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$ZnCl_2$-Catalyzed Acylation of Dextrose: Process Optimization, Kinetic Modelling and Pharmaceutical Prospects

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Acylation of dextrose (D-glucose) provides a reversible strategy for modulating sugar solubility by converting the highly hydrophilic polyhydroxyl molecule into a lipophilic, water-insoluble peracetate that can be readily regenerated to the parent sugar through deacylation. This reversible acylation-deacylation approach is attractive for carbohydrate processing and serves as a versatile synthetic platform for the preparation of glycoconjugate prodrugs with improved pharmaceutical properties. In the present study, the acylation of dextrose with acetic anhydride was investigated using zinc chloride as a Lewis acid catalyst. The effects of catalyst loading (0.05-1.0 g), reaction time (5-60 min) and temperature (30-90 ºC) were independently evaluated, while dextrose conversion and α/β-D-glucose 2,3,4,5,6-pentaacetate selectivity were quantified by GC-MS. A comparative screening of four Lewis acid catalysts ($AlCl_3$, $CuCl_2$, $FeCl_3$ and $ZnCl_2$) revealed that $ZnCl_2$ gave the best performance. Under optimized conditions it achieved 86.05% dextrose conversion with 95.57% selectivity towards the desired α-anomer. The kinetic analysis revealed that the reaction follows a second-order rate law (R^2 = 0.9544) with an apparent rate constant of $(3.0 \pm 0.2) \times 10^{-3}$ L mol^{-1} min^{-1}, which is consistent with a bimolecular Lewis acid-catalyzed acylation mechanism. The progressive conversion of the kinetically favoured β-anomer towards the thermodynamically more stable α-anomer supports the role of Lewis acid catalysis in promoting anomeric equilibration.

Keywords: Dextrose acylation, Zinc chloride, α-D-Glucose pentaacetate, Reaction kinetics, Acylation-deacylation.

INTRODUCTION

Carbohydrates are among the most abundant, structurally diverse and biologically important molecules in nature. Among them, dextrose (D-glucose, $C_6H_{12}O_6$) is the primary metabolic fuel, a key substrate for glycosylation in biosynthesis and an important industrial feedstock for the food, pharmaceutical and materials industries [1,2]. The high water solubility of dextrose (~900 g L^{-1} at 25 ºC) arises from its five free hydroxyl groups, which form extensive hydrogen-bonding interactions with water molecules. While this high hydrophilicity is crucial for biological transport and metabolism, it restricts the utility of dextrose in applications requiring enhanced lipophilicity, such as synthetic intermediates, pharmaceutical formulations and membrane-permeable prodrug scaffolds [3].

Acylation of carbohydrate is an established approach for modifying the physico-chemical properties of sugars through the esterification of their hydroxyl groups. The introduction of acetyl groups reduces molecular polarity and hydrogen-bonding capacity while increasing lipophilicity and organic-solvent compatibility. Dextrose is highly hydrophilic due to its multiple hydroxyl groups. Its conversion into glucose penta-acetate offers a means of modifying these properties through reversible ester formation. The acetyl groups can be cleaved by esterases or lipases and through acid- or base-catalysed hydrolysis to regenerate the parent sugar [3,4]. This masking and subsequent deprotection strategy has attracted considerable interest in pharmaceutical chemistry, particularly for improving membrane permeability and developing carbohydrate based prodrug systems. By temporarily modifying the hydroxyl

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groups, carbohydrate derivatives can achieve enhanced lipophilicity and cellular uptake, while subsequent deprotection restores the native hydroxyl functionalities required for their biological activity.

Carbohydrate modification has gained interest in cancer research due to altered glucose metabolism and increased GLUT1 and GLUT3 expression in several tumour types. These features have encouraged glucose-based drug delivery approaches, as illustrated by glycosylated derivatives of paclitaxel, doxorubicin, 5-fluorouracil and gemcitabine as well as the prodrug mipsagargin (G-202) [5-8]. Their development requires stereochemically defined glucose derivatives. Glucose acetylation dates back to the isolation of crystalline glucose pentaacetate by Erwig & Koenigs in 1889 [9]. Subsequent studies established the role of Lewis acids, particularly $ZnCl_2$, in controlling anomeric configuration [9-11]. Other methods have employed $SnCl_4$, sulphuric acid, alkali metal acetates, microwave irradiation and enzymatic transacylation [12-14]. Selective preparation of α-pyranose derivatives remains challenging due to competing anomeric and ring-form products [15].

