Carbohydrate Research, 86 (1980) 33–41
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

ENEDIOL-ANION FORMATION AND β-ELIMINATION OF CYCLIC α-HYDROXYCARBONYL COMPOUNDS AS STUDIED BY U.V. AND N.M.R. SPECTROSCOPY

G. DE WIT*, C. DE HAAN†, A. P. G. KIEBOOM, AND H. VAN BEKKUM
Laboratory of Organic Chemistry, Delft University of Technology, Julianalaan 136, P.O. Box 5045, 2600 GA Delft (The Netherlands)

(Received January 7th, 1980; accepted for publication, February 15th, 1980)

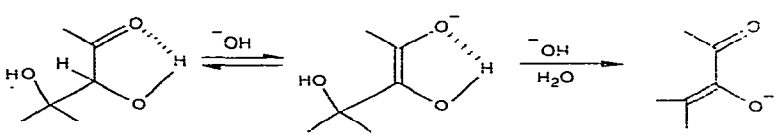
ABSTRACT

The behaviour of three cyclic α-hydroxycarbonyl compounds in aqueous, alkaline medium has been studied in order to establish the origin of the 310-nm band that shows up in the u.v. spectra of monosaccharides in alkaline medium. From u.v. and n.m.r. spectroscopy, it appears (*i*) that both enediol anions and β-elimination products give rise to an absorption band at ~310 nm, and (*ii*) that enolisation and β-elimination are strongly dependent on the reaction conditions and on the structure of the compound. A recent literature report on Mg(II)–enediol anion complexes of methyl hexosiduloses needs revision.

INTRODUCTION

Enolisation is generally considered to be an important process in the reactions of carbohydrates in alkaline solution[1–6]. It is assumed that relatively simple isomerisation reactions as well as degradation reactions of monosaccharides occurring in alkaline medium, *e.g.*, β-C–O or β-C–C bond fission, proceed *via* enediol-anion intermediates.

U.v. spectra of monosaccharides in alkaline medium show[5,6] an absorption band at 310 nm which can be attributed to the enediol anion and/or to the β-elimination product.



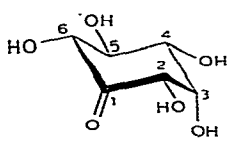
enediol anion β-elimination product

*Present address: Analytical Laboratory, Department of Research and Development, General Electric Plastics BV, Plasticslaan 1, Bergen op Zoom, The Netherlands.
†Present address: National Cash Register, Drommedarislaan 17, Utrecht, The Netherlands.

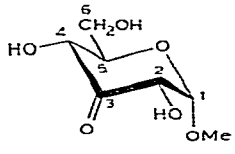
In the stable enediols described in the literature, the double bond is always conjugated, *e.g.*, with a carbonyl group as in ascorbic acid. The intermediate occurrence of non-conjugated enediol anions in alkaline solutions of α-hydroxycarbonyl compounds has been demonstrated by H/D and H/T exchange[1–4,7]. U.v. spectra[8–14] of cyclic α-hydroxyketones in protic solvents, as with the monosaccharides, sometimes contain absorptions at ~310 nm when recorded in alkaline medium[8,9]. However, both for the monosaccharides and for these α-hydroxyketones it is not clear whether this absorption is due to the enediol anion, to the β-elimination product, or to further degradation products.

Protected, non-conjugated enediols have been described. Heyns *et al.*[15] isolated acetylated enediols from 1,6-anhydro-β-D-hexopyranosuloses. Defaye *et al.*[16,17] reported the formation of an enediol complex with Mg(II) from methyl α-D-*arabino*-hexopyranosid-2-ulose and from methyl α-D-*ribo*-hexopyranosid-3-ulose.

