P.M.R. SPECTROSCOPY OF *O*-METHYL DERIVATIVES OF D-GALACTOPYRANOSE AND RELATED COMPOUNDS IN SOLUTION IN DEUTERIUM OXIDE

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ABSTRACT

The results obtained from a study of the p.m.r. spectroscopy of deuterium oxide solutions of D-galactopyranose and its partially and fully methylated derivatives are discussed. The methoxyl-proton chemical-shifts for some of these compounds are compared with those of corresponding derivatives of D-glucose, D-mannose, and the hydrochlorides of 2-deoxy-2-(methylamino)-D-glucose and -D-galactose. The effects, on the methoxyl and anomeric proton chemical-shifts, of anomeric change, methylation of neighboring hydroxyl groups, and change in configuration of adjacent carbon atoms bearing a hydroxyl or methoxyl group are noted.

INTRODUCTION

The p.m.r. spectroscopy of deuterium oxide solutions of mono-[1], di-[2], tri-[3], and tetra-methyl[4] ethers of D-galactopyranose, methyl D-galactopyranoside, and galactitol has been described in previous papers. These studies, together with those of other workers[5–9], have shown that the chemical shifts of certain methoxyl groups depend on (*a*) their disposition (axial or equatorial), (*b*) whether hydroxyl or methoxyl groups are attached to the neighboring carbon atoms, and (*c*) the configurations of the neighboring carbon atoms bearing a hydroxyl or a methoxyl group. The present paper discusses the observations made for the D-galactose derivatives, together with those obtained[5] for certain derivatives of D-glucose and D-mannose. A correlation between D-glucose and D-galactose derivatives in which $-\overset{+}{N}H_2MeCl^-$ replaces -OMe at C-2 has been made possible by the results published in two recent articles[10,11]. The chemical shifts of the methoxyl protons in these compounds bear similar relationships to each other, as do those of the methoxyl protons in the D-galactose derivatives now summarized.

RESULTS AND DISCUSSION

Chemical shifts of methoxyl groups. — (*a*) *Methyl ethers of* D-*galactose.* The methoxyl chemical-shifts for these compounds (compare with ref. 5) are presented in Diagram 1, from which the following observations can be made. (*i*) There appear to be three definite groups of methoxyl signals in the spectra of these compounds: (*a*) 2-OMe (β anomers) at lowest field, τ' 6.42–6.45; (*b*) 3-OMe (α and β anomers having OMe at C-4) and 4-OMe (α and β anomers) in the central region (τ' 6.48–6.53), and (*c*) 2-OMe (α anomers), 3-OMe (α and β anomers having OH at C-4), and 6-OMe (α and β anomers) at highest field (τ' 6.55–6.64). (*ii*) Anomeric change (axial to equatorial OH at C-1) produces a significant downfield shift (0.13 p.p.m.) of the 2-OMe signal. Other methoxyl signals are not affected by change in configuration at C-1. For methyl ethers of the hydrochlorides of 2-deoxy-2-(methylamino)-D-glucose[10] and -D-galactose[11], however, anomeric change (α to β) produces a downfield shift of only 0.03–0.04 p.p.m. of the NCH_3 signal. (*iii*) *O*-Methylation at C-4 produces a downfield shift (~0.07 p.p.m.) of the 3-OMe signal. A similar downfield shift (0.09 p.p.m.) of the 3-OMe signal of 2-deoxy-3-*O*-methyl-2-(methylamino)-D-galactose hydrochloride is observed[10] when the spectrum of this compound is compared with that of the 3,4-di-*O*-methyl derivative. The 2-OMe and 4-OMe signals are not affected by methylation of neighboring hydroxyl groups.

