Carbohydrate Research, 137 (1985) 13–20
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

INTRAMOLECULAR HYDROGEN-BONDING IN PHENYL MONO-, DI-, AND TRI-*O*-METHYL-β-D-GLUCOPYRANOSIDES

AKIKO MATSUMOTO
Department of Chemistry, Kinki University School of Medicine, Sayama-cho, Osaka 589 (Japan)

AND MAMORU TAKASUKA*
Shionogi Research Laboratories, Shionogi and Co. Ltd., Fukushima-ku, Osaka 553 (Japan)
(Received August 1st, 1984; accepted for publication, August 24th, 1984)

ABSTRACT

I.r spectroscopy has been used to obtain frequency shifts and integrated intensities of the hydroxyl-stretching vibration band for intramolecular hydrogen-bonding in 14 phenyl mono-, di-, and tri-*O*-methyl-β-D-glucopyranosides in solution in dilute carbon tetrachloride. Intramolecular hydrogen-bonding with characteristic differences were exhibited by these compounds and the results were interpreted in terms of the conformation of the hydroxyl group. For *p*-substituted phenyl 3,4,6-tri-*O*-methyl-β-D-glucopyranosides, the hydroxyl-stretching vibration bands were also measured for dilute solutions in carbon tetrachloride, and a linear relationship was found between the shift to a lower wave number and the Hammett σ_p constant. This shift was attributed to intramolecular hydrogen-bonding between HO-2 and O-1 which has a weaker proton-accepting ability than that of MeO-3.

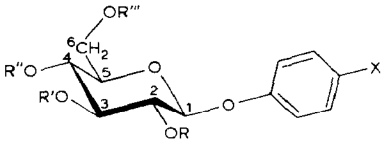
INTRODUCTION

Intramolecular hydrogen-bonding in alicyclic compounds has often been studied by i.r. spectroscopy because hydroxyl-stretching vibration bands provide much information on the molecular conformation[1–5]. However, although i.r. studies have been conducted on intramolecular hydrogen-bonds in sugars[6–9], no systematic studies have been carried out on methylated derivatives of phenyl β-D-glucopyranoside which possess a bitter taste. We now report on intramolecular hydrogen-bonding in the phenyl mono-, di-, and tri-*O*-methyl-β-D-glucopyranosides **1–14** and the *p*-substituted phenyl 3,4,6-tri-*O*-methyl-β-D-glucopyranosides **15–17**.

---

*To whom correspondence should be addressed.

0008-6215/85/$ 03.30



	R	*R'*	*R''*	*R'''*	*X*		*R*	*R'*	*R''*	*R'''*	*X*
1	H	Me	Me	Me	H	**10**	Me	Me	H	H	H
2	Me	H	Me	Me	H	**11**	H	H	H	Me	H
3	Me	Me	H	Me	H	**12**	H	H	Me	H	H
4	Me	Me	Me	H	H	**13**	H	Me	H	H	H
5	H	H	Me	Me	H	**14**	Me	H	H	H	H
6	H	Me	H	Me	H	**15**	H	Me	Me	Me	NO_2
7	H	Me	Me	H	H	**16**	H	Me	Me	Me	Cl
8	Me	H	H	Me	H	**17**	H	Me	Me	Me	Me
9	Me	H	Me	H	H						

RESULTS AND DISCUSSION

The spectra of **1**–**17** showed only the hydroxyl-stretching vibration bands (v_{OH} band) of the intramolecularly hydrogen-bonded hydroxyl groups. The i.r. parameters obtained are shown in Table I, together with the Hammett σ_p constants[10] of the substituents (X) in the *p*-substituted phenyl glycosides; ν_{OH} and A_{OH} are the