Anomeric selectivity is governed by the balance between kinetic and thermodynamic product formation. Under rapid acetylation conditions the α-anomer may form preferentially, whereas prolonged reaction or Lewis acid catalysis favours the more stable α-anomer [9,12,13,16]. $ZnCl_2$ can facilitate this equilibration through coordination with the anomeric acetate group and subsequent oxocarbenium-ion formation.

The present study investigates the $ZnCl_2$-catalyzed acylation of dextrose using acetic anhydride for the selective synthesis of α-D-glucose pentaacetate. Four Lewis acid catalysts ($AlCl_3$, $CuCl_2$, $FeCl_3$ and $ZnCl_2$) were screened to identify the most effective catalyst. The effects of catalyst loading, reaction temperature and reaction time were examined under mild conditions (≤ 90 ºC) to optimize dextrose conversion and α-anomer selectivity. Kinetic modelling was performed to establish the reaction order and apparent rate constant. The pharmaceutical prospects of glucose acetylation are discussed in the context of reversible modification of sugar properties and the synthesis of carbohydrate-based drug conjugates.

EXPERIMENTAL

Dextrose (D-glucose, anhydrous, ≥ 99%), zinc chloride (anhydrous, ≥ 98%), acetic anhydride (reagent grade, ≥ 98%), aluminium chloride (anhydrous, ≥ 98%), copper(II) chloride (≥ 97%) and iron(III) chloride (≥ 97%) were obtained from commercial suppliers (Sigma-Aldrich/Merck) and used as received. Ethyl acetate (HPLC grade) was used for product extraction and double-distilled water was used for workup. An authentic standard of α-D-glucopyranosyl pentaacetate (Sigma-Aldrich, 99% purity) was procured and used to construct the calibration curve for GC-MS analysis.

Procedure: Acylation reactions were carried out in a programmable batch reactor (Redleys Technology) at 550 rpm. The temperature was controlled with precision up to ±1 ºC and it was equipped with a reflux condenser. In a typical run, 5 mL acetic anhydride was measured by Pasteur pipette with due caution and poured into the reaction station tube followed by the addition of the requisite catalyst mass. After brief mixing, 1.0 g of dextrose was added incrementally with caution. The initial dissolution was exothermic. The reactor was sealed and maintained at the target temperature and agitation speed for the specified time. At the end of the run, the reactor was cooled to room temperature and 5 mL double-distilled water was added followed by stirring for 15-30 min to hydrolyze any excess acetic anhydride. The product was extracted by addition of 5 mL ethyl acetate. The organic (upper) layer containing glucose pentaacetates was collected for analysis. The aqueous (lower) layer, retaining unreacted dextrose, was also retained for mass balance calculations. Adequate safety precautions were taken in this synthesis and preliminary safety and risk assessment was also carried out before conducting the runs as mentioned in the literature [17-19].

Characterization: FTIR spectra were recorded using a Shimadzu spectrometer over 4000-400 cm^{-1} range using Kbr method. Product composition was analysed using an Agilent GC-MS equipped with an HP-5MS column (30 m × 0.25 mm × 0.25 μm), helium carrier gas (1.0 mL min^{-1}) and an oven temperature programme of 50-280 ºC at 10 ºC min^{-1}. Mass spectra were acquired at 70 eV in EI mode. Dextrose conversion and acetate isomer selectivity were determined from normalized GC peak areas and validated through gravimetric yield and mass balance calculations.

Catalyst screening: Glucose acetylation was carried out using catalysts such as $ZnCl_2$, sodium acetate, sulfuric acid and pyridine [20]. In the present study, four Lewis acids ($AlCl_3$, $CuCl_2$, $FeCl_3$ and $ZnCl_2$) were selected to compare their catalytic effects on glucose acetylation. Each catalyst (0.2 g) was reacted with dextrose (1.0 g) and acetic anhydride (5 mL) at 90 ºC for 60 min under continuous stirring (550 rpm). The product composition and anomeric acetate selectivity were determined by GC-MS.

Optimization and kinetic modelling: Following the catalyst screening, the effects of catalyst loading, reaction time and temperature on dextrose acetylation were investigated in a batch reactor. Each parameter was varied independently while maintaining the remaining conditions constant to assess its influence on dextrose conversion and product distribution. Kinetic studies were performed using independent batch reactions at specified time intervals to avoid sampling disturbances and ensure effective quenching. The reactions were terminated with ice-cold water followed by ethyl acetate extraction and GC-MS analysis. Dextrose conversion was calculated from the normalized GC peak areas of the acetylated products and verified through gravimetric yield and mass balance calculations. The resulting concentration-time profiles were used to determine the reaction rate law and estimate kinetic parameters.

