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Contribution of the *O*-benzoyl groups of tetra-*O*-benzoyl-α,β-L-arabinopyranoses to the formation of 1,1-bis(benzamido)-1-deoxy-L-arabinitol

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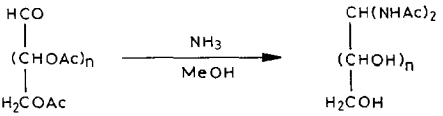
ABSTRACT

Several 1,2,3,4-tetra-*O*-benzoyl-L-arabinopyranoses selectively labeled with $C_6H_5[^{14}C]CO$ groups at different positions were synthesized. Their reactions with methanolic ammonia afforded a labeled 1,1-bis(benzamido)-1-deoxy-L-arabinitol (**18**). The contribution of each benzoyl group to the formation of the two benzamido linkages in **18** was ascertained by activity measurements. C_6H_5CO-2 made the smallest contribution to the formation of **18**, whereas those at O-3 and O-4 made the greatest contribution. C_6H_5CO-1 did not contribute to the migration reaction.

INTRODUCTION

The ammonolysis of peracetylated aldoses (**1**) is a complex reaction that leads to the formation of 1,1-bis(acylamido)-1-deoxyalditols (**2**). Many aspects of this reaction have been investigated[1], including the individual contributions of *O*-benzoyl groups to the formation of 1,1-bis(benzamido)-1-deoxyhexitols. We report herein the study of the ammonolysis of 1,2,3,4-tetra-*O*-benzoyl-L-arabinopyranose, labeled with $C_6H_5[^{14}C]CO$ groups at different positions, in order to evaluate the effects of configuration and structure of pentose perbenzoates on the mechanism of this reaction.



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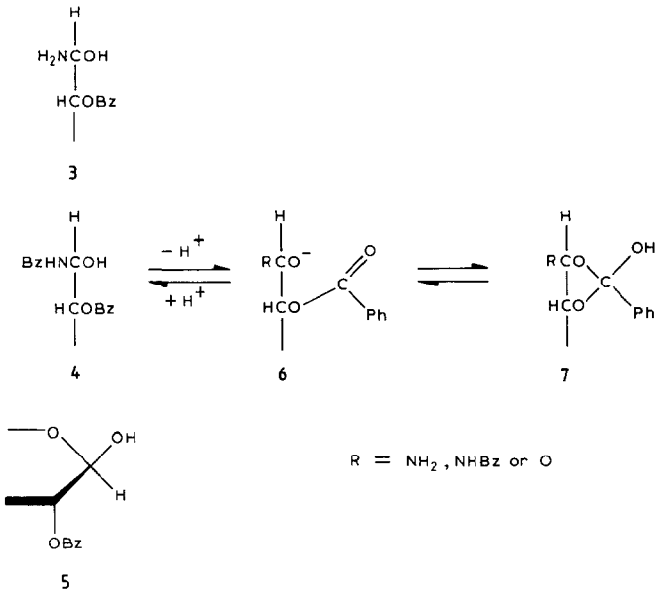
RESULTS AND DISCUSSION

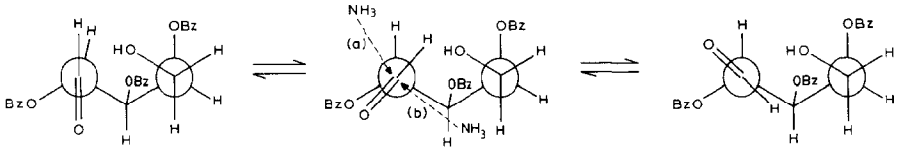
The relative contributions of benzoyl groups in the ammomolysis of L-arabinose perbenzoate were similar to those observed for hexose perbenzoates. As expected, the correlation with D-galactose perbenzoate is high since both compounds are configurationally related. Our results indicated that the absence of C_6H_5CO-6 in pentose perbenzoates does not affect the yield of benzamido derivative **2**, since C_6H_5CO-3 substitutes for C_6H_5CO-6 in the reaction. The contribution of C_6H_5CO-3 was 0.85 mol/mol, as compared with 0.62 mol/mol in the ammonolysis of 1,2,3,4,6-penta-*O*-benzoyl-D-galactopyranose[2]. C_6H_5CO-1 does not intervene in the reaction; its contribution was calculated as the difference between the total contributions of C_6H_5CO-1, -3, and -4 (1.82 mol/mol) in the ammonolysis of **17** and the contributions of C_6H_5CO-3 and -4 obtained from the ammonolysis of the corresponding labeled α-tetrabenzoates **15** and **16**. We assumed that the environment of C_6H_5CO-3 and -4 is essentially the same in α- and β-L-tetrabenzoates and, therefore, that its effect on the formation of the diamide **18** will also be the same in both anomers. With respect to the other labeled substituents, the C_6H_5CO-2 was transferred to a very low degree (0.14 mol/mol), whereas the C_6H_5CO-4 was almost completely transferred (0.98 mol/mol), as previously observed for the galactose derivative[2].

