PROTON SPIN–LATTICE RELAXATION-RATES AND NUCLEAR OVER-HAUSER ENHANCEMENT, IN RELATION TO THE STEREOCHEMIS-TRY OF β -D-MANNOPYRANOSE 1,2-ORTHOACETATES

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ABSTRACT

Data are reported on spin-lattice relaxation-rates and nuclear Overhauser enhancement of protons of *exo* and *endo* diastereoisomers of 1,2-O-(1methoxyethylidene) and 1,2-O-(1-benzyloxyethylidene) derivatives of 3,4,6-tri-Oacetyl- β -D-mannopyranose, and of some specifically deuterated analogs of these derivatives. The results verified assignments of the orientation at the quaternary carbon atom of the acetal ring, and yielded information about the orientations favored by the exocyclic C-methyl and benzyloxy substituents.

INTRODUCTION

Some years ago, it was reported¹ that mixtures of diastereoisomeric 1,2-orthoacetates of β -D-mannopyranose are formed from the corresponding glycosyl bromide under Koenigs-Knorr conditions. Both the *exo* and the *endo* isomers of 3,4,6-tri-O-acetyl-1,2-O-(1-methoxyethylidene)- and -1,2-O-(1-benzyloxyethylidene)- β -D-mannopyranose (1, 3, 4, and 6, respectively) were obtained, and configurational assignments for them were proposed on the basis of ¹H-n.m.r. chemical-shift data. It was then shown² that the use of 2,6-di- or 2,4,6-tri-methylpyridine as the acid acceptor instead of silver oxide produced only one of the diastereomers, designated *exo* (1 or 4), and this assignment was subsequently confirmed³ for isomer 1 by X-ray crystallography. In the study described here, some



1 R = CH₃, R' = OCH₃ **2** R = CH₃, R' = OCHD₂ **3** R = OCH₃, R' = CH₃ **4** R = CH₃, R' = OCH₂Ph **5** R = CH₃, R' = OCHDPh **6** R = OCH₂Ph, R' = CH₃ aspects of the stereochemistry of these orthoesters in solution have been examined by ¹H-n.m.r. measurements of steady-state, nuclear Overhauser enhancement (n.O.e.) and nonselective, spin-lattice relaxation-rates (R_1). In particular, the n.O.e. experiments, which permit^{4,5} determination of the interproton distances, have been utilized in order to obtain quantitative data on the molecular geometry.

EXPERIMENTAL

¹H- and ¹³C-N.m.r. spin-lattice relaxation and n.O.e. measurements. — All of the n.m.r. experiments were performed with a Varian XL-200 spectrometer operated at 200 MHz and 20°. 0.06M Solutions in acetone- d_6 were used for the ¹H experiments, to minimize undesirable, dipolar, intermolecular interactions, and 0.5M solutions in acetone- d_6 for the ¹³C experiments. Each sample was carefully degassed by using 5 to 6 "freeze-pump-thaw" cycles, following which, the n.m.r. tube was sealed. The ¹H-relaxation rates (R_1) were determined by the null method⁶; each value is the result of three separate determinations, with a reproducibility of $\pm 5\%$. The ¹³C spin-lattice relaxation measurements were made under conditions of full ¹H-noise decoupling, by the two-pulse, inversion-recovery technique, experimental details for which are given elsewhere⁷; statistical errors in these T_1 data are within $\pm 5\%$. Steady-state, proton n.O.e. values were obtained by comparing the integrated intensities of the observed peaks in double-resonance spectra with the areas of the same peaks in the normal spectra. Delays of >10 times the longest T_1 value were used between 90° pulses (6.9 μ s), and the irradiating power was the minimum required for effective saturation of the irradiated nucleus. At least 8 experiments were performed for each n.O.e. value.

Preparation of compounds. — The exo and endo diastereoisomers of 3,4,6-tri-O-acetyl-1,2-O-(1-methoxyethylidene)- β -D-mannopyranose (1 and 3, respectively), and of 3,4,6-tri-O-acetyl-1,2-O-(1-benzyloxyethylidene)- β -D-mannopyranose (4 and 6, respectively) were synthesized as described previously¹.