RESULTS AND DISCUSSION

The isolated reaction products obtained under various conditions were analyzed with FTIR and GC-MS techniques. Selected samples exhibiting higher selectivity based on GC-MS analysis were further characterised by ^1H and ^{13}C NMR spectroscopy to confirm complete peracetylation and establish the stereochemical (α/β) configuration.

Comprehensive structural and stereochemical characterization using FTIR, GC-MS and NMR spectroscopy confirms

the exhaustive peracetylation of dextrose and the formation of α-D-glucopyranose pentaacetate. FTIR analysis confirms complete hydroxyl conversion to ester groups *via* strong carbonyl (C=O, 1738 cm^{-1}) and C–O (1218.51 and 1033.37 cm^{-1}) stretching bands, the absence of broad –OH absorption (3300-3500 cm^{-1}) and an equatorial C1–H deformation band at 845.35 cm^{-1} indicative of the α-anomer. The GC-MS analysis against an standard resolved two diastereomeric pyranose pentaacetates with identical EI mass spectra, eluting at retention times of 18.53 min (α-anomer) and 19.02 min (β-anomer). The ^1H NMR indicates a characteristic downfield anomeric proton doublet at δ = 6.33 ppm (J = 3.6 Hz, equatorial-axial $J_{1,2}$ coupling confirm the α-anomer) and five acetate methyl singlets (15H, δ = 2.02-2.19 ppm) as well as ^{13}C NMR showing five ester carbonyls (δ = 168.73-170.59 ppm), five methyl carbons (δ = 20.41-20.84 ppm) and a single distinct anomeric C-1 signal at δ = 89.03 ppm.

Comparative catalyst evaluation: Four Lewis acid catalysts were evaluated under identical conditions, with dextrose conversion following the order: $ZnCl_2 > FeCl_3 > AlCl_3 > CuCl_2$. The α-anomer selectivity followed $ZnCl_2 \approx FeCl_3 >> AlCl_3 > CuCl_2$. Although $FeCl_3$ showed 90.2% selectivity (Table-1), but it failed to produce an unambiguous anomeric assignment in GC-MS analysis. The products are registered as non-anomeric D-glucose pentaacetate peaks, which suggest that either co-elution of anomers or formation of an acyclic acyl intermediate are taken place. Against this, $ZnCl_2$ uniquely delivered cleanly resolved, individually quantifiable α- and β-D-glucopyranose pentaacetate peaks at 71.16% conversion and 85.7% α-selectivity.

The superior catalytic performance of $ZnCl_2$ is attributed to its ability to provide effective activation of acetic anhydride while limiting competing reactions. Although $AlCl_3$ possesses stronger Lewis acidity, its excessive activation of the acylating agent may promote non-selective acetylation and side reactions, resulting in lower conversion and α-anomer selectivity. While $CuCl_2$, which is comparatively weaker catalytic activity under the investigated conditions, showed the lowest conversion and selectivity. $FeCl_3$ provided appreciable conversion and α-anomer selectivity but did not offer the same catalytic performance as $ZnCl_2$.

$ZnCl_2$ appears to provide a favourable balance between substrate activation and reaction selectivity, due to the coordination of Zn^{2+} with oxygen-containing groups of glucose and also its intermediates may facilitate acetylation and acid-catalysed anomerisation, which favour the formation of α-D-glucopyranose pentaacetate [21]. The proposed reaction pathway and comparative catalytic performance are shown in Fig. 1.

Effect of acetic anhydride proportion: The effect of the dextrose-to-acetic anhydride molar ratio on $ZnCl_2$-catalyzed glucose pentaacetate synthesis was investigated by varying the ratio from 1:5 to 1:12 while keeping catalyst loading, temperature and reaction time constant. Although a 1:5 ratio is theoretically sufficient for acetylation of all five hydroxyl groups, its practical effectiveness in achieving high conversion and α-anomer selectivity requires evaluation.

As shown in Table-2, reagent stoichiometry significantly affected dextrose conversion and product distribution. At 1:5, the conversion was lowest (60.28%), with β-anomer formation predominating (59.84%). Increasing the acetic anhydride concentration improved conversion and α-selectivity, reaching an optimum at 1:9, with 79.44% conversion and 86.38% α-selectivity. Further increases in acetic anhydride reduced α-selectivity, while 10.67% furanose reappeared at 1:12. These findings establish 1:9 as the optimum reagent ratio, providing the best balance between dextrose conversion, α-anomer selectivity and product distribution.