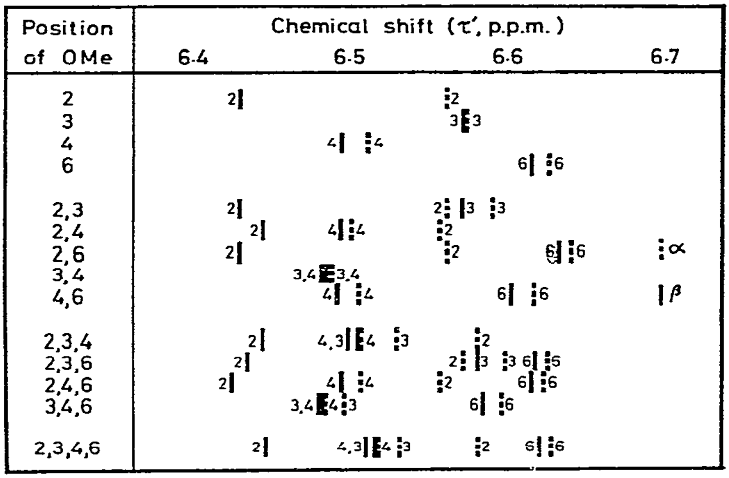

Diagram 1. Methoxyl-group chemical-shifts of methyl ethers of D-galactopyranose.

(*b*) *Methyl ethers of methyl* α- *and* β-D-*galactopyranoside.* Diagram 2 shows the methoxyl-group chemical-shifts of the methyl glycosides studied. The following generalizations can be made from this Diagram, and by comparison with Diagram 1. (*i*) The introduction of a glycosidic methyl group does not have a marked effect on the chemical shifts of any of the methoxyl groups. Most affected are the 2-OMe signals of the β glycosides, which are shifted slightly upfield (0.01–0.04 p.p.m.). (*ii*) The

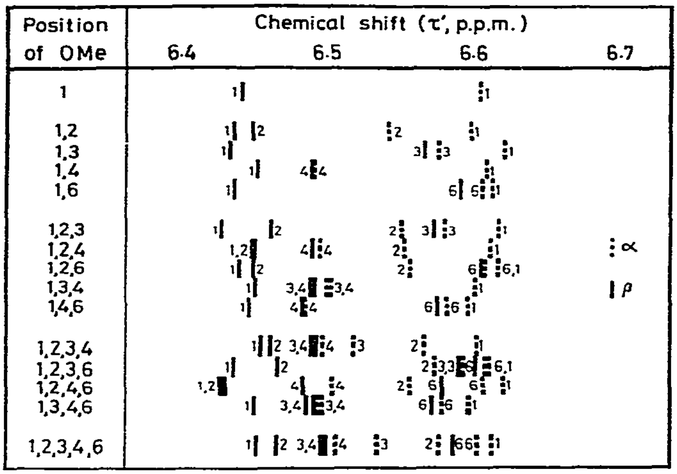

Diagram 2. Methoxyl-group chemical-shifts of methyl ethers of methyl D-galactopyranosides.

effects just noted for the D-galactose methyl ethers [(*ii*) and (*iii*)] also apply to their methyl glycosides. In addition, there is a relatively large difference (0.16 p.p.m.) between the chemical shift of the 1-OMe in the α glycosides (this signal appears at high field) and the corresponding chemical shift for the β glycosides (low field). The chemical-shift ranges given in (*i*) for the galactose methyl ethers are slightly modified by the presence of the glycosidic methyl group: (*a*) 1-OMe (β anomers) and 2-OMe (β anomers) at lowest field (τ′ 6.43–6.47), (*b*) 3-OMe (α and β anomers having OMe at C-4) and 4-OMe (α and β anomers) in the central region (τ′ 6.48–6.54), and (*c*) 1-OMe (α anomers), 2-OMe (α anomers), 3-OMe (α and β anomers having OH at C-4) and 6-OMe (α and β anomers) at highest field (τ′ 6.54–6.63).

The chemical shifts of the methoxyl groups of the methyl ethers of D-galactopyranose and its methyl glycosides in relation to the configuration of neighboring carbon atoms bearing a hydroxyl or methoxyl group are given in Table I.

(*c*) *Methyl ethers of galactitol.* The methoxyl chemical-shifts for the methyl ethers of galactitol studied are shown in Diagram 3, from which it may be seen that these chemical shifts are not greatly influenced by methylation of neighboring hydroxyl groups. There does, however, seem to be a general upfield shift of methoxyl signals as neighboring methyl groups are introduced into these compounds; this shift is presumably due to the greater electron-releasing capacity (and, hence, greater shielding) of a methyl group compared with a proton.