Flash column chromatography of the crude, crystalline mixture of **1** and **3** (1.1 g) on Celite, using 3:2 ether–hexane as eluant, afforded **3** (0.38 g); m.p. 104–105° (after recrystallization from ether–hexane), $[\alpha]_{D}^{25} -37.1^{\circ}$ (*c* 2.1. chloroform) ($R_{\rm F}$ 0.45 in 2:1 ether–hexane); mixtures of **1** and **3** were then eluted, followed by pure **1**, m.p. 112–113° (after recrystallization from ether), $[\alpha]_{D}^{25} -22.2^{\circ}$ (*c* 2.5, chloroform) ($R_{\rm F}$ 0.40 in 2:1 ether–hexane) [lit.² for **1**, m.p. 111–113°, $[\alpha]_{D} -23^{\circ}$ (chloroform)]; ¹H-n.m.r. data for **1** (acetone- d_6): δ 5.68 (d, H-1), 5.27–5.17 (m, H-3,4), 4.64 (dd, H-2), 3.88 (m, H-5), 4.21 (dd, H-6), 4.07 (dd, H-6'), 3.18 (s, OMe), 2.02, 2.00, 1.99 (s, 3 Ac), and 1.64 (s, Me); $J_{1,2}$ 2.41, $J_{2,3}$ 3.55, $J_{3,4}$ 9.95, $J_{4,5}$ 9.60, $J_{5,6}$ 4.57, $J_{5,6'}$ 2.56, and $J_{6,6}$ 12.17 Hz; ¹³C-n.m.r. data for **1** (acetone- d_6): δ 170.63, 170.45, 170.06 (3 CO), 125.08 (CCH₃), 98.34 (C-1), 78.40 (C-2), 71.48 and 71.44 (C-3 or C-4), 66.44 (C-5), 62.82 (C-6), 54.95 (OCH₃), 25.82 (CCH₃), and 20.62, 20.56, and 20.56 (3 COCH₃).

¹H-N.m.r. data for 3 (acetone- d_6): δ 5.44 (d, H-1), 5.37–5.33 (m, H-3,4),

4.45 (dd, H-2), 4.24 (dd, H-6), 4.07 (dd, H-6'), 3.95 (m, H-5), 3.44 (s, OMe), 2.02, 2.00, 1.95 (s, 3 Ac), and 1.42 (s, Me): $J_{1,2}$ 2.42, $J_{2,3}$ 3.75, $J_{3,4}$ 9.90, $J_{4,5}$ 9.53, $J_{5,6}$ 4.11, $J_{5,6'}$ 2.44, and $J_{6,6'}$ 12.23 Hz; ¹³C-n.m.r. data for **3** (acetone-*d*₆): δ 170.54, 170.40, 170.01 (3 CO), 125.12 (CCH₃), 95.66 (C-1), 76.70 (C-2), 71.64 and 71.35 (C-3 or C-4), 66.34 (C-5), 62.54 (C-6), 50.08 (OCH₃), 24.40 (CCH₃), and 20.62, 20.54, and 20.47 (3 COCH₃).

Anal. (for 3): Calc. for C₁₅H₂₂O₁₀: C, 49.7; H, 6.1. Found: C, 49.8, H, 6.2.

exo-3,4,6-Tri-O-acetyl-1,2-O-(1-methoxy-(d₂)-ethylidene-β-D-mannopyranose (2). — A solution of 2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl bromide (1.4 g) in dichloromethane (5 mL) containing methan- d_2 -ol (2 mL) and 2,4,6-trimethyl-pyridine² (2.5 mL) was stirred for 36 h at room temperature, diluted with chloroform (20 mL), washed successively with dilute hydrochloric acid, sodium hydrogencarbonate, and water, dried, and evaporated. The solid residue was recrystallized from cold ether in the form of white needles, m.p. 114–115°, $[\alpha]_D^{25} -21.4^\circ$ (*c* 1.8, chloroform); (R_F 0.40 in 2:1 ether–hexane); ¹H-n.m.r. data (acetone- d_6): δ 5.68 (d, H-1), 4.64 (q, H-2), 5.27–5.17 (m, H-3,4), 3.88 (m, H-5), 4.21 (dd, H-6), 4.07 (dd, H-6'), 1.64 (s, Me), 3.19 (s, CD₂H), and 2.02, 2.00, and 1.99 (s, Ac); $J_{1,2}$ 2.41, $J_{2,3}$ 3.55, $J_{3,4}$ 9.95, $J_{4,5}$ 9.60, $J_{5,6}$ 4.57, $J_{5,6'}$ 2.56, and $J_{6,6'}$ 12.17 Hz.