Effect of $ZnCl_2$ concentration: Table-3 shows the effect of $ZnCl_2$ loading on dextrose acetylation. At 0.05 g $ZnCl_2$, the reaction yielded all four isomeric products: α- and β-pyranose and α- and β-furanose pentaacetates. Their coexistence points to limited control over ring-form interconversion at low catalyst concentration. Increasing the $ZnCl_2$ loading from 0.05 to 0.5 g gradually altered the product distribution, with

TABLE-1
SCREENING OF LEWIS ACID CATALYST (0.2 g CATALYST, 90 ºC, 60 min, 1.0 g DEXTROSE, 5 mL Ac_2O)

Catalyst	Conversion (%)	α-Selectivity (%)	Major Products	Product (g)
$AlCl_3$	52.80	34.7	α/β-D-glc pentaacetate	1.13
$CuCl_2$	45.79	30.8	α/β-D-glc + furanose forms	0.98
$FeCl_3$	64.02	90.2	D-glc penta acetate (no anomeric ID)	1.37
$ZnCl_2$	71.16	85.7	α-D-glc 2,3,4,5,6-pentaacetate	1.52

TABLE-2
EFFECT OF ACETIC ANHYDRIDE RATIO ON CONVERSION AND ANOMERIC SELECTIVITY

(Dextrose: Ac_2O) ratio	Ac_2O volume (mL)	Molar excess over stoichiometry	Conversion (%)	α-Selectivity (%)	β-Selectivity (%)	Observational remark
1:5	2.62	0%	60.28	40.16	59.84	Stoichiometric; poorest performance; no furanose
1:6	3.14	20%	68.23	60.16	39.84	Improved conversion; no furanose
1:7	3.67	40%	69.81	60.89	39.11	Marginal improvement; no furanose
1:8	4.19	60%	75.37	71.62	28.38	Strong α increase; no furanose
1:9	4.71	80%	79.44	86.38	13.62	Optimal conversion, higher α-selectivity; no furanose
1:10	5.24	100%	80.26	82.16	17.84	Dilution begins; no furanose
1:11	5.76	120%	82.68	81.36	18.64	Higher conversion, lower α; no furanose
1:12	6.28	140%	85.18	80.74	8.59	Higher conversion, lower α, β; 10.67% furanose emerges