(*d*) *General.* The observed effects of change in configuration on the chemical shifts of methoxyl groups may be summarized as follows; published data[5] for derivatives of D-glucose and D-mannose are included for comparison. (*i*) Anomeric change (axial to equatorial OMe) produces a downfield shift (0.16 p.p.m.) of the 1-OMe signal. This shift has been found not only for the derivatives of D-galactose but also (as expected) for D-glucose derivatives[5]. For the corresponding derivatives of D-mannose (axial 2-OH), data are available only for methyl α-D-mannopyranoside[5],

TABLE I

METHOXYL-GROUP CHEMICAL-SHIFTS IN RELATION TO THE DISPOSITION OF NEIGHBORING HYDROXYL OR METHOXYL GROUPS IN METHYL ETHERS OF D-GALACTOPYRANOSE AND ITS METHYL GLYCOSIDES

Methoxyl group[a]	*Neighboring group(s)*[a]	*Number of examples*	*Chemical shifts*[b] *of methoxyl groups*	
			Range	*Mean*
1(*a*)	2-OH(*e*)	7	6.58–6.63	6.61 ±0.03
1(*e*)	2-OH(*e*)	7	6.44–6.46	6.45 ±0.01
1(*a*)	2-OMe(*e*)	8	6.60–6.62	6.61 ±0.01
1(*e*)	2-OMe(*e*)	8	6.43–6.46	6.45 ±0.02
2(*e*)	1-OH(*e*), 3-OH(*e*)	4	6.43–6.445	6.43 ±0.02
2(*e*)	1-OH(*a*), 3-OH(*e*)	4	6.55–6.56	6.56 ±0.01
2(*e*)	1-OMe(*e*), 3-OH(*e*)	4	6.43–6.45	6.44 ±0.01
2(*e*)	1-OMe(*a*), 3-OH(*e*)	4	6.54–6.56	6.56 ±0.02
2(*e*)	1-OMe(*e*), 3-OMe(*e*)	4	6.43–6.45	6.44 ±0.01
2(*e*)	1-OH(*a*), 3-OMe(*e*)	4	6.56–6.58	6.57 ±0.01
2(*e*)	1-OMe(*e*), 3-OMe(*e*)	4	6.46–6.47	6.47 ±0.01
2(*e*)	1-OMe(*a*), 3-OMe(*e*)	4	6.55–6.58	6.57 ±0.02
3(*e*)	2-OH(*e*), 4-OH(*a*)	4	6.57–6.58	6.57 ±0.01
3(*e*)	2-OMe(*e*), 4-OH(*a*)	8	6.57–6.60	6.59 ±0.02
3(*e*)	2-OH(*e*), 4-OMe(*a*)	8	6.48–6.50	6.49 ±0.01
3(*e*)	2-OMe(*e*), 4-OMe(*a*)	8	6.50–6.54	6.52 ±0.02
4(*a*)	3-OH(*e*)	16	6.49–6.51	6.50 ±0.01
4(*a*)	3-OMe(*e*)	16	6.48–6.51	6.50 ±0.02
6	1-OH(*a*,*e*)	14	6.60–6.64	6.62 ±0.03
6	1-OMe(*a*,*e*)	14	6.58–6.62	6.60 ±0.02

[a] The numbers refer to the carbon atoms on which the methoxyl or hydroxyl groups are situated; *a* = axial, and *e* = equatorial disposition. [b] Taken from published papers[1–4], for solutions in deuterium oxide (τ′ scale).

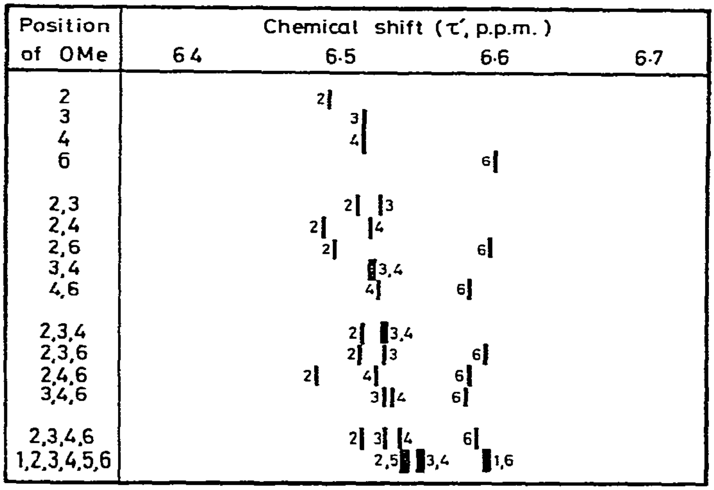

Diagram 3. Methoxyl-group chemical-shifts of methyl ethers of galactitol.

for which the glycosidic methoxyl group has a chemical shift similar to those of the methyl α-glycosides of D-glucose and D-galactose.