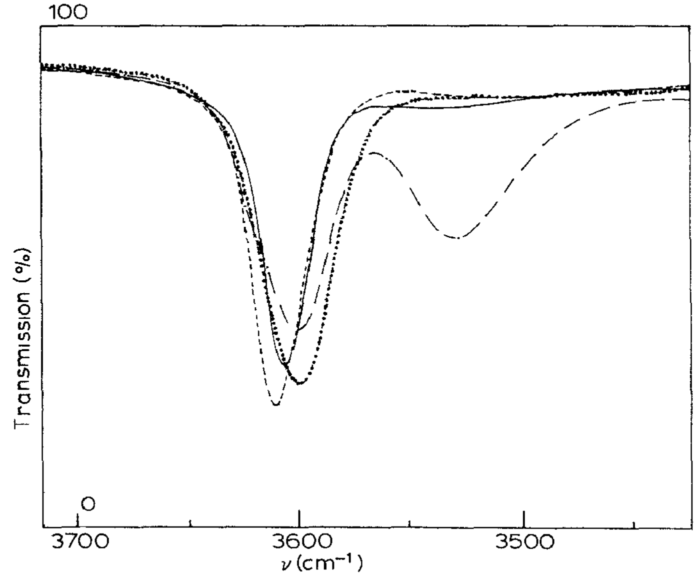


Fig. 1. I.r. spectra (2-cm cell) of phenyl tri-*O*-methyl-β-D-glucopyranosides in carbon tetrachloride: **1** (2.893 mM, -------), **2** (3.245 mM, · · · · · · ·), **3** (3.104 mM, ·—·—·—·), **4** (2 554 mM, ———).

TABLE I

I R PARAMETERS[a]

Compound	ν_{OH} *(cm^{-1})*	$\Delta\nu_{OH}$[b] *(cm^{-1})*	ε *(mol^{-1}.dm^3.cm^{-1})*	$\Delta\nu_{1/2}$ *(cm^{-1})*	10^{-4} A_{OH} *(mol^{-1}.dm^3.cm^{-2})*	σ_p[c]
Tri-O-methyl derivatives						
1	3610	16	97.8	22.4	0.79	0
2	3598	28	75.3	33.5	0.91	
3	3600	26	60.0	35.5	0.77	
	3528	98	29.6	57.0	0.61	
4	3606	34	87.3	21.4	0.68	
Di-O-methyl derivatives						
5	3612	14	202.0	27.2	2.0	
	~3599	~27				
6	3605	21	160.0	30.2	1.7	
	3524	102	29.5	57.0	0.61	
7	3608	—	185.0	22.8	1.5	
8	3604	22	196.0	26.1	1.9	
	3533	93	28.3	61.0	0.62	
9	3604	—	157.0	28.4	1.6	
10	3605	—	153.0	30.6	1.7	
	~3562	~78	~14.7	~42.2	~0.22	
Mono-O-methyl derivatives						
11	3608	18	—	—	—	
	~3530	~96				
12	3603	—	—	—	—	
13	3605	—	—	—	—	
14	3608	—	270.0	26.1	2.6	
p-*Substituted phenyl 3,4,6-tri-O-methyl derivatives*						
15	3615	11	99.9	23.5	0.85	+0.778
	~3593sh	~33				
16	3611	15	91.2	22.6	0.74	+0.227
17	3608	18	102.0	21.6	0.80	−0.170

[a]Concentration below 4mM. [b]$\Delta\nu_{OH} = 3640 - \nu_{OH}$ or $\Delta\nu_{OH} = 3626 - \nu_{OH}$; 3640 and 3626 cm^{-1} are the ν_{OH} values of free primary and secondary alcohols, respectively[11]. [c]Hammett σ_p constant[10].

frequency and the integrated intensity of the v_{OH} band, respectively, and $\Delta\nu_{OH}$ is the magnitude of the shift to a lower wave number from the corresponding free v_{OH} band. The ν_{OH} values for free hydroxyl groups were assumed to be 3640 and 3626 cm^{-1} for primary and secondary alcohols, respectively, as reported by Ōki and Iwamura[11]. Typical spectra are shown in Fig. 1.