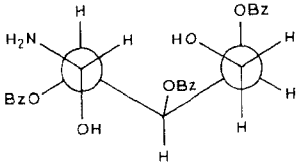
A reappraisal of previous conclusions about the course of this reaction could be made. The low participation of C_6H_5CO-2 in the $O \rightarrow N$ migration that is observed when perbenzoylated D-gluco- and D-galacto-pyranoses are ammonolyzed was explained by two different hypotheses[3,4]. However, since the perbenzoylated molecule is immersed in an ammoniacal, highly reactive medium, these explanations appear to simplify a complex situation. It is more likely that competitive alternatives exist in which molecules, in different stages of reaction, produce cyclic intermediates, represented by the general structure **7** involving C_6H_5CO-2. The possibility of this group to migrate to O-1 as an amide would then be diminished. Intermediates **3**, **4**, and **5** would afford the ionized structure **6** to give **7**. Calculations[5] showed that the hydroxyl group in the intermediates **3**, **4**, and **5** is highly ionized in methanolic ammonia (0.16, 0.86, and 0.88 mol fractions for **3**, **4**, and **5**, respectively). When the orientation at C-2 changes, as in the case for perbenzoylated D-mannopyranoside[6], the contribution of C_6H_5CO-2 in the ammonolysis reaction, although low, is twice as large as that observed for D-glucose[7] and D-galactose perbenzoates, thus suggesting that the conformational factors postulated by Zanlungo et al.[3] may also play a role.

For a preferred reaction pathway for the formation of **2**, we postulated that, after a first step in which C_6H_5CO-1 is detached as benzamide, the pyranoid ring opens to regenerate the carbonyl group. The benzoylated sugar backbone does not relax to an acyclic, extended conformation, but reacts as a puckered structure[3]. The conformations[5] for the L-arabinopyranose tetrabenzoate prior to attack by ammonia are represented by structures **8**, **9**, and **10**. In **8** and **10**, O-5 is oriented in



a favored position for intramolecular attack on the carbonyl group[8–12] to give the anomers of 1,2,3,4-tetra-*O*-benzoyl-L-arabinopyranose. On the other hand, in conformation **9**, the carbonyl group is best oriented for nucleophilic attack by solvent ammonia and the two possible paths for attack are indicated by (a) and (b). The less hindered path (a) leads to the carbinolamine **11**, which is related to the general structure **3**. The formation of the cyclic intermediate **7** from **11** gives **12**. The formation of **12** is consistent with the low contribution of C_6H_5CO-2, and with the easy migration of C_6H_5CO-4 to the favorably oriented NH_2-1 to give the corresponding *N*-benzoylcarbinolamine **13**. Some benzoyl groups would be simultaneously ammonolyzed and the cyclized C_6H_5CO-2 group separated as ammonium tetrabenzoate[5]. After this first migration, the unfolding of the molecule makes C_6H_5CO-3 the most favored by proximity and orientation for the second one, as shown by molecular models.





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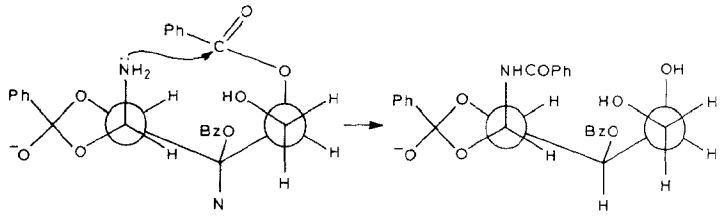

