Carbohydrate Research, 123 (1983) 13–22
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

SELECTIVE DEUTERATION. THE RATE OF PROTIUM–DEUTERIUM EXCHANGE IN INOSITOLS WITH RANEY-NICKEL CATALYST, AND THE EFFECT THEREON OF *O*-METHYLATION

STEPHEN J. ANGYAL
School of Chemistry, University of New South Wales, Kensington, N.S.W. 2033 (Australia)

AND LÉON ODIER*
Laboratoires de Chimie, Département de Recherche Fondamentale, Groupe Macromolécules Végétales, Centre d'Etudes Nucléaires de Grenoble, 85 X, 38041 Grenoble cédex (France)

(Received May 6th, 1983; accepted for publication, May 27th, 1983)

ABSTRACT

The rate of protium–deuterium exchange, catalyzed by deuterated Raney nickel, on all carbon atoms of four inositols, was measured. The rate of exchange is lowered by methylation of an adjacent hydroxyl group; this effect was studied on seven isomeric, inositol methyl ethers. Correlations between the rate of exchange and the configuration, the conformation, and the site of *O*-methylation of the inositols have been established.

INTRODUCTION

A convenient method for the introduction into carbohydrates of deuterium atoms bonded to carbon atoms has been described by Koch and Stuart[1,2]. It consists of heating an appropriate carbohydrate derivative with deuterated Raney nickel in deuterium oxide. In most cases, only hydrogen atoms bonded to carbon atoms having a free hydroxyl group undergo exchange (see, however, ref. 3); the method has been used mainly for the complete exchange of all such hydrogen atoms[2,4–6]. The work of Perlin and co-workers[4–6] and of Stevens[7] demonstrated that various hydrogen atoms are exchanged at different rates under these conditions. In particular, equatorial hydrogen atoms exchange faster than axial ones, and a hydrogen atom *syn*-axial with an oxygen atom in a pyranose ring exchanges particularly slowly. In methyl glycosides, the methoxyl group hinders the exchange reaction of the hydrogen atom in the adjacent position, the extent of this hindrance depending, in a way not yet fully understood, on their steric relationship.

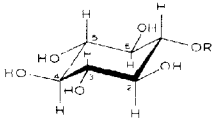
It appeared to us possible that carbohydrate derivatives could be so chosen that they are predominantly deuterated in only one or two positions by this

*On the staff of Université Scientique et Médicale de Grenoble.

0008-6215/83/$ 03.00

method. We therefore undertook the study of the effect of steric relations and of methoxyl substituents on the rate of exchange. As model compounds, we chose the inositols, so as to avoid, at this stage, the effects of a hetero-atom in the ring. Moreover, inositol methyl ethers were available to represent most of the possible steric arrangements of a methoxyl group and two neighboring hydroxyl groups.

The extent of deuterium exchange was measured by evaluating the n.m.r. spectra, both ^1H and ^{13}C-n.m.r. spectra being used for this purpose. The former are, in principle, more accurate, because the proton signal completely disappears when the proton is replaced by deuterium. The ^{13}C signal becomes much smaller and broadens to a triplet[8], but does not disappear completely. In some instances, however, the proton signals are not completely separated in the spectrum, even at 250 MHz, and therefore, the integrations are not reliable; this difficulty does not arise with ^{13}C-n.m.r. spectra. Spectra for both nuclei were also recorded in order to provide cross-checks of our results; this proved to be a wise precaution. The ^1H- and ^{13}C-n.m.r. spectra of all of the inositols[9] and inositol methyl ethers[10] involved in this study had already been assigned.