In the tri-*O*-methyl derivatives **1**–**4**, which have one unsubstituted hydroxyl group, two conformations containing the hydrogen bond are possible, as shown in the formulae **1a**–**4b**. The $\Delta\nu_{OH}$ value of **1** is the smallest in the series **1**–**4**, and about half the value for **2** which has the hydrogen bond between hydroxyl and methoxyl groups. These findings suggest that HO-2 of **1** is hydrogen-bonded to O-1 (**1a**). In order to confirm this view, the effect of the substituent on the v_{OH} band of the *p*-substituted phenyl 3,4,6-tri-*O*-methyl-β-D-glucopyranosides **1** and **15–17** was examined since the proton-accepting ability is proportional to the electron density on O-1. The $\Delta\nu_{OH}$ value in these compounds decreased as the electron-withdrawing character of the *p*-substituent increased. As shown in Fig. 2, a good linear relationship (**r** 0.99) was obtained between the $\Delta\nu_{OH}$ values and the Hammett σ_p constants. Furthermore, a symmetrical ν_{OH} band was obtained for **1**, **16**, and **17**, but not **15**. These results indicate that, in these compounds, conformation **1a** is preferred and **1b** does not exist, in spite of the fact that the proton-accepting ability of O-1 is weaker than that of O-3. However, **15**, which has a *p*-nitro group, gives an unsymmetrical band at 3615 cm^{-1} with a shoulder at 3593 cm^{-1} ($\Delta\nu_{OH}$ 33). Since the latter absorption agrees with the hydrogen-bonded ν_{OH} band at 3592 cm^{-1} ($\Delta\nu_{OH}$ 34) of 3α-methoxy-5β,25D-spirostan-2β-ol[4,5], which possesses a similar relationship of the hydroxyl and methoxyl groups, the band was assigned to the hydrogen-bonded hydroxyl group as in **1b**, indicating that an equilibrium exists between **1a** and **1b** in **15**.

For **2**, a symmetrical ν_{OH} band was observed at 3598 cm^{-1} ($\Delta\nu_{OH}$ 28), indicative of a hydrogen bond involving HO-3 and O-2 or O-4, and its absorption also agreed with the ν_{OH} band of 3α-methoxy-5β,25D-spirostan-2β-ol[4,5]. Therefore, **2** may exist in conformation **2a** and/or **2b**.

As shown in Fig. 1, **3** gives two symmetrical bands, with peaks at 3600 ($\Delta\nu_{OH}$ 26) and 3528 cm^{-1} ($\Delta\nu_{OH}$ 98). The bands at 3600 and 3528 cm^{-1} were assigned to the hydrogen-bonded hydroxyl groups as in **3a** and **3b**, respectively, because the former absorption corresponds to that of **2** and the latter to the hydrogen-bonded ν_{OH} band of 3547 cm^{-1} ($\Delta\nu_{OH}$ 93) of 3-methoxypropanol[4a]. Based on the A_{OH} value of the ν_{OH} band of **2**, it is estimated that **3** consists of ~85% of **3a** and ~15% of **3b**.

For **4**, a symmetrical ν_{OH} band was recorded at 3606 cm^{-1} ($\Delta\nu_{OH}$ 34). This band was assigned to HO-6 hydrogen-bonded to the ring oxygen (O-5) as in **4b**,

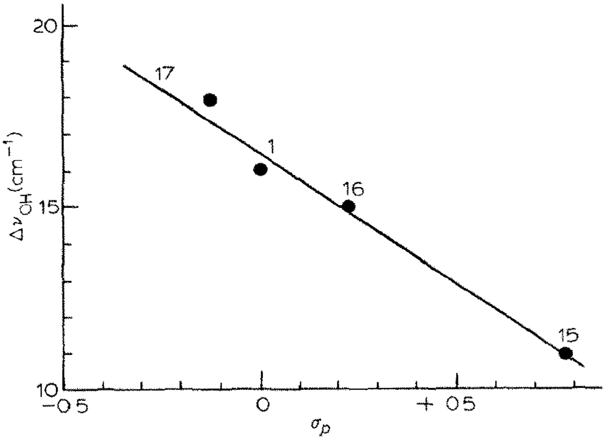
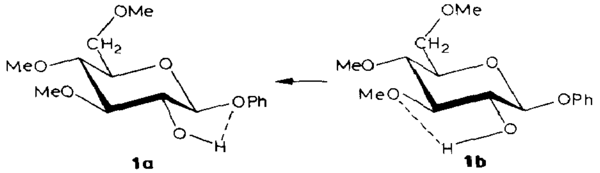


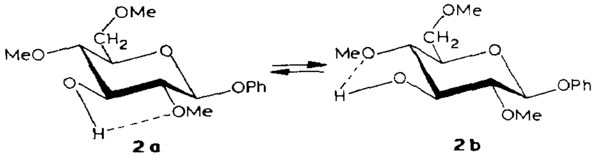
Fig. 2. Plots of the $\Delta\nu_{OH}$ values against Hammett σ_p constants in *p*-substituted phenyl 3,4,6-tri-*O*-methyl-β-D-glucopyranosides **17** (X = Me), **1** (X = H), **16** (X = Cl), and **15** (X = NO_2)

because the band corresponds to that at 3607 cm^{-1} ($\Delta\nu$ 33) for 2-methoxyethanol[4a] and indicates a preference for the formation of a five-membered rather than a six-membered ring in **4**.