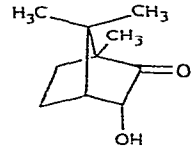
In connection with studies of the formation of enediol anions and β-elimination products from monosaccharides in aqueous, alkaline medium[18], the hydroxycarbonyl compounds *epi*-inosose (**1**), methyl α-D-*ribo*-hexopyranosid-3-ulose (**2**), and a mixture of 3-*endo*-hydroxycamphor (**3**) and 2-*endo*-hydroxy-*epi*-camphor have been examined in aqueous, alkaline solution by u.v. and n.m.r. spectroscopy in order to determine their behaviour and the possible origins of the 310-nm band in this medium. According to von Euler and Glaser[9], *epi*-inosose (**1**) shows a strong absorption at 305 nm in alkaline medium. This absorption may be due not only to the enediol anion but also to the β-elimination product. In view of the literature[16,17], methyl-α-D-*ribo*-hexopyranosid-3-ulose (**2**) was expected to be an excellent model compound for the formation of the enediol anion. However, some doubt arose about the correctness of the interpretation of the n.m.r. spectra, so that the behaviour of this model compound was reinvestigated. Both enolisation and β-elimination may occur with **1** and **2**, whereas only enolisation (and isomerisation) is possible for **3**, and this compound therefore seemed to be very suitable for finding out whether enediol anions can show an absorption at ~310 nm.



1



2



3

RESULTS AND DISCUSSION

epi-*Inosose* (1)

An aqueous, alkaline solution of *epi*-inosose shows an increasing u.v. absorption at 310 nm as a function of time. After 1–3 h, the maximum absorption value (D_∞) was attained under the conditions used (**1**, 0.11mM; KOH, 5mM; $CaCl_2$, up

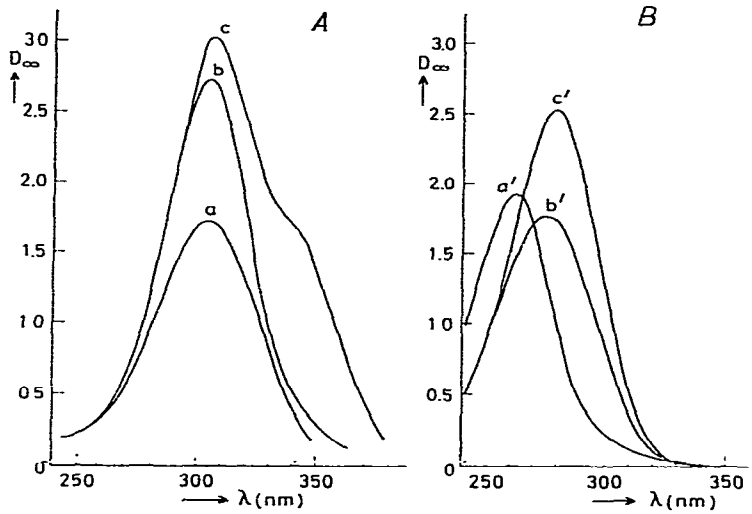


Fig. 1. (*A*) U.v. spectra of *epi*-inosose (**2**, 0.11mM) at 10° under N_2 after the attainment of the maximum absorption; (*a*) 5mM KOH, (*b*) 5mM KOH and 2mM $CaCl_2$, and (*c*) 5mM KOH and 10mM $CaCl_2$. (*B*) After acidification of solutions *a*, *b*, and *c* to pH ~4.

to 0.01M; T, 10°). The u.v. spectra are shown in Fig. 1 for the alkaline and the subsequently acidified solution. Analogously to the results of von Euler and Glaser[9], an absorption appears at ~305 nm in alkaline medium (KOH). After acidification (with HCl), an absorption appears instantaneously at 262 nm. When the solution is made alkaline again, the maximum absorption (D_∞) appears *instantaneously* at 305 nm. The presence of Ca(II) gives, in addition to a stronger absorption at 305 nm (curve *b*), an absorption band at ~340 nm if the Ca(II) concentration is high enough (curve *c*). Acidification of these solutions gives an absorption at 275 nm.