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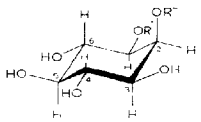
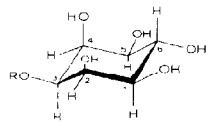


2 $R^1 = R^2 = H$

2a R^1 = Me, R^2 = H

2b R^1 = H, R^2 = Me



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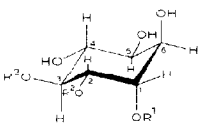
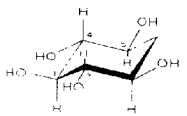


4 $R^1 = R^2 = R^3 = H$

4a R^1 = Me, $R^2 = R^3$ = H

4b $R^1 = R^3$ = H, R^2 = Me

4c $R^1 = R^3$ = H, R^2 = Me



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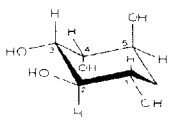

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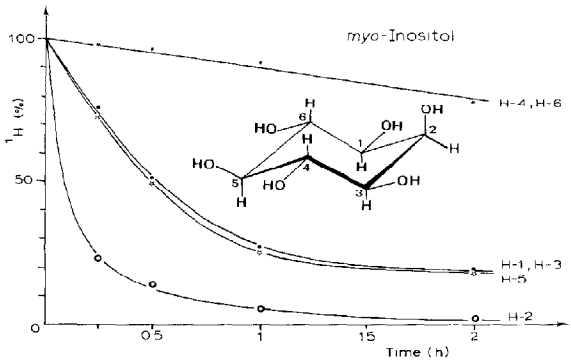

Fig. 1. The exchange of the hydrogen atoms of *myo*-inositol at 60°

Inositols

The reaction of four inositols was monitored until at least one hydrogen atom of each was almost completely replaced by deuterium. It was soon realized that the reaction was inconveniently fast in boiling deuterium oxide, and we therefore conducted the measurements at 60°. Even at that temperature, the exchange of unhindered hydrogen atoms is rapid: 50% of the hydrogen atoms of *scyllo*-inositol (**1**), all of which are equivalent, were replaced in ~10 min, and, after 1 h, the exchange was practically complete.

The exchange of the hydrogen atoms of *myo*-inositol (**2**) is shown in Fig. 1. It demonstrates clearly the characteristic behavior of hydrogen atoms on six-membered rings: equatorial hydrogen atoms (H-2) are rapidly exchanged (half-time, ~10 min); axial ones (H-1,3,5), somewhat more slowly (~30 min); and those *syn*-axial with a bulky substituent (H-4,6), very slowly (~300 min).

Caution should be used in drawing conclusions about deuterium exchange from a comparison of different compounds. Because the catalyst is stored under a liquid (deuterium oxide), it cannot be weighed accurately, and its amount may vary considerably from one experiment to another; its reactivity is affected by age; and, as the reaction is heterogeneous, its rate will depend on the rate of stirring, which is not rigorously controlled. From each experiment, reliable comparisons can be drawn only between the rate of exchange of different hydrogen atoms in the same molecule. Nevertheless, it is interesting to observe that the hydrogen atoms of *scyllo*-inositol (**1**) exchange more rapidly than does H-5 of *myo*-inositol, which has exactly the same environment.

The reaction occurs on the surface of the catalyst. When a better adsorption site (equatorial H) is available, only a small proportion of the molecules will be adsorbed at the site containing the axial hydrogen atom. The presence of a rapidly ex-

changing hydrogen atom therefore retards the exchange of a slower one. The reaction does not end, of course, when all of the hydrogen atoms at a site have been replaced by deuterium; it continues at the same rate, but is no longer observed, deuterium being replaced by deuterium.

The results for *myo*-inositol were obtained by observing the ^{1}H-n.m.r. spectrum, in which the signals are all well separated. When the ^{13}C-n.m.r. spectra were obtained, it was found that the signal assigned[11] to C-4 and C-6 (at δ 72.1) rapidly diminished during the reaction, whereas that assigned to C-1 and C-3 (at δ 73.4) remained almost constant. Obviously, the assignment for this ^{13}C-n.m.r. spectrum[11], one of the earliest in carbohydrate chemistry, was wrong; the values given for C-1,3 and C-4,6 have to be interchanged[9]. This is yet another example of the proposition[1-4] that the Koch–Stuart exchange-reaction is a valuable aid to the assignment of ^{13}C-n.m.r.-spectral signals.