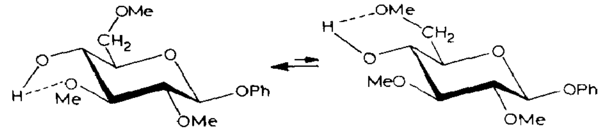
The di-*O*-methyl derivatives **5–10** have two hydroxyl groups, which are vicinal in **5**, **8**, and **10**. The spectral data (ν_{OH} and A_{OH}) of **6**, **7**, and **9** agree well with the values estimated from the sums of those of the corresponding tri-*O*-methyl derivatives **1** and **3**, **1** and **4**, and **2** and **4**, respectively, indicating that, in these compounds, the conformations of the two hydroxyl groups are identical to those in the tri-*O*-methyl derivatives described above. The spectral data of **5** and **8**, but not of **10**, agree approximately with the values estimated from the sums of those of the corresponding derivatives **1** and **2**, and **2** and **3**, respectively, suggesting that the conformations of the two hydroxyl groups are similar in these two series of compounds. However, the spectral data of **10** do not agree with the sum of the values for **3** and **4**.



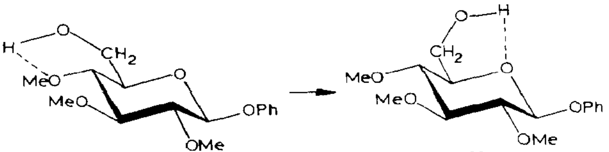
1a **1b**



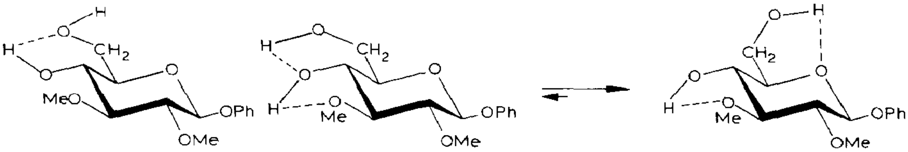
2a **2b**



3a **3b**



4a **4b**



5a **5b** **5c**

For **10**, the three conformations **5a–c** are possible. The band at 3562 cm^{-1} of **10** is very close to that of the hydrogen-bonded hydroxyl group at 3565 cm^{-1} ($\Delta\nu_{OH}$ 75) of 1,3-propanediol[12]. Thus, this band was assigned to the hydroxyl group that functions as a proton donor in conformation **5a**, in which hydrogen bonding can occur between HO-4 and O-6, or in **5b**, between HO-6 and O-4. The conformation **5a** should show a free ν_{OH} band for HO-6, since the distance between HO-6 and O-5 is greater than the maximum for hydrogen-bonding[1,5]. Consequently, the absence of the free ν_{OH} band in the spectrum of **10** was regarded as evidence of the absence of conformation **5a**, corresponding to **3b**, whereas the hydrogen-bonded ν_{OH} band at 3562 cm^{-1} ($\Delta\nu_{OH}$ 78) was regarded as being for **5b**, corresponding to **4a** which does not occur, with the band at 3605 cm^{-1} being mainly for **5c**. Based on the relationship[5] of $\Delta\nu_{OH}$ and A_{OH}, conformation **5b** was estimated to be ~15% and **5c** 85% for **10**.

The ν_{OH} values of mono-*O*-methyl derivatives **11–14** having three hydroxyl groups were obtained, but not their A_{OH} values, except for **14**, because of their low solubilities in carbon tetrachloride. Only **11** showed a main ν_{OH} band at 3608 cm^{-1} and a weak ν_{OH} band at 3530 cm^{-1} ($\Delta\nu_{OH}$ 96); the latter corresponds to the ν_{OH} band in **3b**, but the others, **12–14**, showed only one ν_{OH} band at 3603, 3605, and 3608 cm^{-1}, respectively. Therefore, clear relationships between the hydrogen-bonding patterns and the conformation equilibria could not be established, although these compounds may be distinguishable from each other.