Benzyl- α -d-alcohol. — Sodium borodeuteride (2.1 g, 0.05 mol) was added during 2 h to a stirred solution of benzaldehyde (20 g, 0.19 mol) in methanol (20 mL) at 0°. After decomposition of the excess of the reducing agent with acetic acid, and evaporation of the methanol, the residue was extracted into dichloromethane (30 mL) and water (30 mL). The organic layer was washed with sodium hydrogencarbonate, and water, dried, and evaporated, and the residual liquid was distilled at 120°/2.4 kPa (18 mm Hg).

exo-3,4,6-*Tri*-O-*acetyl*-1,2-O-(*1-benzyloxy-α*-d-*ethylidene*)-β-D-*mannopyranose* (5). — A solution of 2,3,4,6-tetra-O-acetyl-*α*-D-mannopyranosyl bromide (5.3 g) in dichloromethane (15 mL) containing benzyl-*α*-d-alcohol (10 mL) and 2,4,6-trimethylpyridine (9.5 mL) was stirred for 48 h at room temperature, diluted with chloroform (50 mL), washed successively with cold dil. hydrochloric acid, sodium hydrogencarbonate, and water, dried, and evaporated. The solid residue was recrystallized from ether in the form of white needles, m.p. 137–138°, $[\alpha]_D^{25}$ –1.3° (*c* 1.9, chloroform); R_F 0.45 in 2:1 ether–hexane; ¹H-n.m.r. data (acetone-*d*₆): δ 7.33–7.24 (m, Ar), 5.74 (d, H-1), 5.32–5.22 (m, H-3,4), 4.71 (dd, H-2), 4.63 (s, CDH*α*), 4.54 (s, CDH*α'*), 3.92 (m, H-5), 2.02, 2.01, 2.00 (s, 3 Ac), and 1.75 (s, Me); $J_{1,2}$ 2.43, $J_{2,3}$ 3.60, $J_{3,4}$ 9.99, $J_{4,5}$ 9.50, $J_{5,6}$ 4.59, $J_{5,6'}$ 2.59, and $J_{6,6'}$ 12.19 Hz; ¹³C-n.m.r. data (acetone-*d*₆): δ 170.62, 170.37, 170.04 (3 CO), 125.0 (CCH₃), 98.36 (C-1), 78.19 (C-2), 71.55 and 71.26 (C-3 or C-4), 66.42 (C-5), 64.32 (CHD), 62.82 (C-6), and 20.62, 20.57, and 20.57 (3 COCH₃).

RESULTS AND DISCUSSION

Determination of the configurations of diastereoisomeric 1,2-orthoacetates by

Protons irradiated	Com- pound	Protons observed ^a							
		H-1	H-2	OCH ₂	OCH ₃	CCH ₃			
H-1	1		0.122 ± 0.003						
H-1	3		0.127 ± 0.003						
H-1	4		0.075 ± 0.003						
H-2	1	0.152 ± 0.003			0.031 ± 0.002				
H-2	3	0.119 ± 0.007							
H-2	4	0.089 ± 0.004		-0.047 ± 0.005					
OCH ₂	4		0.122 ± 0.005						
CCH ₃	1				-				
CCH ₃	3		0.099 ± 0.002		1.100 A				
CCH ₃	4			-					
OCH ₃	1		0.092 ± 0.004						
OCH ₃	3		MARK WE WITH THE PARTY OF THE P						

TABLE I

¹H-NUCLEAR OVERHAUSER ENHANCEMENT DATA FOR *exo-* and *endo-*3,4,6-tri-*O*-acetyl-1,2-*O*-(1-METHOXYETHYLIDENE)- β -D-MANNOPYRANOSE (1 and 3). AND 3,4,6-tri-*O*-acetyl-1,2-*O*-(1-BEN-ZYLOXYETHYLIDENE)- β -D-MANNOPYRANOSE (4)

^{*a*}The errors (\pm) are given as standard deviations; dashes (-) indicate n.O.e. values of <0.005.

measurements of nuclear Overhauser enhancement and relaxation rates. — A direct means for assigning the configuration of isomers 1 and 3 was afforded by n.O.e. measurements (see Table I). Saturation of the *O*-methyl protons caused a significant enhancement of the H-2 resonance of 1, whereas H-2 (or H-1) of isomer 3 was unaffected. In full accord with these results, irradiation of the *C*-methyl protons produced a 10% increase in the intensity of the H-2 signal of 3, although there was no enhancement of the H-2 (or the H-1) signal of 1. Clearly, these observations are consistent only with the C–OMe bond of 1 occupying the *exo* position, and that of 3, the *endo* position.