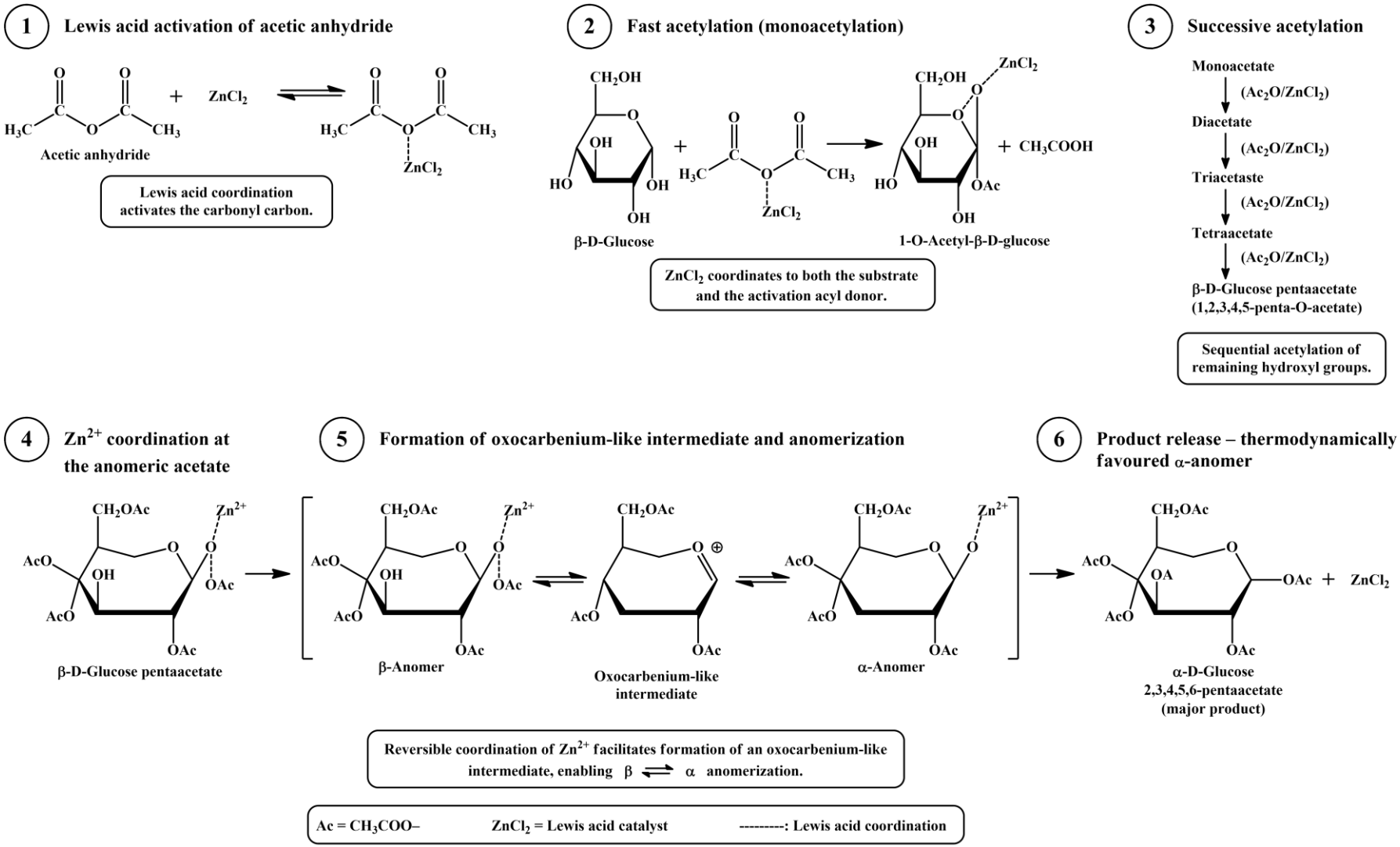


Fig. 1. Proposed mechanism for $ZnCl_2$-catalyzed acetylation of D-glucose with acetic anhydride

TABLE-3
EFFECT OF $ZnCl_2$ CONCENTRATION ON DEXTROSE CONVERSION AND ISOMER DISTRIBUTION (90 ºC, 60 min, 1.0 g DEXTROSE, 5 mL Ac_2O)

$ZnCl_2$ (g)	Conversion (%)	α-Selectivity (%)	Product distribution
0.05	66.51	60.0	α (30.0), β (40.0), α-furanose (8.6), β-furanose (11.4)
0.07	69.30	62.0	α (62.0), β (36.3), minor furanose forms
0.10	70.69	72.4	α (72.4), β (26.8), trace furanose
0.20	71.16	85.7	α (85.7), β (14.3)
0.30	81.86	86.0	α (86.0), β (11.5), trace furanose
0.50	86.05	95.6	α (95.6), β (4.4)
0.70	85.86	95.5	α (95.5), β (4.5)
1.00	86.01	84.9	α (84.9), β (15.1)

furanose derivatives disappearing and α-D-glucose penta-acetate becoming the major product. During this increase in catalyst loading, dextrose conversion rose from 66.5% to 86.05%, which may be attributed to more effective activation of acetic anhydride and acid-catalyzed anomerisation.

The catalyst loading beyond 0.5 g had little effect on conversion, which remained close to 86%, while α-selectivity decreases to 84.9% at 1.0 g. This decline points to an adverse effect of excess Lewis acid on product selectivity and possibly through changes in substrate coordination or increased competing reactions. The best result was obtained with 0.5 g $ZnCl_2$ per 1.0 g dextrose, corresponding to an ≈ 3.7:1 molar ratio, with 86.05% conversion and 95.57% α-selectivity.

Effect of reaction time: Table-4 presents the effect of reaction time on dextrose acetylation. At the initial stages (5-10 min), β-D-glucose pentaacetate was the major product, which account ~54-55% of the acetylated products. With increasing reaction time, the product distribution gradually shifted towards the α-anomer, while the β-anomer content decreases to 13-14% at 60-90 min. The α-selectivity reached 85.7-86.8% within this period. This change in product distribution points to the initial formation of the kinetically favoured β-anomer followed by $ZnCl_2$-catalyzed anomerization towards the thermodynamically favoured α-anomer. Dextrose conversion increased from 26.3% at 5 min to 76.5% at 90 min, consistent with the simultaneous progression of acetylation and anomeric equilibration. Extending the reaction to 120 min gave only a marginal increase in conversion (77.1%), while α-selectivity decreased to 79.1%. Prolonged exposure to the acidic reaction medium may promote secondary reactions, such as partial deacetylation and acetyl migration.