The following three observations refer to the effect of change in configuration of an adjacent hydroxyl group on the chemical shift of a methoxyl group. (*ii*) A downfield shift of 0.14 p.p.m .is noted for the 2-methoxyl signals of both 2-*O*-methyl-D-galactose and 2-*O*-methyl-D-glucose[5], when the disposition of the hydroxyl group at C-1 is changed from axial to equatorial. As was seen in (*i*), the opposite effect is not observed. A change in the disposition of the hydroxyl group at C-2 from axial (D-mannose derivative) to equatorial (D-glucose or D-galactose derivative) has no resultant effect on the chemical shift of an axial methoxyl group at C-1. Whether this also holds for an equatorial methoxyl group at C-1 (the situation necessary for a true comparison with the effect observed here) is not yet known. (*iii*) The effect noted in (*ii*) for D-galactose and D-glucose derivatives (equatorial 2-OMe) holds for D-mannose (axial 2-OMe) also. (*iv*) An effect analogous to that in (*ii*) and (*iii*) is observed when the 3-OMe signals for 3-*O*-methyl-D-galactose (axial 4-OH) are compared with those for 3-*O*-methyl-D-glucose[5] (equatorial 4-OH), the change in disposition of the neighboring hydroxyl group from axial to equatorial producing a downfield shift of 0.16 p.p.m. in the 3-OMe signal. This effect is observed for both anomers of these compounds. The downfield shift is 0.19 p.p.m. when a 2-($\overset{+}{N}H_2Me$) group is present instead of a 2-OMe group[10]. (*v*) In addition it should be noted[5] that the 2-OMe groups (axial) of 2-*O*-methyl-D-mannose have the same chemical shifts as the 2-OMe groups (equatorial) of the corresponding anomers of 2-*O*-methyl-D-galactose and -glucose, and that the 4-OMe groups (axial) of 4-*O*-methyl-D-galactose have the same chemical shifts as the 4-OMe groups (equatorial of) 4-*O*-methyl-D-glucose. This is also true for the chemical shifts of the 4-OMe groups of the hydrochlorides of 2-deoxy-2-(methylamino)-D-glucose and -D-galactose[10,11]. These facts indicate that the chemical shifts of methoxyl groups on C-2 and C-4 (at least) are independent of the configuration of these carbon atoms. It is known that this observation does not apply to a OMe group on the anomeric carbon atom [see (*i*)], but it probably applies to a 3-OMe group. These effects are summarized in Diagrams 4 and 5.

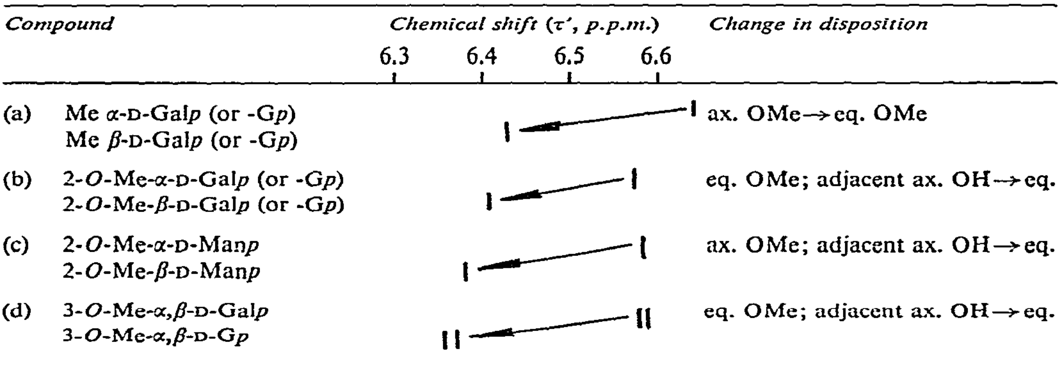

Diagram 4. Summary of the effects observed on the chemical shift of a methoxyl group by change of its disposition (a), or change in the disposition of an adjacent hydroxyl group (b, c, and d).