The validity of this comparison is strengthened by the evidence from ${}^{1}\text{H}{-}{}^{1}\text{H}$ coupling that the conformation of the D-mannopyranose ring is virtually identical in **1** and **3** and, therefore, that stereochemical differences between them are confined to the orthoester structure. That is, ${}^{3}J$ values observed for the ring protons (see the Experimental section) are all within 0.2 Hz: $J_{1,2} = 2.41$ or 2.42, $J_{2,3} = 3.55$ or 3.75, $J_{3,4} = 9.90$ or 9.95, and $J_{4,5} = 9.53$ or 9.60 Hz*.

Close similarities between the chemical shifts of H-1, H-2, and the CCH₃ of benzyloxyderivative 4 and those of 1 have been cited¹ as evidence that the two compounds have the same orientation at the acetal carbon atom; an analogous re-

^{*}These coupling data suggest, as proposed earlier¹, that the D-mannopyranose ring may be represented *approximately* by the ${}^{4}C_{1}$ conformation implied by formulas **1–6**, which also is consistent³ with the X-ray data for crystalline **1**.

TABLE II

Compound	Protons								
	H-1	H-2	OCH ₂	OCH ₃	CCH ₃	H - α^a	H - α'^a	OCD_2H	
1	0.39	0.54	_	0.55	1.08	_	_		
3	0.46	0.59		0.60	1.25			<u> </u>	
4	0.75	0.86	0.75	_	1.46		_		
2	0.36	0.43		_	1.06			0.19	
5	0.55	0.77	_		1.47	0.57	0.57		

 1 H-n.m.r., spin-lattice relaxation-rates (s $^{-1}$) for orthoacetates 1, 3, and 4, and the selectively deuterated analogs 2 and 5

^aMethylene protons of diastereoisomers of 5.

lationship was found¹ between* 3 and 6. Having concluded from the n.O.e. experiments that 1 is an *exo* diastereoisomer, the affinity between 1 and 4 was substantiated in the same way by the fact (see Table I) that the intensity of the H-2 signal of 4 was increased by 12% when the benzylic protons were irradiated.

A parallel set of data was obtained from measurements of spin-lattice relaxation-rates (R_1) (see Table II). As a general observation, R_1 values for all of the protons associated with the orthoester structure in **1** were appreciably lower than those of **3**. Also, the *C*-methyl protons of both compounds relaxed at about twice the rate of the *O*-methyl protons. As the relaxation processes of methyl groups in structurally related acetals are dominated by intra-methyl dipole–dipole and spin–rotation interactions^{8,9}, this two-fold difference reflects mainly a difference in the degree of hindrance to the internal motions of these groups when bonded to carbon, as compared with oxygen.

There appears to be no straightforward basis for relating the variations in R_1 , evident in Table II, with the orientations at the quaternary carbon atoms of 1 and 3. However, evidence that the O-methyl group of 1 occupies the *exo* position is afforded by a comparison of the R_1 values of 1 with those of its O-methyl- d_2 analog (2) (see Table II). That is, the relaxation rates of H-1 and, in particular, H-2 were decreased by the incorporation of the deuterium atoms, which indicates that the O-methyl protons of 1 are sufficiently close to H-1 and H-2 to influence their relaxation processes materially. In addition, the fact that R_1 for the C-methyl protons of 1 and 2 is the same, whereas that of the lone proton of the OCHD₂ group of 2 is lower by a factor of one-third, is a clear reflection of the dominance of the intramethyl interactions mentioned earlier.

An analogous combination of measurements of R_1 with deuterium substitu-

^{*}Added to the differentiation¹ between diastereoisomers 1 and 3 (or 4 and 6), on the basis of ¹H-chemical shifts, are equally striking differences in the ¹³C-chemical shifts (see the Experimental section). Hence, C-1, C-2, CCH₃, and OCH₃ are all much more strongly shielded in 3 than in 1. It is also worth noting that the corresponding ¹³C-chemical shifts of the latter and isomer 4 are essentially the same (see the Experimental section).