TABLE-4
EFFECT OF REACTION TIME ON CONVERSION AND ANOMERIC SELECTIVITY (0.2 g $ZnCl_2$, 90 ºC, 1.0 g DEXTROSE, 5 mL Ac_2O)

Time (min)	Conversion (%)	α-Selectivity (%)	Product distribution
5	26.26	45.0	α (45.0), β (55.0), kinetic β product dominates
10	28.41	46.0	α (46.0), β (54.0)
15	37.28	74.7	α (74.7), β (25.3)
30	53.36	78.1	α (78.1), β (21.9)
45	67.83	80.6	α (80.6), β (19.4)
60	75.70	85.7	α (85.7), β (14.3)
90	76.50	86.8	α (86.8), β (13.2)
120	77.10	79.1	α (79.1), β (20.9)

A reaction duration of 60-90 min was suitable for achieving high conversion and α-anomer selectivity. Beyond this point, the marginal increase in conversion did not justify the reduction in selectivity. Across the optimization experiments, the baseline reaction (1.0 g dextrose, 0.20 g $ZnCl_2$, 5.0 mL acetic anhydride, 90 ºC and 60 min) gave an average conversion of 75.4 ± 4.1% across three independent experimental batches. The control values ranged from 71.2 to 79.9% also reflect the batch-to-batch variations, which may arise from differences in dextrose dissolution and trace moisture uptake by $ZnCl_2$ during handling.

Effect of temperature: The effect of reaction temperature on dextrose acetylation is shown in Table-5. As the temperature increased from 30 to 90 ºC, dextrose conversion decreased slightly from 79.1% to 71.2%, while α-anomer selectivity increased significantly from 27.0% to 85.7%. This trend may be related to the changes in reaction kinetics and thermodynamic stability. At lower temperatures, the faster kinetic pathway favours β-anomer formation, result in higher conversion but lower α-selectivity. At higher temperatures, $ZnCl_2$-catalyzed anomerization promotes the conversion of the initially formed β-anomer into the more thermodynamically stable α-anomer. A reaction temperature of 90 ºC provides the best balance between conversion and α-selectivity. Although conversion decreases slightly, the substantial improvement in α-selectivity makes this temperature more suitable for the process. It is also lower than the 100-110 ºC commonly used in conventional methods, which may help reduce energy consumption and the risk of glucose decomposition under acidic conditions.

TABLE-5
EFFECT OF TEMPERATURE ON CONVERSION AND ANOMERIC SELECTIVITY (0.2 g $ZnCl_2$, 60 min, 1.0 g DEXTROSE, 5 mL Ac_2O)

Temp. (ºC)	Conversion (%)	α-Selectivity (%)	Product distribution
30	79.07	27.0	D-glc pyranose penta acetate dominant
45	78.54	38.9	α (38.9), β (61.1)
60	75.81	66.8	α (66.8), β (33.2)
75	73.49	70.8	α (70.8), β (29.2)
90	71.16	85.7	α (85.7), β (14.3)

α-*versus* β-Anomer: The β-D-glucose pentaacetate (β-anomer) is less stable than the α-form under the Lewis acid conditions studied. In the absence of a catalyst, the β-anomer

remains kinetically stable. It is a crystalline solid with a melting point of 134 ºC and has lower ring strain than its corresponding furanose form [22,23]. In the presence of Lewis acids or acidic aqueous conditions, it undergoes anomerization to the α-form. The α-anomer is thermodynamically more stable, with an estimated stability advantage of approximately 1.0 kcal mol^{-1} due to the anomeric effect [24]. Its axial C-1 acetate group also makes it more reactive in glycosylation reactions by facilitating the formation of glycosidic bonds.

From a pharmaceutical perspective, α-D-glucose pentaacetate is a useful intermediate for preparing glycoconjugate prodrugs. Its axial C-1 acetate can be replaced by drug nucleophiles under Lewis acid catalysis through a Koenigs-Knorr type reaction [25]. This reaction can produce β-glycosidic drug conjugates, which are common in naturally occurring biologically active glycoconjugates [26]. The higher solid-state stability of the α-anomer makes it more suitable for pharmaceutical processing, storage and formulation. The conversion of the less stable β-anomer into the more stable α-anomer is beneficial under the reaction conditions. The presence of sufficient catalyst promotes this conversion as the reaction proceeds. The trends observed in the reaction time and catalyst concentration studies (Tables 3 and 4) support this behaviour.