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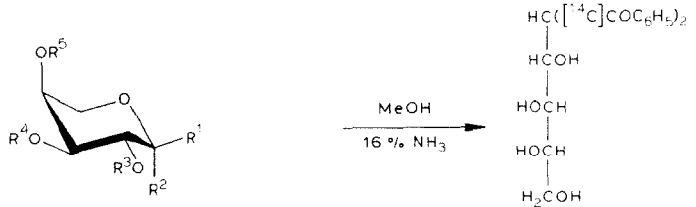

18

14 $R^1 = H, R^2 = OBz, R^4 = R^5 = Bz, R^3 = C_6H_5[^{14}C]CO$

15 $R^1 = OBz, R^2 = H, R^3 = R^5 = Bz, R^4 = C_6H_5[^{14}C]CO$

16 $R^1 = OBz, R^2 = H, R^3 = R^4 = Bz, R^5 = C_6H_5[^{14}C]CO$

17 $R^1 = H, R^2 = OC_6H_5[^{14}C]CO, R^3 = Bz, R^4 = R^5 = C_6H_5[^{14}C]CO$

EXPERIMENTAL

General methods.—Melting points were determined with a Fischer–Johns apparatus and are uncorrected. Optical rotations were determined in 1-dm tubes with a Perkin–Elmer 141 polarimeter at 25°C unless stated otherwise. IR spectra were recorded for Nujol mulls with a Perkin–Elmer 137-B Infracord spectrometer. ^1H NMR spectra (60 MHz) were recorded with a Varian A-60 spectrometer (internal Me_4Si). TLC was conducted on Silica Gel (Merck, 0.25-mm layer thickness). The labeled compounds described here for the first time were previously described as unlabeled in the literature. The synthesis of the first labeled compound in each reaction sequence was performed with $C_6H_5[^{14}C]COCl$ (activity 10.08×10^6 cpm/mmol). Radioactive compounds were recrystallized to constant specific activ-

ity. Activities were measured with a Packard Tri-Carb 3003 liquid scintillation counter (external standard). Counts are expressed per min per millimole (cpm/mmol). The isolation of 1,1-bis(benzamido)-1-deoxy-L-arabinitol (**18**) was carried out as described by Deferrari et al.[13].

*1,3,4-Tri-*O*-benzoyl-2-*O*-[*carbonyl-^{14}C*]benzoyl-β-*L*-arabinopyranose* (**14**).—Benzyl 2-*O*-[*carbonyl*-^{14}C]benzoyl-3,4-*O*-isopropylidene-β-L-arabinopyranoside [mp 110–111°C; $[\alpha]_D$ +211° (*c* 0.9, $CHCl_3$); activity 10.5×10^6 cpm/mmol] was synthesized from benzyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside by reaction[16] with C_6H_5[^{14}C]COCl. Hydrolysis[16] gave benzyl 2-*O*-[*carbonyl*-^{14}C]benzoyl-β-L-arabinopyranoside; mp 131–132°C; $[\alpha]_D$ +173° (*c* 0.8, $CHCl_3$); activity 9.8×10^6 cpm/mmol. Hydrogenolysis[17] gave 2-*O*-[*carbonyl*^{14}C]benzoyl-β-L-arabinopyranose; mp 133–134°C; $[\alpha]_D$ +153 → 101.5° (*c* 0.8, MeOH, final value); activity 10.3×10^6 cpm/mmol. Benzoylation gave **14**; mp 174–175°C; $[\alpha]_D$ +326° (*c* 3.5, $CHCl_3$); activity 10.39×10^6 cpm/mmol; after isotopic dilution 1.17×10^6 cpm/mmol; unlabeled **14**, see ref. 18.

