.1 ppm and the occurrence of two signals at 100.2 (C-1′) and 102.4 ppm (C-1), a complete functionalisation at the primary OH-group and partial functionalisation in position 2 can be concluded for samples with DS values higher than 1.4 (Table 5.26, entries **4–6**). These findings are comparable with results for furan-2-carboxylic acid esters synthesised homogeneously by conversion of cellulose in DMAc/LiCl applying the acid chloride [170, 235].

Table 5.27. GPC analysis (in DMSO) of 3-(2-furyl)-acrylcarboxylic acid ester of cellulose (Table 5.26, entry **3**) and furan-2-carboxylic acid esters (entries **4**, **6**)

Entry	DS	M_w (g mol^{-1})	DP
3	1.52	7.21×10^4	208
4	0.80	6.55×10^4	275
6	1.97	6.91×10^4	200

GPC studies for the unsaturated cellulose esters reveal a bimodal distribution, as usually observed for partially functionalised cellulose derivatives. The low-molecular mass fraction can be assigned to polymers dissolved in a molecular-dispersed manner. The depolymerisation during the conversion is rather small (Table 5.27). Product **4** possesses a DP of 275 (the starting cellulose Avicel® has a DP of 280).

For the cellulose furan-2-carboxylic acid esters, the cross-linking process, which can be exploited for subsequent modification (see Application) of the derivative, e.g. in membrane shape, can be initiated by means of UV irradiation [234].

The introduction of crown ether moieties into the cellulose backbone is usually achieved by reactive coupling of amino-functionalised crown ethers with cyanuric chloride onto cellulose diacetate [236]. The material is valued as basis for an alkaline-ion sensitive electrode. A more efficient approach is the homogeneous esterification of cellulose with 4′-carboxybenzo-18-crown-6. Homogeneous conversion in DMAc/LiCl and in situ activation of the carboxylic acid with CDI is the reaction of choice. Cellulose 4′-carboxybenzo-18-crown-6 esters can be obtained
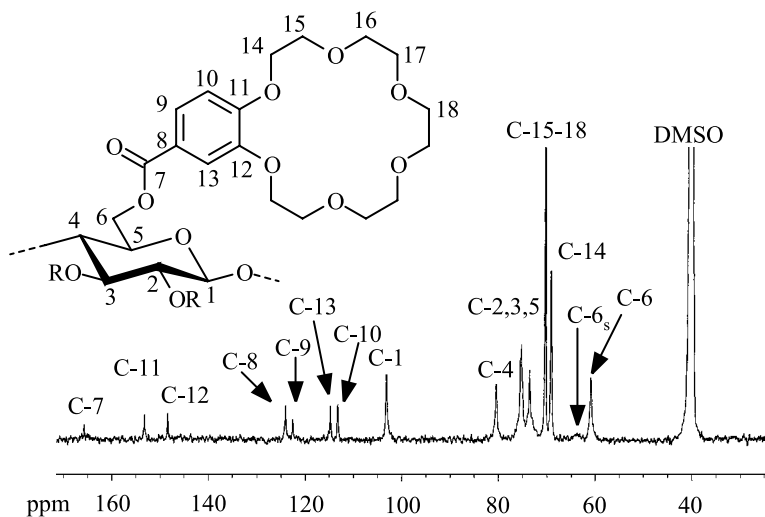
Fig. 5.37. ^{13}C NMR spectrum of a cellulose 4′-carboxybenzo-18-crown-6 ester (DS = 0.4, adapted from [234])

as white substances that dissolve in DMSO (Table 5.26). The polymer yields well-resolved ^{13}C NMR spectra, as shown in Fig. 5.37. In addition to the signals for the carbons of the modified AGU (103.2 to 60.1 ppm), resonances assigned to the carbon atoms of the carbonyl group of the ester function at 165.8 ppm, resonances of the crown ether moiety at 69.3, 70.4 ppm, and those for the carbons of the aromatic system at 113.3, 114.8, 148.5 and 153.3 ppm are observed.