Fig. 1. Partial, ¹H-n.m.r. spectra (200 MHz) of (a) 3,4,6-tri-O-acetyl-1,2-O-(1-benzyloxyethylidene)- β -D-mannopyranose (4), and (b) an analog of 4 (*i.e.*, 5) in which one of the benzylic protons is replaced by a deuteron (solvent, acetone- d_6).

tion was also applied to compound 4. One of the benzylic protons was replaced by deuterium so as to give 5, an equimolar mixture of two diastereoisomers containing either an α - or α' -proton. The composition of 5 was determined from the relative intensities of the benzylic protons in the spectra of 4 and 5 (see Figs. 1a and 1b). As shown in Table II, the R_1 values for H-1 and H-2 were notably smaller in the presence of the isotope, whereas the C-methyl protons exhibited no change. Hence, the *exo* designation for 4 was again verified by these results.

Orientation of the methoxyl and benzyloxy substituents of isomers 1 and 4. — Although the n.O.e. and relaxation-rate experiments just described permitted unambiguous assignments of orientation for the 1,2-orthoesters, they were not suitable for determining the orientations of the O-methyl or O-benzyl substituents. There are two main reasons for this: (a) the dominant influence of intra-methyl dipole-dipole relaxation^{8.9} limits the usefulness of the C-methyl or O-methyl groups of 1 and 3 as effective probes of intramolecular interactions present, and (b) the close spacing of the strongly coupled methylene AB pair of protons of 4 (see Fig. 1a) prevents determination of their individual n.O. effects on neighboring protons. However, these restrictions were circumvented by employing the specifically deuterated analogs of 1 and 4, *i.e.*, 2 and 5.

The n.O.e. data for 2 and 5 (see Table III) reflect the proximities of the *O*-methyl- d_2 group and *O*-benzyl-d group with respect to H-1 and H-2, *i.e.*, the rota-

TABLE III

¹H-NUCLEAR OVERHAUSER ENHANCEMENT DATA FOR *exo-*3,4,6-TRI-*O*-ACETYL-1,2-*O*-(1-METHOXY- d_2 -ETHYLIDENE)- β -D-MANNOPYRANOSE (2) AND *exo-*3,4,6-TRI-*O*-ACETYL-1,2-*O*-(1-BENZYL- α -d-OXY-ETHYLIDENE)- α -D-MANNOPYRANOSE (5)

Protons	Com-	Protons obser	ved ^a				
irradiated	pound	H-1	H-2	H-α ^b	<i>Η-</i> α' ^b	ССН3	OCD₂H
H-1	2		0.132 ±0.005				-
H-1	5		0.071 ± 0.007	-0.060 ± 0.002			
H-2	2	0.133 ± 0.004					0.074 ± 0.018
H-2	5						
Η-α	5		0.042 ± 0.004			_	
Η-α'	5	0.030 ± 0.06	0.040 ± 0.003				
CCH ₃	2						
CCH ₃	5						
OCD ₂ H	2	0.015 ± 0.006	0.055 ± 0.006				

^aThe errors (\pm) are given as standard deviations; dashes (-) indicate n.O.e. values of <0.005. ^bMethylene protons of diastereoisomers of 4.

tional orientations of the O_2C-O-R moieties* in these molecules. Within a molecule, interproton distances (which represent thermodynamic averaging in 2 and 5) may be determined from n.O.e. values when the overall motion is isotropic in the extreme narrowing range and relaxation occurs mainly by the dipole-dipole mechanism. Compounds 2 and 5 were found to fulfil these requirements. Hence, in each molecule, all of the ring-carbon atoms bearing a single proton were shown to have essentially the same ${}^{13}C-T_1$ value**, which is diagnostic for an overall, isotropic motion. Moreover, all of these carbon atoms relax by dipole-dipole interactions, as evidenced by ${}^{13}C-[{}^{1}H]$ nuclear Overhauser enhancements of ~100%.