*1,2,4-Tri-*O*-benzoyl-3-*O*-[*carbonyl-^{14}C*]benzoyl-α-*L*-arabinopyranose* (**15**).—Benzyl 2-*O*-benzoyl-4-*O*-nitro-β-L-arabinopyranoside was benzoylated[19] with C_6H_5[^{14}C]COCl to give benzyl 2-*O*-benzoyl-3-*O*-[*carbonyl*-^{14}C]benzoyl-4-*O*-nitro-β-L-arabinopyranoside; mp 95–96°C; $[\alpha]_D$ +210° (*c* 0.8, $CHCl_3$); activity 10.0×10^6 cpm/mmol. Denitration[19,20] gave benzyl 2-*O*-benzoyl-3-*O*-[*carbonyl*-^{14}C]benzoyl-β-L-arabinopyranoside; mp 122–123°C; $[\alpha]_D$ +205° (*c* 0.7, $CHCl_3$); activity 10.1×10^6 cpm/mmol. Benzoylation[16] gave benzyl 2,4-di-*O*-benzoyl-3-*O*-[*carbonyl*-^{14}C]benzoyl-β-L-arabinopyranoside. Hydrogenolysis [17] gave 2,4-di-*O*-benzoyl-3-*O*-[*carbonyl*-^{14}C]benzoyl-α-L-arabinopyranose; mp 164–165°C; $[\alpha]_D$ +239° (*c* 3.0, $CHCl_3$), $[\alpha]_D$ +144 → 195° (*c* 4.0, pyridine, final value); activity 10.12×10^6 cpm/mmol. Benzoylation gave **15**; mp 162–163°C; $[\alpha]_D$ +113° (*c* 2.0, $CHCl_3$); activity 10.3×10^6 cpm/mmol, after isotopic dilution, 1.79×10^6 cpm/mmol.

*1,2,3-Tri-*O*-benzoyl-4-*O*-[*carbonyl^{14}C*]benzoyl-α-*L*-arabinopyranose* (**16**).—Benzyl 2,3-di-*O*-benzoyl-β-L-arabinopyranoside[19] [mp 122–123°C; $[\alpha]_D$ +206° (*c* 0.6, $CHCl_3$)] was treated with C_6H_5[^{14}C]COCl to give benzyl 2,3-di-*O*-benzoyl-4-*O*-[*carbonyl*-^{14}C]benzoyl-β-L-arabinopyranoside[16] as a syrup; $[\alpha]_D$ +277° (*c* 0.6, $CHCl_3$). Hydrogenolysis[17] gave 2,3-di-*O*-benzoyl-4-*O*-[*carbonyl*-^{14}C]benzoyl-α-L-arabinopyranose, mp 164–165°C, $[\alpha]_D$ +238° (*c* 3.0, $CHCl_3$), $[\alpha]_D$ +143 → 194° (*c* 3.0, pyridine, final value); activity 10.02×10^6 cpm/mmol. Benzoylation gave **16**; mp 162–163°C; $[\alpha]_D$ +113° (*c* 1.6, $CHCl_3$); activity 10.05×10^6 cpm/mmol.

*1,3,4-Tri-*O*-[*carbonyl-^{14}C*]benzoyl-2-*O*-benzoyl-β-*L*-arabinopyranose* (**17**).—Compound **17** (mp 174–175°C; $[\alpha]_D$ +325° (*c* 3.0, $CHCl_3$); activity 3.01×10^7 cpm/mmol) was synthesized by benzoylation of 2-*O*-benzoyl-β-L-arabinopyranose with C_6H_5[^{14}C]COCl; isotopic dilution gave activity of, 2.8×10^6 cpm/mmol.

Ammonolysis of **14**, **15**, **16**, *and* **17**.—A suspension of the labeled compound (1 g) in 16% methanolic NH_3 (25 mL) was shaken at room temperature for 18 h. The solution was concentrated to dryness, and the residue washed by suspension with EtOAc (3 × 50 mL) and petroleum ether (2 × 30 mL), and then dried in vacuo

overnight. Crystallization from EtOH until constant activity afforded, in all cases, the labeled 1,1-bis([*carbonyl*-^{14}C]benzamido)-1-deoxy-L-arabinitol (**18**) with a yield between 30 and 36%; mp 199–200°C; $[\alpha]_D$ −5.2° (*c* 0.8, pyridine); lit.[13] for the unlabeled compound; mp 197–198°C; $[\alpha]_D^{30}$ −5.2° (*c* 1.2, pyridine.

Compound **14** gave **18**; activity 1.62×10^5 cpm/mmol; contribution of the 2-*O*-benzoyl group: 0.14 ± 0.01 mol/mol. Compound **15** gave **18**; activity 1.53×10^6 cpm/mmol; contribution of the 3-*O*-benzoyl group: 0.85 ± 0.02 mol/mol. Compound **16** gave **18**; activity 1.07×10^6 cpm/mmol; contribution of the 4-*O*-benzoyl group: 0.98 ± 0.02 mol/mol. Compound **17** gave **18**, activity 1.70×10^6 cpm/mM; contribution of the 1-, 3-, and 4-*O*-benzoyl groups: 1.82 ± 0.01 mol/mol.

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