The rates of deuterium exchange of *epi*-inositol (**3**) present a similar picture. Again, the equatorial hydrogen atoms, H-2 and H-4, exchange most rapidly (half-time, ~3 min), the axial ones slower (H-1 and H-5, ~15; H-3, ~25 min), and the *syn*-axial, H-6 atom is the slowest (~30 min). In this case, however, although there are two *syn*-axial hydroxyl groups, the retardation caused by them is slight. An explanation is not apparent; possibly, in solution, there is a hydrogen bond between the two axial hydroxyl groups (although there is none in the crystal of the compound[12]), the hydrogen atom of which serves as a point of attachment to the catalyst surface.

The equatorial H-1 and H-6 atoms of *chiro*-inositol (**4**) exchange more rapidly than the others (half-time, ~18 min). All of the other hydrogen atoms of the molecule are *syn*-axial with an oxygen atom, but they all exchange faster (H-3 and H-4, half-time 40; H-2 and H-5, 70 min) than the *syn*-axial H-4 and H-6 of *myo*-inositol. As the axial O-1 and O-6 atoms of *chiro*-inositol have only one equatorial oxygen neighbor, they can bend outwards towards the other side and thus interfere less with adsorption on the catalyst surface. It appears that the full extent of steric hindrance by a *syn* axial hydroxyl group is only shown when it is bolstered by two *cis* hydroxyl groups, as it is in *myo*-inositol (**2**).

Because steric hindrance appears to have such a strong effect on the exchange reaction, 1,3,5/2,4-cyclohexanepentol (**5**) was investigated, in order to ascertain whether a hydroxyl group on the neighboring carbon atom has any effect on the reaction. From the ^{13}C-n.m.r. spectrum, it was found that H-1 and H-5, the two hydrogen atoms adjacent to the methylene group, exchange twice as fast as the other ring-hydrogen atoms. Adsorption on the catalyst surface is therefore somewhat hindered by a neighboring hydroxyl group.

A similar effect was expected in the reaction of D-1,3,4/2,5-cyclohexanepentol (**6**); this compound has an axial and an equatorial ring-hydrogen atom adjacent to the methylene group. Surprisingly, the equatorial H-5 atom exchanged more *slowly* than the equatorial H-4 which is not adjacent to the methylene group, even slower than the axial hydrogen atoms. After reaction for 15 min at 80°, >90% of

H-4 had been exchanged, but only ~45% of H-5, and ~60% of the other hydrogen atoms, as determined from the ^{1}H-n.m.r. spectrum[13].

The protium–deuterium exchange over Raney nickel is accompanied by two other reactions; fortunately, they are both much slower than the exchange, and, after the short runs described here, only very small signals of other compounds were apparent in the n.m.r. spectra. One of these reactions is epimerization[1,2–4,6]. The signal of *scyllo*-inositol can be detected in the spectrum of *myo*-inositol after only 15 min of exchange; this signal, of course, is particularly noticeable because it represents six H or C atoms. It is therefore essential, in the preparation of labelled compounds by this method, to recrystallize the product.

When *myo*-inositol was heated with the catalyst in water for 3 days, a complicated ^{13}C-n.m.r. spectrum was obtained in which the signals of *scyllo*- (**1**), *chiro*- (**4**), and *neo*- (1,2,3/4,5,6) inositols were seen, in addition to those of *myo*-inositol, in the approx. ratios of ~12:7:1:25. This corresponds approximately to the thermodynamic equilibrium[14]. The other four diastereomeric inositols each have *syn*-axial hydroxyl groups, and are therefore less stable; their signals were not detected in the spectrum. If there was any *epi*-inositol present, its proportion was less than 2%. Balza and Perlin[6] suggested that the epimerization is not controlled by the thermodynamic stability of the products. Certainly, epimerization is rapid at those positions where deuterium exchange occurs rapidly; but, after prolonged reaction, as our results, as well as those of Wu *et al.*[3], show, thermodynamic equilibrium is reached.