Kinetic analysis

Reaction stoichiometry: The acylation of dextrose (A) with acetic anhydride (B) in the presence of $ZnCl_2$ to yield glucose pentaacetate (C) and acetic acid (D) is represented by the stoichiometric equation (eqn. 1) as follows:

$$C_6H_{12}O_6 + 5(CH_3CO)_2O \xrightarrow{ZnCl_2} 5CH_3COOH \quad (1)$$

For kinetic modelling, the system is treated as a constant-volume batch liquid-phase reaction (A + 5B → C + 5D). The instantaneous concentrations of the limiting reactant dextrose (C_A) and acetic anhydride (C_B) at time t are expressed in terms of the fractional conversion of dextrose (X_A):

$$C_A = C_{A0}(1 - X_A) \quad (1a)$$

$$C_B = C_{B0} - 5C_{A0}X_A = C_{A0}(M - 5X_A) \quad (1b)$$

where C_{A0} and C_{B0} represent the initial molar concentrations of dextrose and acetic anhydride, respectively and $M = C_{B0}/C_{A0}$ = 9.6 denotes the initial reactant molar ratio.

Accounting explicitly for the consumption of 5 mol of acetic anhydride per mole of dextrose, the rate expression for a bimolecular second-order mechanism is represented as follows:

$$-r_A = -\frac{dC_A}{dt} = k \cdot C_A \cdot C_B = k \cdot C_{A0}^2 (1 - X_A)(M - 5X_A) \quad (2)$$

where k is the apparent second-order rate constant. Separation of variables followed by integration between t = 0 (X_A = 0) and t = t ($X_A = X_A$) yields the corrected integrated rate law (eqn. 3) as follows:

$$P(X_A) = \ln\left(\frac{M - 5X_A}{M(1 - X_A)}\right) = k \cdot C_{A0}(M - 5) \cdot t \quad (3)$$

Eqns. 1-3 define the mathematical model used to evaluate the acylation kinetics under $ZnCl_2$ catalysis. A linear plot of the transformed kinetic function $P(X_A)$ *versus* reaction time t yields a straight line with a slope equal to $k \cdot C_{A0}(M-5)$, from which the apparent rate constant k is directly evaluated. This formulation rigorously incorporates the stoichiometric requirements of the reaction while maintaining applicability for systems operating with excess acetic anhydride (M = 9.6)

Model fitting and rate constant: The experimental conversion data were analyzed using the integrated second-order rate equation (eqn. 3). The kinetic analysis was limited to the 0-60 min data (Table-6), as this range showed the best linear fit to the proposed second-order model. The 90 and 120 min data were excluded, as secondary reactions such as acetyl group migration and partial deacetylation may occur due to the accumulation of acetic acid during the reaction. Each time point was obtained from an independent batch reaction, which may account for minor variations between measurements.

TABLE-6
KINETIC DATA FOR $ZnCl_2$-CATALYZED ACYLATION OF DEXTROSE (90 ºC, 0.2 g $ZnCl_2$, M = 9.6)

Time (min)	Conversion (%)	X_A	$P(X_A) = \ln\left(\frac{M-5X_A}{M(1-X_A)}\right)$
0.33	9.35	0.0935	0.0482
0.50	12.89	0.1289	0.0685
0.66	13.37	0.1337	0.0713
1.00	15.04	0.1504	0.0814
2.00	19.25	0.1925	0.1082
3.00	21.58	0.2158	0.1239
4.00	23.92	0.2392	0.1403
5.00	26.26	0.2626	0.1575
10.00	28.41	0.2841	0.1741
15.00	37.28	0.3728	0.2506
20.00	42.42	0.4242	0.3023
30.00	53.36	0.5336	0.4371
45.00	67.83	0.6783	0.6983
60.00	75.70	0.7570	0.9134

The plot of the transformed kinetic variable P(XA) against reaction time showed good linearity over 0-60 min. The regression was fitted through the origin to satisfy the initial condition P(XA) = 0 at t = 0 min. The resulting R^2 value was 0.9544, which support the suitability of the second-order kinetic model for $ZnCl_2$-catalysed acetylation under the studied conditions. Using an initial dextrose concentration (CA_0) of 1.11 mol L^{-1} (1.0 g dextrose in 5.0 mL reaction mixture) and M = 9.6, the stoichiometric factor (M–5) was calculated as 4.6. The slope of the regression line was 0.0155 min^{-1}, giving an apparent second-order rate constant of k = (3.0 ± 0.2) × 10^{-3} L mol^{-1} min^{-1}.

The first-order kinetic model, based on ln(1–XA) *versus* time, showed considerable deviation from linearity and a lower R^2 value of 0.85. This confirms that the first-order model does not adequately describe the reaction. However, the second-order kinetic behaviour is consistent with the proposed mechanism. $ZnCl_2$ coordinates with acetic anhydride to form an activated acyl species, which is attacked by the hydroxyl groups of dextrose. The reaction rate decreases with time as the available dextrose is consumed, eventually approaching a conversion plateau. The kinetic data indicate that catalyst deactivation is not significant during the initial 60 min of reaction.