The A_{OH} values for the ν_{OH} band at wave numbers higher than 3598 cm^{-1} in the di-*O*-methyl derivatives **5–10** and mono-*O*-methyl derivative **14** are about two and three times greater, respectively, than those of the tri-*O*-methyl derivatives **1–4**.

The findings reported here should be useful for understanding the i.r. behaviour in analogous systems and for investigating intramolecular hydrogen-bonding.

EXPERIMENTAL

General methods. — Melting points (uncorrected) were determined with a Shimazu MM-2 apparatus. ^{1}H-N.m.r. spectra (internal Me_4Si) were recorded with a JEOL PS-100 spectrometer. Optical rotations were determined with a Union PM-101 polarimeter. Routine i.r. spectra were obtained with an Hitachi Model 215 instrument. Measurements of intramolecular hydrogen-bonding were carried out using a JASCO DS-403G spectrometer calibrated in the usual manner, <4mM solutions in carbon tetrachloride (distilled from and stored over P_2O_5), and a cell length (l) of 2 or 5 cm. Ramsay's method[13] was used to calculate the values of A_{OH}, defined as $A = (\pi/2)[\ln(I_0/I)/c \cdot l]\Delta\nu_{1/2}$ ($mol^{-1}.dm^3.cm^{-2}$), where $\ln(I_0/I)c \cdot l$ is the absorption coefficient ($mol^{-1}.dm^3.cm^{-1}$) at the band maximum and $\Delta\nu_{1/2}$ is the band width (cm^{-1}) at half intensity. The accuracies of ν_{OH} and A_{OH} are within ±1 cm^{-1} and ±3%, respectively. All measurements were carried out at ~27°.

The phenyl β-D-glucopyranoside derivatives **1–14** were purified by recrystallisation until their physical constants agreed with the published values[14].

p-*Nitrophenyl 3,4,6-tri-*O*-methyl-β-*D*-glucopyranoside* (**15**). — A suspension of 3,4,6-tri-*O*-methyl-β-D-glucose[15] (1.20 g) and anhydrous sodium acetate (1.32 g) in acetic anhydride (8.2 mL) was stirred at 100° for 1 h, cooled, and poured into ice and water. After being stirred for 3 h, the mixture was extracted with ethyl acetate, and the extract was washed with water, aqueous $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated under reduced pressure. A mixture of a portion (1.40 g) of the resulting acetate (1.48 g), *p*-nitrophenyl (4.04 g), and toluene-*p*-sulfonic acid (0.04 g) was stirred at 80° for 1 h, and then extracted with ethyl acetate. The extract was washed with water, aqueous 5% NaOH, and water, dried (Na_2SO_4), and concentrated under reduced pressure. The yellowish, oily residue was subjected to column chromatography (silica gel 30 g; hexane–ethyl acetate) to give a major (520 mg, 30%) and a minor product (239 mg, 14%). A solution of the minor product in methanolic 0.1M sodium methoxide (5 mL) was stirred at room temperature for 20 min, neutralised with Amberlite IR-120 (H^+) resin, filtered, and concentrated under reduced pressure. The residue (189 mg) was purified by column chromatography (silica gel, 10 g; chloroform–ethyl acetate) to give **15** (149 mg, 62%), m.p. 118.3–119.3° (from carbon tetrachloride), $[\alpha]_D^{27}$ −81° (*c* 0.7, chloroform); $\nu_{max}^{CHCl_3}$ 3600 (OH), 1590 (C=C, phenyl), 1340 (NO_2), and 1079 cm^{-1} (C–O–C). ^{1}H-N.m.r. data ($CDCl_3$): δ 3.39, 3.56, and 3.70 (3 s, 9 H, 3 OMe), 4.94 (d, 1 H, $J_{1,2}$ 9 Hz, H-1), 7.08 and 8.14 (2 d, each 2 H, *J* 9 Hz, aromatic protons).