The ^{1}H,^{1}H-COSY NMR spectrum (CDCl$_3$) of perpropionylated cellulose 4'-carboxybenzo-18-crown-6 ester is shown in Fig. 5.38. These complex esters give only seven signals for the protons of the AGU, meaning that the pattern of substitution does not yield signal splitting. ^{1}H NMR spectroscopy can still be applied
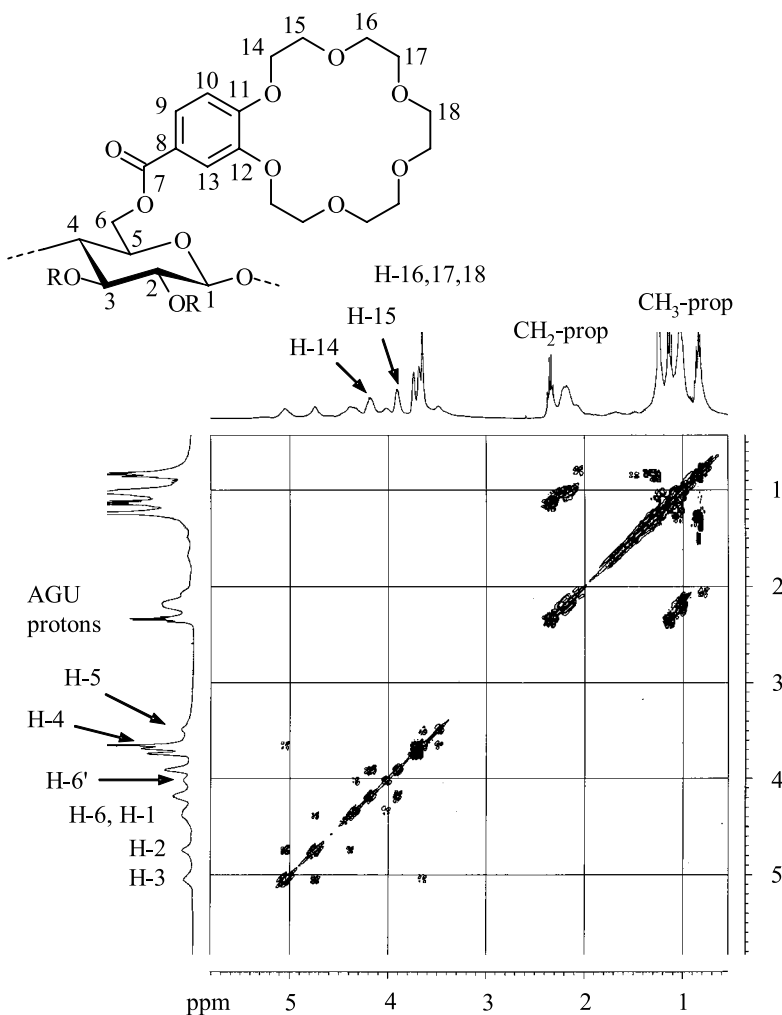

Fig. 5.38. ^{1}H,^{1}H-COSY NMR spectrum (CDCl$_3$) of a perpropionylated cellulose 4'-carboxybenzo-18-crown-6 ester (adapted from [324])

for the DS determination (see Sect. 8.3). The DS is calculated from the ratio of the spectral integrals of the H-3 and H-2 protons of the repeating unit at 5.00 (H-3), 4.85 ppm (H-2) versus the CH_2-protons of the propionate moiety at 2.04–2.39 ppm and, gives a value of 0.40.

Cyclodextrin moieties may be bound to the polysaccharide backbones via formation of a Schiff's base [237] of chitosan with 2-*O*-(formylmethyl)-β-cyclodextrin or via immobilisation of cyclodextrin on polysaccharides using cross-linking agents, e.g. polymeric anionic reactive compounds [238]. An efficient alternative is the conversion of cellulose with carboxymethyl-β-cyclodextrin. The commercially available sodium salt form of the cyclodextrin derivative is converted to the free acid form by treatment with methanolic HCl (20% w/w). The in situ activation with CDI and the reaction with the polysaccharide should be carried out in one step in DMSO. Otherwise, i.e. during a separate activation step, the carboxymethyl-β-cyclodextrin reacts according to an intermolecular cross-linking of the imidazolide formed with remaining OH groups, and yields an insoluble precipitate. Thus, cellulose dissolved in DMAc/LiCl is treated directly with carboxymethyl-β-cyclodextrin and CDI for 16 h at 80 °C, leading to an insoluble product. The formation of the ester can be confirmed by the carbonyl group signal in the FTIR spectrum (ν(C=O) at 1724 cm^{-1}). Moreover, signals of unesterified carboxy moieties of the cyclodextrine not involved in ester formation are observed at 1655 and 1426 cm^{-1}.