Ratios of interproton distances were calculated by using the inverse, sixthroot dependence implicit in the formalism of steady-state n.O.e. for three nonequivalent spins^{3,4}. These ratios were then converted into interproton distances (r_{ij}) by using a value of 243 pm as the distance between H-1 and H-2, based on crystal data³ for 1; the corresponding value obtained from stereomodels, by assuming a dihedral angle^{1,2} of 30° between H-1 and H-2, was 245 pm. A comparison of the interproton distances calculated with those obtained from the X-ray diffraction data³, and the use of stereomodels (see Table IV), shows excellent agreement between the three sets of data; the largest discrepancy (~12%) is found for the H-2– H- α (benzylic) interatomic distance in 5.

^{*}The orientation of the phenyl group of 5 has not been assessed.

^{**&}lt;sup>13</sup>C-*T*₁ values measured for 0.5M solutions of 1 and 4 in acetone-*d*₆ at 20° were: for 1, C-1, 2.51; C-2, 2.57; C-3, 2.60; C-4, 2.52; and C-5, 2.56 s; for 4, C-1, 1.80; C-2, 1.82; C-3, 1.79; C-4, 1.75; and C-5, 1.80 s.

Protons	Compound 1			Compound 4			
(ij)	<i>H-1–OCH</i> ₃	<i>H-2–OCH</i> ₃	Η-1-Η-α	Η-1–Π-α΄	Н-2-Н-а	<i>H-2–Hα</i> ′	
r_{ij} from $p \ \Omega = data^{a,b}$	328 + 2	270 + 1	413 + 13	282 +15	264 + 7	265 +8	
r_{ij} from	040.24	217 21	410 - 10	202 - 10	2011 - 1	Sector march	
Dreiding models r_{ii} from	331 ± 2^c	$302 \pm 2^{\circ}$	452 ±2	313 ±2	301 ±2	298 ± 2	
X-ray diffraction	$329 \pm 2^{\circ}$	275 ± 2^c			ar 1981		

TABLE IV

INTERPROTON DISTANCES (pm) FOR *exo-*3,4,6-TRI-*O*-ACETYL-1,2-*O*-(1-METHOXYETHYLIDENE)- α -D-MAN-NOPYRANOSE (1) AND *exo-*3,4,6-TRI-*O*-ACETYL-1,2-*O*-(1-BENZYLOXYETHYLIDENE)- β -D-MANNOPYRANOSE (4)

"A value of $r_{1,2} = 243$ pm was used for these calculations. ^bError calculations are based on the propagation of errors in the n.O.e. measurements. 'Internuclear distance to OCH₃ protons refers to that between the single proton and the point defined by the intersection of the three-fold rotation-axis of the *O*-methyl group and the plane through the three protons of the *O*-methyl group.

Clearly, these data indicate that, in acetone- d_6 solution, the O-methyl substituent of *exo* isomer 1 favors essentially the same orientation as in the solid state³, as depicted in the "Newman" projection along the C_{quat} .-O bond (7). For the benzyloxy derivative 4, the facts that the α , α' -methylene protons are equidistant from H-2 and that the interproton distances calculated agree with those given by the stereomodels (see Table IV) constitute evidence that the average orientation of the O-benzyl substituent may be represented by rotamers 8 and 9 along the C_{quat}.-O and O-CH₂ bonds, respectively. Rotamers 7 and 8 are expected to be stabilized by virtue of the fact that both of the oxygen lone-pairs of the OR substituent are *anti* (or nearly so) with respect to the two C_{quat}.-O bonds of the orthoester ring, as pointed out recently¹⁰ for similar types of structures in 2-methoxy-1,3-dioxanes.



The level of contribution by other possible rotamers (*e.g.*, 10 and 11) to the overall conformation of *exo* isomers 1 and 4 in solution has not been determined. In principle, a fuller description of the rotamer populations may be derived^{4,11} from an analysis of the n.O.e. effects observed on a resonance, *i*, as a consequence of the saturation of neighboring protons, *j*, *i.e.*,

$$f_i(j) = K \sum_{s} P_s / r_{ij}(s)$$

where K is a constant, r_{ij} is the distance between protons *i* and *j* in the various rotamers, *s*, and P_s is the population of rotamers *s*. However, the problem is indeterminate in the present instance, because five and fifteen possibilities, respectively, must be evaluated for 1 and 4.

ACKNOWLEDGMENTS

The authors express their gratitude to the Natural Sciences and Engineering Research Council for support, and to McGill University for the Harold Hibbert Fellowship (granted to P.D.).

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