The other concurrent reaction, even slower than epimerization, is deoxygenation[7]. In the ^{13}C-n.m.r. spectrum of *myo*-inositol treated for 3 days, small signals appeared at δ ~35; these are the signals of the methylene groups of cyclohexanepentols. Because the ^{13}C-n.m.r. spectra of all of the diastereomers are known[9], it was possible to recognize those of the 1,3,5/2,4, the 1,2,4/3,5, and the 1,2,3,5/4 isomers, each in a proportion of ~3%, and a lesser amount of the 1,2,3/4,5 isomer. None of these isomers have *syn*-axial hydroxyl groups.

Inositol methyl ethers

To evaluate the retarding effect of *O*-methylation, the catalyzed deuteration of inositol methyl ethers was studied. For these, the rate of exchange was not measured; only one or two runs, of a length chosen in anticipation of giving the desired information, were conducted with each isomer. The results are shown in Table I.

There are six possible geometrical arrangements of a methoxyl group situated between two neighboring hydroxyl groups on a six-membered ring in a chair conformation. The methyl ethers were so chosen as to represent five of them; the sixth, having an axial methoxyl group situated between axial hydroxyl groups, is not available in the monocyclic inositol system, but it can be predicted, on the basis of the other cases, that *O*-methylation in this instance would cause a small decrease in the rate of exchange of the hydrogen atoms on the neighboring carbon atoms.

TABLE I

EXTENT OF PROTIUM–DEUTERIUM EXCHANGE (% ±5) AT VARIOUS POSITIONS OF INOSITOL METHYL ETHERS, AT 90–95°

Inositol	*Time (h)*	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*
O-Methyl-*scyllo*- (**1a**)	0.5	—	35	>95	>95	>95	35
D-1-*O*-Methyl-*myo*- (**2a**)	10	—	10	50	<10	35	<5
2-*O*-Methyl-*myo*- (**2b**)	0.25	40	—	40	0	60	0
3-*O*-Methyl-*epi*- (**3a**)	1	>95	>95	—	>95	>95	80
D-1-*O*-Methyl-*chiro*- (**4a**)	1	—	33	0	<70	0	67
L-2-*O*-Methyl-*chiro*- (**4b**)	8	0	—	0	>95	>95	100
D-3-*O*-Methyl-*chiro*- (**4c**)	10	100	<10	0	<20	80	100

The extent of the retardation caused by *O*-methylation will depend on the proximity of the methyl group (in the predominant, rotameric orientation of the methoxyl group) to the hydrogen atom to be exchanged. In 2-*O*-methyl-*myo*-inositol (**2b**), the methoxyl group is axial, and the neighboring hydroxyl groups are equatorial (denoted as Type **D** by Angyal and Odier[10]), and in none of the rotamers is the methyl group close to H-1 or H-3. There is, therefore, only a slight retardation in their exchange by deuterium (see Table I), compared to unsubstituted *myo*-inositol, in which H-1, H-3, and H-5 exchange with deuterium at nearly identical rates.

O-Methyl-*scyllo*-inositol (**1a**) is an example of an equatorial methoxyl group between two equatorial hydroxyl groups (Type **A**). Methylation here causes considerable retardation of the exchange of H-2 and H-6. Another example of this Type is 3-*O*-methyl-*chiro*-inositol (**4c**); here, H-2 and H-4, already impeded by a *syn*-axial oxygen atom, are further hindered by the methyl group, and are hardly affected, even by treatment for 10 h. It has been suggested that, in this geometrical arrangement, the methyl group assumes only those rotameric orientations in which it is *gauche* to only one of the ring-carbon atoms[15]; but its retarding effect on the exchange reaction implies that the rotamer having the methyl group *gauche* to both neighboring, ring-carbon atoms is an important contributor to the orientational equilibrium (see discussion in ref. 10). In this rotamer, the methyl group is close to the neighboring hydrogen atoms.