The ^{1}H- and ^{13}C-n.m.r. spectra do not leave any doubt that, upon addition of alkali to a solution of **1** in D_2O under mild conditions (4.2mM **1** in 5mM NaOD at 3–5°), the β-elimination product (4*R*,5*S*,6*R*)-2,4,5,6-tetrahydroxy-2-cyclohexen-1-one (**4**) is formed. The ^{1}H-n.m.r. spectra (Fig. 2*a*,*b*) show complete conversion of **1** into **4** with elimination of H-2. The signal at 6 p.p.m. (Fig. 2*c*) indicates that H-3 is adjacent to a double bond as in **4** and not as in the enediol. The ^{13}C-n.m.r. spectrum (Fig. 3) further confirms the presence of both a carbonyl (C-1) and an alkenic (C-2 and C-3) group in **4**. This result supports the proposal of Angyal *et al.*[19] that the conversion of *epi*-inosose into *trans*-2,3,4,5-tetrahydroxy-2-cyclohexen-1-one occurs *via* **4**. Apparently, the somewhat more-rigorous reaction conditions 75mM **1** in 0.6M $Ba(OH)_2$ at 31° applied by these authors caused fast isomerisation of **4**.

In the β-elimination reaction, HO-3 is eliminated selectively, and this process is assumed to be irreversible. It is not clear whether direct E-2 elimination in **1** occurs or whether reaction *via* the 1,2-enediol anion is involved. In both cases, elimination of the axial HO-3 is expected to be favoured.

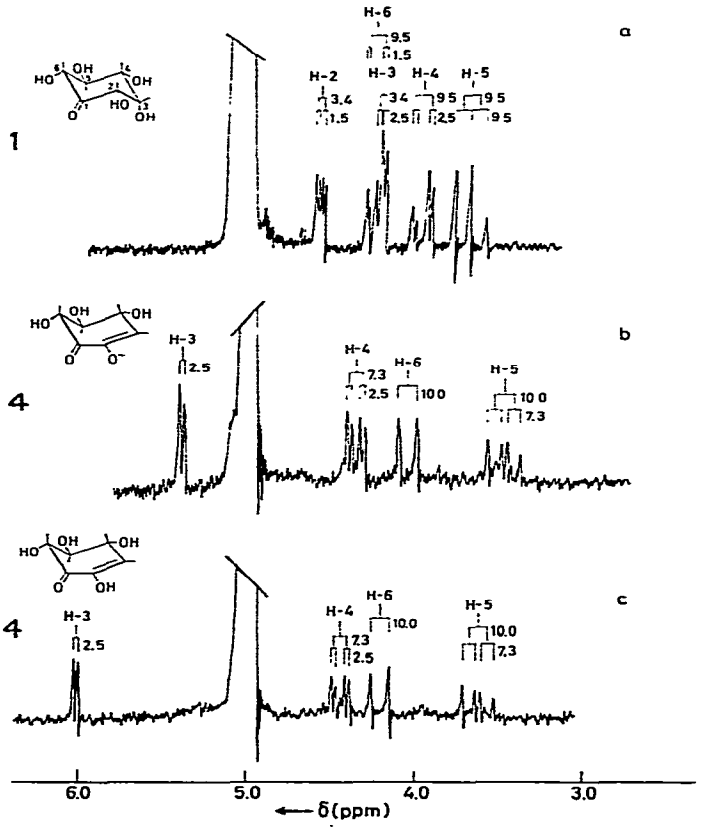


Fig. 2. ^{1}H-N.m.r. spectrum (100 MHz) of *epi*-inosose (**1**, 4.2mM) at 3-5° in (*a*) D_2O, (*b*) 5mM NaOD, and (*c*) solution *b* after acidification to pH ~4.

