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Note

^{13}C-N.m.r. structural study on an enteric pharmaceutical coating cellulose derivative having ether and ester substituents*

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A cellulose derivative having two types of ether (methyl and 2-hydroxypropyl) and ester (acetyl and succinyl) substituents, namely *O*-(2-hydroxypropyl)-*O*-methylcellulose acetate succinate (HPMCAS), has been recently introduced as an entero-soluble material for pharmaceutical coating[1,2]. The enteric property, which is characterized by the combination of gastric resistance and intestinal solubility, may be optimized through control of the detailed distribution pattern of four substituent groups on a glucose residue. Consequently, a simple and reliable analytical method for HPMCAS samples would be of significant value both for elucidating structure–property relationships and for quality control in production.

We have recently reported ^{13}C-n.m.r. structural studies on a series of cellulose ethers[3–7], in which hydroxyl groups on the glucose residues and, in some cases, also those at the end of substituent groups are peracetylated, and have demonstrated that the acetyl carbonyl carbon signal may be utilized as a remarkably sensitive n.m.r. probe for monitoring its substitution position on a glucose residue. Based on these results, we have performed here a ^{13}C-n.m.r. study on HPMCAS samples having different acetyl and succinyl contents. Both acetyl and succinyl ester-carbon signals were found particularly informative for providing the complete distribution pattern of both ester substituents, either on the 2-, 3-, and 6-position of the glucose residue or at the end of hydroxypropyl substituents.

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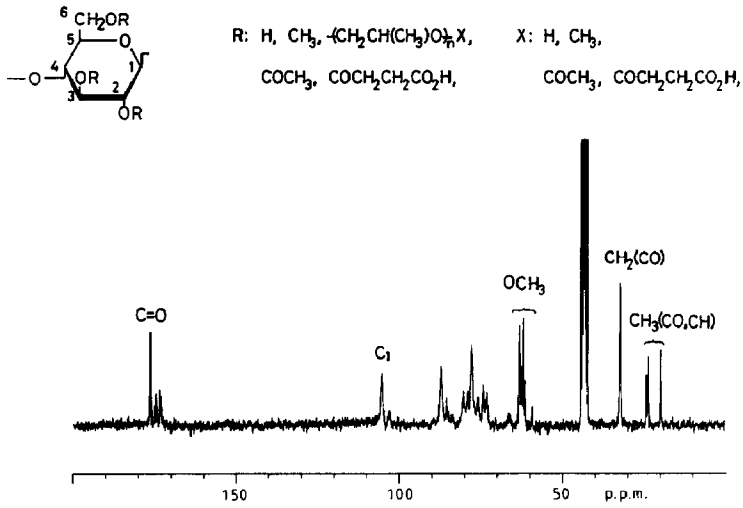

Fig. 1. Full-range ^{13}C-n.m.r. spectrum of HPMCAS in Me_2SO-d_6 at 100° (Sample 3 in Table I).

A full-range ^{13}C-n.m.r. spectrum of a HPMCAS sample is shown in Fig. 1. Besides the signals for C-2–C-6 in the glucose residue grouped at 60–80 p.p.m., those for the substituent groups are observed separately, being respectively, the hydroxypropyl methyl group at 19.9 p.p.m., the acetyl methyl groups at 23.8 and 24.3 p.p.m., the succinyl methylene groups at 32.4 p.p.m., the terminal methoxymethyl group of the hydroxypropyl groups at 59.2 p.p.m., and that of the glucose residue at 61–63 p.p.m. as four peaks. The signal intensities of these peaks were compared with that of the C-1 signal, which was split into two peaks at 103.1 and 105.2 p.p.m., reflecting the substitution mode on the O-2 position[6], and permitting estimation of the total content of four substituents. In Table I, the total values thus obtained are listed, together with those from chemical analysis; they show satisfactory agreement with each other.