In two geometrical arrangements (Types **B** and **E**), there are one axial and one equatorial hydroxyl group on the neighboring carbon atoms. The preponderant rotamer then is the one in which the methyl group is close to the neighboring, equatorial hydrogen atom, and the exchange of this atom is hindered. Thus, in 1-*O*-methyl-*myo*-inositol (**2a**), the reaction of the equatorial H-2 atom (very fast in the unmethylated compound) is considerably impeded. Similarly, in 2-*O*-methyl-*chiro*-inositol (**4b**), the equatorial H-1 is practically unaltered, even after 8 h; by contrast, H-6, also equatorial, is exchanged to the extent of >90% in 15 min. In

both cases, the neighboring, axial hydrogen atoms (H-6 and H-3, respectively), already hindered by *syn*-axial oxygen atoms, exchange very slowly.

Very long treatment (20 h) of 2-*O*-methyl-*chiro*-inositol (**4b**) resulted in extensive (>50%) isomerization to 1-*O*-methyl-*myo*-inositol (**2a**), but H-1 (and its equivalent, H-2 of the *myo* isomer) were still not fully exchanged.

When the methoxyl group is axial, and lies between an axial and an equatorial hydroxyl group (Type **E**), the steric effect is much smaller. The methyl group in 1-*O*-methyl-*chiro*-inositol (**4a**) retards the exchange of H-6 only moderately, and that of H-2, hardly at all. Another effect is, however, noticed here; namely, that a *syn*-axial methoxyl group hinders exchange more than a *syn*-axial hydroxyl group: H-3 and H-5 are exchanged very slowly. The ^{13}C-n.m.r. spectrum of this partially deuterated sample provided us with the full assignment of the spectrum, which was previously uncertain[10].

When the methoxyl group is equatorial, and situated between two axial hydroxyl groups (Type **C**), as it is in 3-*O*-methyl-*epi*-inositol (**3a**), a moderate retardation of the exchange would be expected, because the methyl group, in two equivalent rotamers, is close to each of the neighboring hydrogen atoms for half the time only. Our experiment shown in Table I is not particularly illuminating. Because the signals of C-1,5 and C-2,4 coincide in the ^{13}C spectrum, and those of H-1,5 are hidden by the methyl signal in the ^{1}H spectrum, we have been unable to obtain quantitative data on this exchange. We could only establish that H-2 and H-4 exchange faster than H-6, but slower than H-1 and H-5; that is, the exchange of H-2 and H-4 is slower for this methyl ether than for the parent *epi*-inositol.

It is interesting to compare the effect of *O*-methylation on the exchange reaction with that on the n.m.r. spectra[10]. *O*-Methylation causes a shift in the signals of the neighboring carbon atoms and of the hydrogen atoms attached to them. Both phenomena are caused by the proximity of the newly introduced methyl group to the hydrogen atoms on the neighboring carbon atoms, and the magnitude of the two effects runs in close parallel. In those cases where methylation shifts, to a considerable extent, the signals of the neighboring carbon atoms upfield, or those of the hydrogen atoms downfield, there is also a considerable retardation of the exchange reaction. If the shifts are small, there is little effect on the exchange reaction.

DISCUSSION

We set ourselves the goal of finding conditions under which some hydrogen atoms exchange to the extent of at least 90% while others exchange <10%. To achieve this, a ratio of the reaction rates of at least 20:1 is required. Such a ratio is found in *myo*-inositol between the equatorial H-2 and the *syn*-axial H-4 and H-6 atoms: after reaction for 1 h, 94% of H-2, but only 6% of H-4 and H-6, had exchanged. The other hydrogen atoms, however, have intermediate rates, and had exchanged to the extent of ~75%. For the study of reaction mechanisms, or of

metabolism, it may be useful to have a sample of *myo*-inositol in which the various positions are labelled by deuterium at three different levels.

Among the compounds here discussed, 1-2-*O*-methyl-*chiro*-inositol (**4b**) (quebrachitol*, a natural product) is the only one in which selective deuteration can be achieved: after 15 min, ~90% of H-6 had exchanged, but there was very little replacement of any other hydrogen atoms. A different specificity is achieved after a long period of heating (see Table I), when H-4, H-5, and H-6 are almost completely replaced but none of the other hydrogen atoms are.