The introduction of bulky alicyclic functions is performed by conversion of cellulose with adamantane carboxylic acid, yielding DS values up to 1.41 [169]. Comparison with reactions using the acid chloride and in situ activation with TosCl gives similar results to those of the esterification with fatty acids, i.e. slightly lower efficiency using CDI but less side reactions (white products) and easier workup. A ^{13}C NMR spectrum of adamantoyl cellulose (DS 0.68, Fig. 5.39) shows

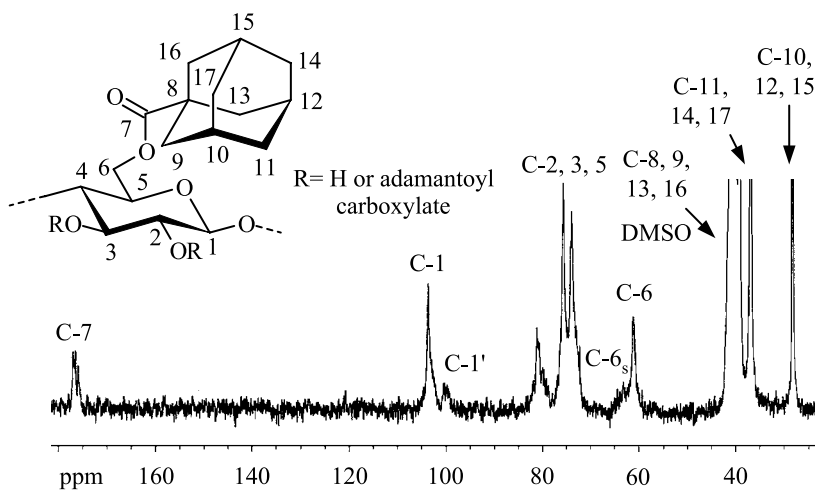**Fig. 5.39.** ^{13}C NMR spectrum of a cellulose adamantane-1-carboxylic acid ester (DS = 0.68, adapted from [169])

signals for the carbons of the modified AGU (103.7 to 60.1 ppm) and resonances of the carbon atoms of the adamantoyl ester moieties at 28.2 (C-10, C-12, C-15), 36.8 (C-11, C-14, C-17) and 39.16 ppm (C-9, C-13, C-16). The C-8 signal is overlapped by the solvent. The splitting of both the C-6 (63.1 ppm, C-6$_s$) and the C-1 signal (100.4 ppm for C-1 adjacent to a C-2 atom bearing an adamantoyl moiety) shows a roughly even distribution of substituents over the AGU. Despite the steric bulk of the adamantoyl moiety, no pronounced regioselectivity is observed.

In addition to DMAc/LiCl, DMSO/TBAF is an appropriate reaction medium for homogeneous acylation of cellulose applying in situ activation with CDI. Results of reactions of cellulose with acetic-, stearic-, adamantane-1-carboxylic- and furan-2-carboxylic acid imidazolides are summarised in Table 5.28.

Table 5.28. Homogeneous acylation of cellulose dissolved in DMSO/TBAF with different carboxylic acids, mediated by CDI

Entry	Conditions				Product	
	Carboxylic acid	Molar ratio			DS	Solubility
		AGU	Acid	CDI		
1	Acetic	1	3	3	0.51	DMSO, DMAc
2	Stearic	1	2	2	0.47	DMSO
3	Stearic	1	3	3	1.35	DMSO
4	Adamantane-1-carboxylic	1	2	2	0.50	DMAc/LiCl
5	Adamantane-1-carboxylic	1	3	3	0.68	DMSO, DMAc
6	Furan-2-carboxylic	1	3	3	1.91	DMSO, DMAc, Py

NMR spectra confirm that pure cellulose esters are obtained by precipitation in ethanol and no side reactions occur (tetra-*N*-alkylammonium fluorides typically decompose under anhydrous conditions [174]). Washing with ethanol is sufficient to completely remove the imidazole, as can be concluded from the lack of signals at 7.13 and 7.70 ppm (^{1}H NMR data).