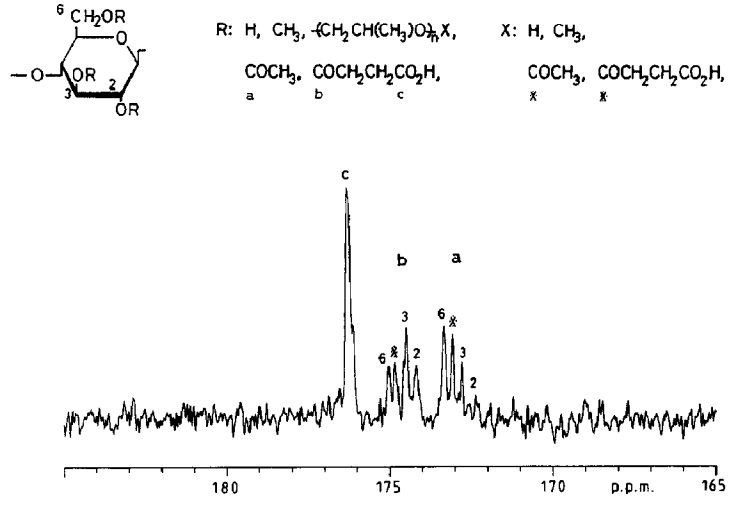

Fig. 2. Carbonyl region of the ^{13}C-n.m.r. spectrum of HPMCAS in Me_2SO-d_6 at 100° (Sample 3 in Table I).

The carbonyl region of the ^{13}C-n.m.r. spectrum of a HPMCAS sample is shown in Fig. 2. Both acetyl and succinyl ester carbonyl signals are observed to be resolved into four peaks, reflecting their substitution positions on either the glucose residue or at the end of hydroxypropyl substituents. The four peaks in the acetyl carbonyl region are assigned as follows[6,7]: those at the 2 (172.2), 3 (172.6), and 6 (173.4) positions of the glucose residue and that at the end of the hydroxypropyl substituent (172.9).

Four peaks in the succinyl ester carbonyl region were similarly assigned: those on the 2 (174.2), 3 (174.5) and 6 (175.1) positions of the glucose residue and that at the end of the hydroxypropyl group (174.9).

The quantitative structural parameters for three HPMCAS samples having different acetyl and succinyl contents are summarized in Table I. The sum of methyl, acetyl, and succinyl groups at the end of the hydroxypropyl substituent was almost equal to the total content of hydroxypropyl groups. This indicates that the hydroxypropyl substituent – in principle a mixture of oligo(propylene oxide) groups of different degrees of polymerization – is comprised of a single hydroxypropyl group and that the hydroxyl groups of the hydroxypropyl substituent are completely capped by either methyl, acetyl, or succinyl groups in these HPMCAS samples.

As the distribution of the sum of methyl and hydroxypropyl groups in a HPMCAS sample could be estimated through ^{13}C-n.m.r. analysis of a methylhydroxypropylcellulose sample after peracetylation of its hydroxyl groups[6,7], the composition of substituents at the 2, 3, and 6 positions of the glucose residue was determined and is listed in Table II. Substitution of the 2- and 6-hydroxyl groups was almost complete, whereas the H-3 position was still partly unsubstituted.

In conclusion, detailed structural parameters of a cellulose derivative having ether and ester substituents may be determined by means of a ^{13}C-n.m.r. technique in which the ester carbonyl carbon signals are utilized as remarkably sensitive structural probes to monitor the distribution pattern of substituents.

EXPERIMENTAL

Materials. — Hydroxypropyl methylcellulose acetate succinate (HPMCAS) samples were prepared by treating *O*-(hydroxypropyl)-*O*-methylcellulose with Ac_2O and with succinic anhydride as described elsewhere[1].

Methods. — The ^{13}C-n.m.r. measurements were performed with a JEOL JNM GX-270 apparatus at 67.8 MHz with a 5- or 10-mm diameter dual C,H probe in Me_2SO-d_6 at 100°; there was no detectable degradation of samples during the measurements. Chemical-shift values are referenced to the solvent signal of Me_2SO-d_6 (43.5 p.p.m.). Quantitative ^{13}C-n.m.r. measurements were performed with a 10-mm diameter dual C,H probe by means of a non-n.O.e. gated-decoupling technique with a pulse-repetition time of 100 s, to avoid errors from T_1 variation of signals. Approximately 2000 transients were accumulated to provide a satisfactory signal-to-noise ratio for the integration of signal areas, and the C-1 signal area was used as the base unit for calibration. The experimental error in the integration of the signal areas[8] in the present study was generally within ± 5–10%.