Our experiments allowed us to draw some conclusions as to the favored geometrical arrangements of the reaction. It occurs on the surface of the nickel catalyst, and the site of the molecule thereof at which the substrate is preferentially adsorbed is the site at which the reaction will be the fastest. For rapid exchange, a hydrogen atom must be geminal to a free hydroxyl group; these are, therefore, two points of attachment to the catalyst surface. But, as Balza and Perlin had already pointed out[6], for rapid exchange, another nearby hydroxyl group is required; hydrogen atoms geminal to isolated hydroxyl groups exchange very slowly. Our experience with 1,3,4/2,5-cyclohexanepentol (**6**) indicated that this second hydroxyl group should be *gauche* to both the hydrogen atom and the geminal hydroxyl group; the three hydrogen atoms then form a close-knit site for adsorption. In pentol **6**, H-5 has a hydroxyl neighbor in *gauche* relation which is, however, *antiperiplanar* to the geminal hydroxyl group, and exchange is slow. An equatorial hydroxyl group on the neighboring carbon atom is, therefore, more effective in promoting exchange than an axial one.

A neighboring methoxyl group does not function as a site of adsorption, but may hinder it by its bulk, especially in some configurations. Scale models show that, when it is effected by a hydrogen atom, a geminal hydroxyl group, and a neighboring hydroxyl group, adsorption onto a planar catalyst surface is less impeded sterically by an axial than by an equatorial methoxyl group on the other, neighboring carbon atom.

To summarize, we have observed the following characteristics of the rate of the Raney-nickel-catalyzed exchange-reaction. We confirmed that (*1*) equatorial hydrogen atoms exchange more rapidly than do axial ones, and (*2*) a *syn*-axial hydroxyl group retards the exchange, and a *syn*-axial methoxyl group even more. (*3*) For rapid exchange, an equatorial hydroxyl group is required on a neighboring carbon atom. (*4*) A neighboring methoxyl group retards the reaction, the extent of the retardation depending on the relative configurations. An equatorial methoxyl group retards more than an axial one; an equatorial hydroxyl group on the other side of the methoxyl group increases the retardation (by altering the favored

*Quebrachitol is not available commercially. The authors would be pleased to provide small quantities to interested workers.

rotameric orientation of the methoxyl group). The greatest retardation is observed when the hydrogen atom to be exchanged and the neighboring methoxyl group are both equatorial.

EXPERIMENTAL

Materials — *myo*-Inositol was a commercial product (Staley); the other isomers and the methyl ethers were synthesized as previously described, or were isolated from natural sources[16–18]. Raney nickel, prepared from nickel–aluminum alloy (Prolabo) by the usual method[19], was washed with deuterium oxide (4 vol.), and stored under the same solvent. About 1 mL of the wet catalyst was used for each 100 mg of substrate. Perlin *et al.*[4] recommended that the product of the deuterium exchange be treated with an ion-exchange resin (in order to remove traces of nickel), before recording of the n.m.r. spectra. We found this precaution unnecessary; good spectra were obtained without it.

N.m.r. spectra were recorded with a Cameca 250 spectrometer in Grenoble, and with a Jeol JNM-FX-100 spectrometer in Sydney. ^{13}C-Chemical shifts are downfield from external tetramethylsilane; 1,4-dioxane (δ_C 67.4) was used as the internal standard. In order to measure the loss of protons during the reaction in inositols (where all of the hydrogen atoms exchange), a standard was required for the integrations, and 2-(hydroxymethyl)-2-methyl-1,3-propanediol was used for this purpose, as all of the hydrogen atoms of this compound, except those of the methyl group, are exchanged for deuterium by the reaction over Raney nickel. A weighed amount of this deuterated product was added to each run, and its methyl signal was used as a standard. For the inositol monomethyl ethers, their methoxyl group and the proton geminal to it were used as standards.

ACKNOWLEDGMENTS

The authors are grateful to Dr. J. D. Stevens for helpful discussion. One of us (L.O.) is indebted to the University of New South Wales for their hospitality and for the provision of facilities.

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