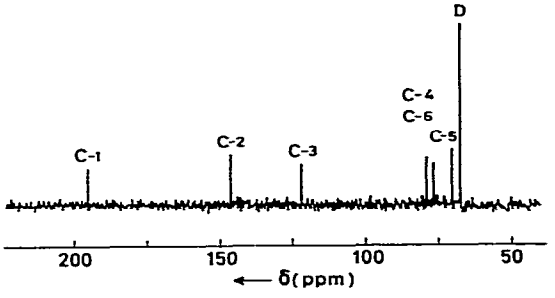


Fig. 3. ^{13}C-N.m.r. spectrum (25.2 MHz, 3–5°, D_2O, pH ~4) of **4** as formed from the reaction of *epi*-inosose (**2**, 4.2mM) in alkaline medium (5mM NaOD in D_2O at 3–5°); 1,4-dioxane as internal reference (D).

Upon acidification of the reaction mixture, the u.v. spectrum changes: pH ≥ 7, λ_{max} 303 nm (log ε = 3.5); pH ≤ 4, λ_{max} 206 nm (log ε = 3.7). On the basis of the n.m.r. results, this change can now be attributed to the formation of ionised and non-ionised* **4**, respectively. It should be noted that Ca(II) has an influence, possibly because of complex formation with **4**, considering the absorption at 275 nm in acid medium (Fig. 1b). The ^{1}H-n.m.r. spectrum of **1** (7.1mM) after reaction in KOH (5.3mM) in the presence of Ca(II) (16mM $CaCl_2$) also showed the formation of **4** at 10°. The absorption at 342 nm is perhaps due to a further degradation product.

Methyl α-D-ribo-*hexopyranosid-3-ulose* (**2**)

According to Defaye *et al.*[16], **2** forms a 2:1 complex in alkaline medium in the presence of Mg(II), the ^{1}H- and ^{13}C-n.m.r. spectra of the product indicating co-ordination of magnesium with O-2 and O-3 of the 2,3-enediol anion. They based this inference on the fact that the H-2 signal was absent in the ^{1}H-n.m.r. spectrum of the "magnesium complex", whereas the other signals had the same chemical shift as those of **2** and the same coupling constants ($J_{1,2}$ was lacking). In the ^{13}C-n.m.r. spectrum of the complex, they found the signals for C-3** and C-2 to be lacking. The other resonances were identical with those[16] of **2**. Some extra signals of small intensity were also present, among which that at 99.4 p.p.m., attributed by Defaye *et al.* to C-2 and C-3 of the Mg(II)–enediol complex, had the greatest intensity.

Preparation of the "Mg(II) complex" according to the procedure of Defaye *et al.*[16] (reaction of **2** in $NaOD/D_2O$ in the presence of $MgCl_2$) gave a product whose ^{1}H-n.m.r. data were analogous to those reported[16]. However, if the reaction was performed in protic medium ($NaOH/H_2O/MgCl_2$), a product was obtained having ^{1}H- and ^{13}C-n.m.r. spectra that are *identical* with those of **2**.

The n.m.r. spectra of **2** after reaction in $NaOD/D_2O/Mg(II)$ can now be accounted for by H/D exchange of H-2 with the solvent, which was overlooked by Defaye *et al.* The disappearance of the C-3 signal was probably due to measurement at too small a spectral width, while the "back-folded" signal was not visible because of a wrong phase setting; the H/D exchange of H-2, involving the 2,3-enediol anion, also affects the relaxation time of C-3. The n.m.r. data indicate that the concentration of the enediol anion is low. We further observed that degradation does not occur in the presence of Mg(II), whereas β-elimination of the methoxyl group takes place in the absence of Mg(II); this indicates a stabilising influence of $Mg(OH)_2$.

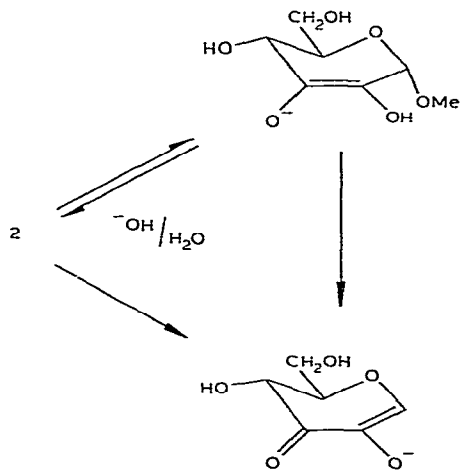
In the u.v. spectrum of **2** in KOH (0.02M with 0.01M $MgCl_2$ at 10°), strong absorptions are observed between 310 and 340 nm, which, upon acidification, change into absorptions at 285–290 nm. This change corresponds to the formation of β-elimination products. The above-mentioned stabilising influence of $Mg(OH)_2$ is not perceptible with the 30-fold dilution under u.v. conditions.