TABLE I

Structural parameters of *O*-(2-hydroxypropyl)-*O*-methylcellulose acetate succinate samples

Sample	CH_3[a]			$CH_2CH(CH_3)O-X$[b]				$COCH_3$[c]				$CO(CH_2)_2CO_2H$			
	Glc	*Hp*	*Total*	*Me*	*Ac*	*Su*	*Total*	*2*	*3*	*6*	*Total*	*2*	*3*	*6*	*Total*
1	1.80	0.06	1.86	0.06	0.13	0.04	0.23	0.10	0.19	0.22	0.64	0.04	0.04	0.04	0.16
			1.82[e]				0.21[e]				0.65[e]				0.14[e]
2	1.79	0.08	1.87	0.08	0.11	0.06	0.25	0.08	0.14	0.16	0.49	0.06	0.09	0.08	0.28
			1.82[e]				0.24[e]				0.50[e]				0.28[e]
3	1.79	0.05	1.84	0.05	0.08	0.09	0.23	0.06	0.13	0.12	0.39	0.08	0.16	0.09	0.42
			1.84[e]				0.23[e]				0.43[e]				0.41[e]

[a] Distribution of methyl groups, Glc: On the glucose residue, Hp: on the hydroxypropyl end group. [b] End groups of the hydroxypropyl group, Me: methyl, Ac: acetyl, and Su: succinyl groups. [c] Distribution of acetyl groups, 2, 3, 6,: positions on the glucose residue. [d] Distribution of succinyl groups, 2, 3, 6,: positions on the glucose residue. [e] From chemical analyses.

TABLE II

Distribution of substituents in *O*-(2-hydroxypropyl)-*O*-methylcellulose acetate succinate

Sample	*2*[a]				*3*[a]				*6*[a]				*Total*
	Me+Hp	*Ac*	*Su*	*Total*	*Me+Hp*	*Ac*	*Su*	*Total*	*Me+Hp*	*Ac*	*Su*	*Total*	
1	0.85	0.10	0.04	0.99	0.58	0.19	0.04	0.81	0.74	0.22	0.04	1.00	2.80
2	0.85	0.08	0.06	0.99	0.58	0.14	0.09	0.81	0.74	0.16	0.08	0.98	2.78
3	0.85	0.06	0.08	0.99	0.58	0.13	0.16	0.87	0.74	0.12	0.09	0.95	2.81

[a] Types of substituent on the glucose residue, Me+Hp: sum of methyl and hydroxypropyl groups; Ac: acetyl, and Su: succinyl groups.

Chemical analysis of methyl, hydroxypropyl, acetyl, and succinyl groups of HPMCAS samples was performed as to the methods reported earlier[1,6].

REFERENCES

1 Y. Onda, H. Muto, and K. Maruyama, U.S. Pat. 4,226,981 (1980).
2 T. Nagai, F. Sekigawa, and N. Hoshi, in J. W. McGinity (Ed.), *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms* (Vol. 36 of "Drugs and the Pharmaceutical Sciences"), Marcel Dekker, New York, 1989, pp. 81–152.
3 Y. Tezuka, K. Imai, M. Oshima, and T. Chiba, *Macromolecules*, 20 (1987) 2413–2423.
4 Y. Tezuka, K. Imai, M. Oshima, and T. Chiba, *Carbohydr. Res.*, 196 (1990) 1–10.
5 Y. Tezuka, K. Imai, M. Oshima, and T. Chiba, *Polymer*, 30 (1989) 2288–2291.
6 Y. Tezuka, K. Imai, M. Oshima, and T. Chiba, *Makromol. Chem.*, 191 (1990) 681–690.
7 Y. Tezuka, K. Imai, M. Oshima, and T. Chiba, *Polym. J.*, 23 (1991) 189–193.
8 R. Chujo, K. Hatada, R. Kitamaru, T. Kitayama, H. Sato, and Y. Tanaka, *Polym. J.*, 19 (1987) 413–424.