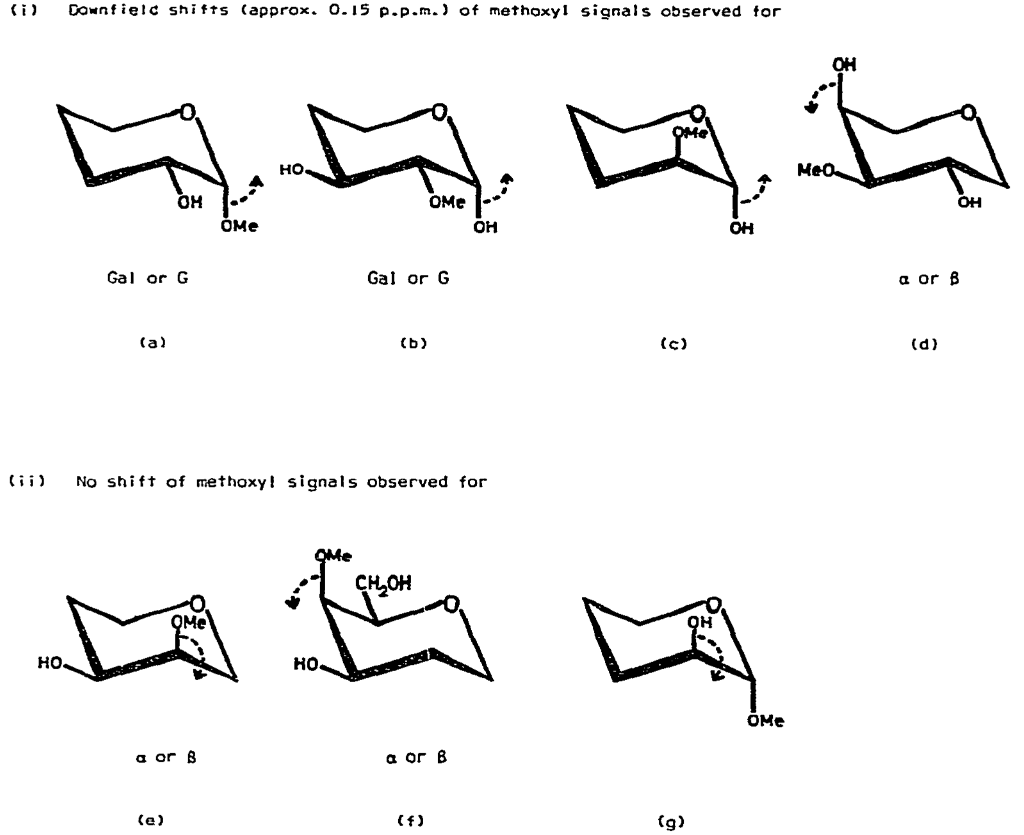

Diagram 5. Effects of changes in disposition on methoxyl-group chemical-shifts.

It is of interest that effects (*i*), (*ii*), and (*iv*) are also observed in the spectra of the fully methylated methyl glycopyranoside derivatives of these compounds[4] (in benzene as the solvent); the magnitude of (*i*) remains the same, whereas those of (*ii*) and (*iv*) both increase to ~0.25 p.p.m.

The effect of a change in the disposition of a methoxyl group on its chemical shift is significant only for a methoxyl group at C-1. The explanation for this observation probably lies in the fact that the anomeric methoxyl groups are uniquely oriented with respect to the nearby ring-oxygen atom (O-5). Considerations involving interactions of the lone pairs[12] or dipoles[13] associated with O-1 and O-5 have been used to explain the differences in shielding of the protons of the anomeric methoxyl group of the two anomers.