---

*The calculated value[13] for the absorption of non-ionised **4** in water is 266 nm.

Defaye *et al.*[16] reported that the C-3 signal of **2 occurred at 179.9 p.p.m., whereas we find the value to be 207.0 p.p.m. They probably measured the spectrum at too small a spectral width (*e.g.*, 5000 Hz = 198 p.p.m. at 25.2 MHz). The signal at 179.9 p.p.m. is then caused by so-called back-folding.

The u.v. spectra of **2** in KOH [without Mg(II)] show absorptions at ~320 nm and at 340 nm. After 16 h, only part of the absorption at 340 nm remains; after acidification, this changes into an absorption at 290 nm. These changes correspond to the formation of the *β*-elimination product **5** in addition to the enediol anion. Moreover, from the u.v. spectra, the conversion of the enediol anion into the *β*-elimination product can be clearly inferred.

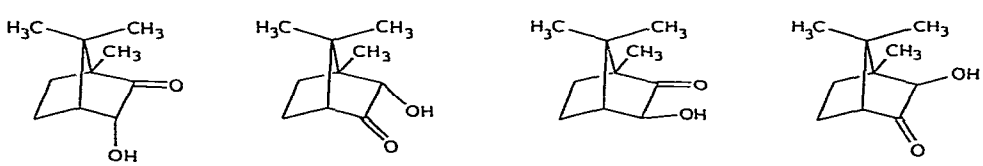


5

Summarising, the u.v. measurements in KOH solution show that enediol formation ($\lambda_{\text{enediol anion}}$ ~320 nm) is followed by *β*-elimination. The conclusion of Defaye *et al.*[16] that, in the presence of Mg(II), a complete conversion of **2** into a Mg(II) complex of the enediol anion takes place in alkaline medium is erroneous and is based on an incorrect interpretation of the n.m.r. spectra. In this medium, enolisation does take place (H/D exchange), but the concentration of the enediol anion is too low to be observed by n.m.r. spectroscopy.

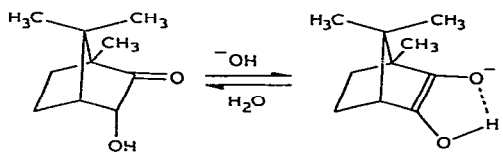
3-endo-*Hydroxycamphor and 2*-endo-*hydroxy*-epi-*camphor*

Coulombeau and Rassat[7] found that, in an alkaline methanol solution, the interconversion **3a–3d** takes place without any side reactions, leading to an equilibrium mixture of the four isomers.



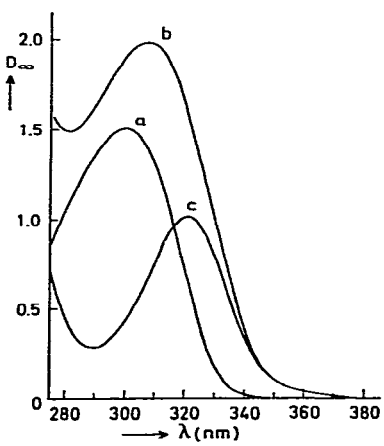
3a 3b 3c 3d

Since 3 is evidently able to form an enedial anion without degradation, it should be a good model compound for identifying the region of u.v. absorption of enediol anions. The u.v. spectrum of 3 in 50% aqueous methanol shows a maximum at 303 nm with $\varepsilon = 29$ (Fig. 4*a*). In alkaline medium, a small shift of the absorption towards greater wavelength occurred at once, together with an increase in the intensity of the absorption (Fig. 4*b*). If the absorption of 3 in $CH_3OH/H_2O/KOH$ is measured with 3 in CH_3OH/H_2O as the reference, absorption curve *c* is obtained. Thus, in addition to the absorption of 3 at 303 nm, which remained constant, an absorption appeared at 323 nm. This D_{323} at first increased linearly with increase in alkalinity of the solution (Fig. 5). Upon acidification of the alkaline solution, the absorption at 323 nm disappeared and no new absorption was formed. The absorption at 323 nm is attributed to the enediol anion of 3:



If an ε value of ~3000 is assumed[18], the concentration of the enediol anion of 3 amounts to $\sim 7 \times 10^{-5}$M (*i.e.*, ~0.7% of 3) in 1.28M KOH in 1:1 methanol–water. A saturated solution of 3 in H_2O (~3mM) also shows an absorption band at 310 nm, which shifts to 320 nm upon addition of alkali (up to ~1.5M KOH).

Thus, it may be concluded that enediol anions should show absorptions in the 310-nm region.



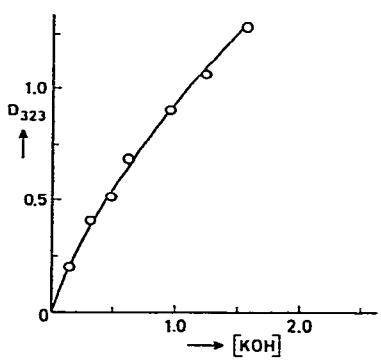


Fig. 4. U.v. spectra of hydroxy(*epi*)camphor (3) at 25° in 50% MeOH; (*a*) 0.01M 3, (*b*) 0.01M 3 in 1.28M KOH, (*c*) *b* with *a* as the reference solution (*b* — *a*).

Fig. 5. Effect of [KOH] on the absorption at 323 nm of hydroxy(*epi*)camphor (3, 0.01M) in 50% MeOH at 25° (with 3 in 50% MeOH as the reference solution).

EXPERIMENTAL

N.m.r. spectra were measured with Varian XL-100, CFT-20, or T-60 spectrometers. U.v. measurements were performed with a Cary Model 15 spectrometer at 10° under N_2, so as to prevent undesirable alkaline degradation and oxidation reactions.

Compounds **1–3** were prepared essentially according to literature methods[21–28]. In general, the syntheses were monitored by t.l.c. (silica gel; dichloromethane–ether, 3:1; detection with 5% H_2SO_4 in ethanol, 30 min at 120°), and the purity of the final products was checked by g.l.c. after trimethylsilylation[29].

epi-Inosose[20] (**1**) had $\lambda_{max}^{H_2O}$ 275 nm (ε 30). ^{1}H-N.m.r. data (D_2O): δ 4.60 (dd, $J_{2,3}$ 3.4, $J_{2,6}$ 1.5 Hz, H-2), 4.20 (dd, $J_{3,4}$ 2.5 Hz, H-3), 3.90 (dd, $J_{4,5}$ 9.5 Hz, H-4), 3.60 (t, $J_{5,6}$ 9.5 Hz, H-5), and 4.24 (d, H-6).

Methyl α-D-*ribo*-hexopyranosid-3-ulose[21–27] (**2**) had $\lambda_{max}^{H_2O}$ 288 nm (ε = 120). ^{1}H-N.m.r. data (D_2O): δ 5.22 (d, $J_{1,2}$ 4.5 Hz, H-1), 4.63 (dd, $J_{2,4}$ 1.2 Hz, H-2), 4.40 (dd, $J_{4,5}$ 10 Hz, H-4), 3.78 (ddd, $J_{5,6}$ 2, $J_{5,6'}$ 4 Hz, H-5), 3.96 (dd, $J_{6,6'}$ −13 Hz, H-6), 3.87 (dd, H-6'), and 3.42 (s, OMe).