Anal. Calc. for $C_{15}H_{21}NO_8$ (343.34): C, 52.47; H, 6.17; N, 4.08. Found: C, 52.25; H, 6.14; N, 4.06.

p-*Chlorophenyl 3,4,6-tri-*O*-methyl-β-*D*-glucopyranoside* (**16**). — This compound, synthesised as described above but using *p*-chlorophenol, had m.p. 120.0–120.5° (from ethanol), $[\alpha]_D^{27}$ 37.5° (*c* 0.5, chloroform); $\nu_{max}^{CHCl_3}$ 3580 (OH), 1580 (C=C, phenyl), and 1058 cm^{-1} (C–O–C). ^{1}H-N.m.r. data ($CDCl_3$): δ 3.40, 3.56, and 3.69 (3 s, 9 H, 3 OMe), 4.78 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 6.95 and 7.24 (2 d, each 2 H, *J* 9 Hz, aromatic protons).

Anal. Calc. for $C_{15}H_{21}ClO_6$ (332.786): C, 54.14; H, 6.36. Found: C, 54.38; H, 6.38.

p-*Methylphenyl 3,4,6-tri-*O*-methyl-β-*D*-glucopyranoside* (**17**). — This compound, synthesised as described above but using *p*-toluol, had m.p. 92.5–93.5° (from benzene–light petroleum), $[\alpha]_D^{27}$ −49° (*c* 0.8, chloroform); $\nu_{max}^{CHCl_3}$ 3575 (OH), 1611 (C=C, phenyl), and 1055 cm^{-1} (C–O–C). ^{1}H-N.m.r. data ($CDCl_3$): δ 2.30 (s, 3 H, *p*-Me), 3.39, 3.56, and 3.68 (3 s, 9 H, 3 OMe), 4.74 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 6.44 and 7.02 (2 d, each 2 H, *J* 9 Hz, aromatic protons).

Anal. Calc. for $C_{16}H_{24}O_6$ (312.368): C, 61.52; H, 7.75. Found: C, 61.51; H, 7.73.

ACKNOWLEDGMENTS

We thank Professor T. Kubota and Dr. Y. Asaka (Kinki Univesity School of Medicine), Professor T. Kubota (Gifu College of Pharmacy), and Dr. Y. Matsui of our laboratories, for helpful discussions.

REFERENCES

1 L P. KUHN, *J. Am. Chem Soc*, 74 (1952) 2492–2499.
2 L. P. KUHN, P. R. SCHLEYER, W. F. BAITINGER, JR, AND L. EBERSON, *J. Am. Chem Soc*, 86 (1964) 650–658.
3 M. TICHY, *Adv. Org Chem*, 5 (1965) 115–298.
4 (*a*) Y. MATSUI, M. TAKASUKA, AND T. KUBOTA, *Annu. Rep. Shionogi Res. Lab.*, 15 (1965) 125–129; (*b*) T KUBOTA, M. TAKASUKA, AND Y. MATSUI, *ibid.*, 16 (1967) 63–67.
5 M. TAKASUKA, Y. MATSUI, AND T. KUBOTA, *Spectrosc Lett.*, 9 (1976) 821–832.
6 H. SPEDDING, *J. Chem. Soc.*, (1961) 3617–3621.
7 F. KORTE, V. CLAUSSEN, AND G. SNATZKE, *Tetrahedron*, 20 (1964) 1477–1487
8 A. B FOSTER, R. HARRISON, J LEHMANN, AND J. M WEBBER, *J. Chem. Soc.*, (1963) 4471–4477.
9 A. J. MICHELL AND H. G. HIGGINS, *Tetrahedron*, 21 (1965) 1109–1120
10 H H. JAFFE, *Chem. Rev.*, 53 (1953) 191–261.
11 M. ŌKI AND H. IWAMURA, *Bull. Chem. Soc. Jpn.*, 32 (1959) 950–955.
12 A. B. FOSTER, A. H. HAINES, AND M. STACEY, *Tetrahedron*, 16 (1961) 177–184.
13 D. A. RAMSAY, *J Am. Chem Soc.*, 74 (1952) 72–80.
14 P. NANASI AND A. LIPTAK, *Magy. Kem. Foly*, 80 (1974) 217–225.
15 R L. SUNDBERG, C. M. MCCLOSKEY, D. E ROSE, AND G. H. COLEMAN, *J. Am. Chem Soc*, 67 (1945) 1080–1084