The proton resonance of a methoxyl group situated between two equatorially attached hydroxyl (or methoxyl) groups appears at relatively low field compared with that of a methoxyl group having one equatorial and one axial neighboring (hydroxyl or methoxyl) group. This effect is illustrated by the methoxyl chemical-shifts of 2-*O*-methyl-β-D-glucose, 2-*O*-methyl-β-D-galactose, 2-*O*-methyl-β-D-mannose, and

3-*O*-methyl-α- and β-D-glucose, these shifts being ~0.15 p.p.m. downfield from the methoxyl signals of 2-*O*-methyl-α-D-glucose, 2-*O*-methyl-α-D-galactose, 2-*O*-methyl-α-D-mannose, and 3-*O*-methyl-α- and β-D-galactose, respectively. It appears that a 1,3-diequatorial hydroxyl or methoxyl system uniquely deshields the protons of a methoxyl group situated between them. This deshielding could possibly be due to differences in the electrical field-effects[14] operating on such a methoxyl group when the disposition of a neighboring group is changed from equatorial to axial, or *vice versa*. At the same time, the steric environment of a methoxyl group will be altered by the neighboring configurational change, making the explanation of the observed effects difficult. Gros *et al.*[6] have presented a conformational study of methyl ethers of D-galactose and D-mannose that affords an explanation of some of the methoxyl chemical-shifts observed.

Chemical shifts of anomeric protons. — It is well known that the chemical shifts of the anomeric proton of α anomers (H-1 equatorial) differ greatly from those of the β anomers (H-1 axial). For D-galactose, the signal for the equatorial anomeric proton appears 0.68 p.p.m. to lower field than that of the axial anomeric proton. Formation of the methyl glycosides of D-galactopyranose produces upfield shifts of the H-1 signals (relative to those for D-galactose) of 0.42 p.p.m. and 0.26 p.p.m. for the α and β glycosides, respectively. On the other hand, methylation at O-2 produces a downfield shift of 0.21 p.p.m. in the signal for the equatorial anomeric proton only, and that for the axial proton at C-1 is not affected significantly. The resultant effect of introduction of methyl groups at both O-1 and O-2 is to produce upfield shifts of 0.20 and 0.24 p.p.m., respectively, of the equatorial and axial anomeric protons.

The variations in the observed spacings of the H-1 doublets are relatively small ($\leq$1 Hz), indicating that the *C1* (D) conformation is retained for the methyl ethers of D-galactose and their methyl glycosides.

The difference in chemical shift of the axial and equatorial protons of cyclohexane (when the solution is "frozen" to stop interconversion of its conformations) has been explained[15,16] as being due to the magnetic anisotropy of the two C–C bonds having 2,3 relationship to the protons under consideration. These relationships (distances and angles) are such that the equatorial proton is deshielded and the axial proton is shielded. For a pyranoid compound, this difference in chemical shift is enhanced by the effects produced by the ring-oxygen atom on the anomeric protons. Additional effects on the anomeric protons are (*a*) the electronegativity of the substituent at C-1 (and of the ring-oxygen atom) — the greater electron-releasing influence of a methyl group compared with hydrogen on O-1 shields the anomeric protons in the methyl glycosides, and (*b*) the influence of the magnetic anistropy of the 1-O–Me bond, which may result in greater shielding of H-1, in addition to that due to the aforementioned effects[8]. The observation that methylation of O-2 produces a downfield shift of H-1 may also be a magnetic anisotropic effect. In its more probable dispositions, the 2-O–Me bond always appears oriented with respect to the 1-C–H bond in such a way as to produce long-range deshielding of H-1 (ref. 8).

The complexity of the electrical fields[14] originating from the dipoles of the methoxyl groups produced on methylation of hydroxyl groups, and of their possible effects on chemical shifts of anomeric protons and methoxyl groups, is too great to permit any explanations to be given at this stage regarding the influence of methylation upon the chemical shifts of neighboring protons. In addition to the influences of paramagnetic anisotropy, electronegativity of a substituent, steric hindrance, and electrical fields on the chemical shift of a proton, the effects of a strongly hydrogen-bonding solvent (such as deuterium oxide) have to be taken into account. It is highly probable that more than one of these effects will operate simultaneously on any single proton. Additional data on related compounds are needed in order that it may be ascertained whether the observations made here are generally applicable.

EXPERIMENTAL

Methyl ethers of methyl α- and β-D-galactopyranoside, D-galactopyranose, and galactitol were obtained as previously described[1-3]. P.m.r. spectra were recorded with a Varian Associates HA-100 n.m.r. spectrometer for 5–10% solutions in deuterium oxide at 32°. Sodium 4,4-dimethyl-4-silapentanesulfonate was used as the internal standard (τ' scale).

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