3-*endo*-Hydroxycamphor (**3a**) and 2-*endo*-hydroxy-*epi*-camphor (**3b**) were obtained as a 2:3 mixture by the method of Coulombeau and Rassat[28]. U.v. data (CH_3OH): λ_{max} 303 nm (ε = 29).

ACKNOWLEDGMENTS

We thank Mr. M. S. Nieuwenhuizen for experimental assistance and Mr. A. Sinnema for helpful discussions.

REFERENCES

1 H. S. Isbell, H. L. Frush, C. W. R. Wade, and C. E. Hunter, *Carbohydr. Res.*, 9 (1969) 163–175.
2 H. S. Isbell, K. Linek, and K. E. Hepner, Jr., *Carbohydr. Res.*, 19 (1971) 319–327.
3 M. S. Feather, *Carbohydr. Res.*, 7 (1968) 86–89.
4 J. C. Sowden and R. Schaffer, *J. Am. Chem. Soc.*, 74 (1952) 505–507.
5 F. Petuely and N. Meixner, *Chem. Ber.*, 86 (1953) 1255–1263.
6 T. I. Khomenko and O. V. Krylov, *Kinet. Catal. (USSR)*, 15 (1974) 555–559.
7 C. Coulombeau and A. Rassat, *Bull. Soc. Chim. Fr.*, (1971) 505–516.
8 K. Heyns and H. Paulsen, *Chem. Ber.*, 86 (1953) 833–840.
9 H. von Euler and A. Glaser, *Ark. Kemi*, 8 (1955) 61–65.
10 O. Theander, *Acta Chem. Scand.*, 12 (1958) 1887–1896.
11 K. Heyns, J. Weyer, and H. Paulsen, *Chem. Ber.*, 98 (1965) 327–333.
12 A. J. Fatiadi and H. S. Isbell, *J. Res. Natl. Bur. Stand., Sect. A*, 68 (1964) 287–299.
13 A. I. Scott, *Interpretation of the Ultraviolet Spectra of Natural Products*, Pergamon Press, Oxford, 1964.
14 H. Dahn and H. Hauth, *Helv. Chim. Acta*, 40 (1957) 2249–2260.
15 K. Heyns, P. Köll, and H. Paulsen, *Chem. Ber.*, 104 (1971) 3096–3100.
16 J. Defaye, H. Driguez, and A. Gadelle, *Appl. Polym. Symp.*, 28 (1976) 955–969.
17 A. Gadelle, Thesis, University of Grenoble, 1976.
18 G. de Wit, A. P. G. Kieboom, and H. van Bekkum, *Carbohydr. Res.*, 74 (1979) 157–175.
19 S. J. Angyal, D. Range, J. Defaye, and A. Gadelle, *Carbohydr. Res.*, 76 (1979) 121–130.
20 Th. Posternak, *Methods Carbohydr. Chem.*, 1 (1962) 289–291.
21 A. N. de Belder and E. Wirén, *Carbohydr. Res.*, 24 (1972) 166–168.

22 R. W. JEANLOZ AND D. A. JEANLOZ, *J. Am. Chem. Soc.*, 79 (1957) 2579–2583.
23 B. H. THEWLIS, *Staerke*, 27 (1975) 336–338.
24 J. DEFAYE AND A. GADELLE, *Carbohydr. Res.*, 35 (1974) 264–269.
25 B. LINDBERG AND K. N. SLESSOR, *Acta Chem. Scand.*, 21 (1967) 910–914.
26 D. C. BAKER, J. DEFAYE, A. GADELLE, AND D. HORTON, *J. Org. Chem.*, 41 (1976) 3834–3840.
27 J. DEFAYE AND A. GADELLE, *Carbohydr. Res.*, 56 (1977) 411–414.
28 C. COULOMBEAU AND A. RASSAT, *Bull. Soc. Chim. Fr.*, (1970) 1199–1209.
29 C. C. SWEELEY, R. BENTLEY, M. MAKITA, AND W. W. WELLS, *J. Am. Chem. Soc.*, 85 (1963) 2497–2507.