The conversion of the dissolved cellulose with furan-2-carboxylic acid imidazolide (with a stoichiometry of AGU:reagent of 1:3) yields a rather high DS of 1.91 (Table 5.28, entry **6**), which corresponds to a remarkable reaction efficiency of 63%. NMR spectroscopy reveals the same pattern of substitution as that determined for a cellulose furan-2-carboxylic acid ester prepared in DMAc/LiCl. The aliphatic esters (cellulose acetate and stearate; entries **1–3**) show DS values up to 1.35. Reaction of cellulose in DMAc/LiCl using the carboxylic acid anhydrides leads to DS values of 1.2 for the acetate and of 2.1 for the stearate under similar conditions. This indicates a comparably high reactivity of the imidazolides of shorter carboxylic acids (C_2–C_4) towards hydrolysis caused by the water in the reaction medium (TBAF trihydrate is used). Imidazolides of long-chain aliphatic acids are less reactive in this solvent.

Cellulose adamantane-1-carboxylic acid esters obtained in DMSO/TBAF exhibit DS values of up to 0.68. The amazing conclusion from ^{13}C NMR spectroscopical studies (Fig. 5.39) is that the functionalisation with the bulky adamantoyl unit occurs more pronounced at position 2 if DMSO/TBAF is applied as medium. The reason might be partial hydrolysis of the ester formed during the reaction. GPC studies show only small depolymerisation (approximately 13%).

One can conclude that homogeneous esterification of cellulose with carboxylic acid/CDI in DMAc/LiCl and DMSO/TBAF with in situ-prepared carboxylic acid imidazolides is one of the simplest and most widely usable synthesis pathways for the preparation of a very broad variety of pure cellulose esters, which can easily be extended to other polysaccharides. In contrast to DCC or TosCl as reagents for in situ activation, the CDI is associated with no significant side reactions, even when DMSO is used as solvent, if the CDI is completely transformed to the imidazolide in the first step. The products obtained are only slightly degraded, pure, and highly soluble compounds. In the case of the reaction of carboxylic acids with active protons, e.g. OH, NH$_2$, terminal double- or triple bonds, protection prior to the esterification is necessary.

The combination DMSO/TBAF as solvent and CDI as reagent for in situ activation is one of the most convenient homogeneous paths for cellulose esterification, even for inexperienced personal. In the case of aromatic acids, the path is superior to the conversion in DMAc/LiCl in terms of efficiency and simplicity. Although the yields are diminished by the presence of water in the case of aliphatic acid imidazolides, the procedure is one of the most promising tools for the synthesis of cellulose derivatives with complex ester moieties, e.g. unsaturated and chiral moieties not accessible via the carboxylic acid anhydrides and -chlorides.

5.2.4 Iminium Chlorides

A mild and efficient method is the in situ activation of carboxylic acids via iminium chlorides. They are simply formed by conversion of DMF with a variety of chlorinating agents, including phosphoryl chloride, phosphorus trichloride and, most frequently, oxalyl chloride and subsequent reaction with the acid. During the reaction of acid iminium chlorides with alcohols, mostly gaseous side products are formed and the solvent is regenerated (Fig. 5.40, [239]).

The reaction is very mild. The synthesis of the intermediate is carried out at −20 °C. The complex formed is stable and no side reactions, such as the formation of HCl or the acid chloride, are observed. Consequently, it is a suitable process for polysaccharide esterification.

Acylation of cellulose with the long-chain aliphatic acids (stearic acid and palmitic acid), the aromatic acid 4-nitrobenzoic acid and adamantane-1-carboxylic acid is easily achieved. The formation of the iminium chloride and the conversion with the carboxylic acid are carried out as "one-pot reaction", i.e. DMF is cooled to −20 °C, oxalyl chloride is added very carefully and, after the gas formation ceases, the carboxylic acid is added. NMR spectroscopy reveals that the conversion succeeds with measurable yield in the case of acetic acid. The mixture is added to