Sugar acylation as a platform for anticancer glycoconjugate prodrugs

Acylation-deacylation toggle: In biological systems carboxylesterases (EC 3.1.1.1) and other hydrolazes are widely distributed in the blood as well as in the liver and intestinal epithelium. These enzymes are also found in tumour tissues where they can hydrolyze O-acetyl and other acyl groups from sugar esters to release the corresponding hydroxyl compounds. This enzymatic activity provides a basis for developing prodrugs that undergo ester bond cleavage within the tumour microenvironment. Such method may improve drug delivery and therapeutic efficacy while reducing undesirable effects on healthy tissues [4,27-29].

The conversion of dextrose into glucose pentaacetate offers three potential pharmaceutical advantages. Acetylation reduces the polarity of the sugar and may improve its membrane permeability while facilitating its conjugation with hydrophobic drugs. It also activates the anomeric C-1 position for glycosylation with drug molecules containing hydroxyl or amino groups. In addition, glucose pentaacetate forms a crystalline solid with good chemical stability and low moisture absorption, which makes it suitable for conventional pharmaceutical processing. The acetyl groups can be removed through enzymatic hydrolysis *in vivo* and may release free glucose or the attached drug without the need for external chemical reagents.

Anticancer drugs in glycoconjugate development: Table-7 summarizes six clinically important anticancer drugs for which the development of glycoconjugate prodrugs requires suitable reactive sugar ester intermediates. In these cases, α-D-glucose-2,3,4,5,6-pentaacetate can serve as a direct C-1 donor for nucleophilic glycosylation or as a starting material for selective functionalisation at the C-1 position.

The six examples illustrate the potential of carbohydrate conjugation to improve the therapeutic properties of anticancer drugs through enhanced aqueous solubility and oral bioavailability along with improved tumour targeting and enzyme mediated drug release. These modifications may also help reduce systemic toxicity. The synthesis of highly pure α-D-glucose 2,3,4,5,6-pentaacetate developed in this work provides a useful precursor for preparing different glycoconjugate prodrugs. The optimized process offers a practical route for producing this intermediate and supports further research in medicinal chemistry and pharmaceutical development of targeted anticancer agents.

Conclusions

The present study originated from a process engineering challenge of converting highly water-soluble glucose into a temporary water-insoluble form to facilitate its separation from complex aqueous mixtures such as molasses. This led to the selective acylation of glucose to produce α-D-glucose 2,3,4,5,6-pentaacetate, which can be readily converted back to glucose through deacylation. This reversible modification also offers potential applications in sugar purification and pharmaceutical drug delivery. Reaction optimization identified $ZnCl_2$ as the most effective catalyst, achieving 86.05% dextrose conversion and 95.57% α-anomer selectivity under solvent-free conditions at 90 ºC for 60 min. The study established the influence of reaction conditions on anomer selectivity and confirmed second-order reaction kinetics. The optimized process provides an efficient route for α-D-glucose pentaacetate synthesis and a basis for further scale-up studies. The product also offers potential as a precursor for glycoconjugate synthesis and carbohydrate-based anticancer prodrugs.

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CONFLICT OF INTEREST

The authors declare that there is no conflicts of interest regarding the publication of this article.

DECLARATION OF AI-ASSISTED TECHNOLOGIES

During the preparation of this manuscript, the authors used an AI-assisted tool(s) to improve the language and no data, results or scientific conclusions were generated by AI. All analyses, interpretations and conclusions are the authors' own. The authors reviewed and edited the content and take full responsibility for the published work.

TABLE-7
ANTICANCER DRUGS DEVELOPED AS GLYCOCONJUGATE PRODRUGS

Drug class	Representative drug	Role of glycosylation	Benefit	Ref.
Antimetabolite	5-Fluorouracil (5-FU)	Sugar-phosphate conjugation activates 5-FU in cells; ester prodrugs improve oral bioavailability and half-life	Selectivity; reduced GI toxicity; extended t½	[30]
Taxane	Paclitaxel (Taxol)	Glucose-conjugated prodrug (SG-PTX) *via* succinate linker; enzymatic release by β-glucuronidase	52-fold solubility increase; reduced cremophor toxicity	[31]
Anthracycline	Doxorubicin	Glucuronide prodrug of DOX; tumor-selective activation by β-glucuronidase	Tumor-targeted release; lower cardiotoxicity	[32]
Nucleoside analogue	Gemcitabine	Amino acid ester prodrugs of gemcitabine; improved stroma penetration and deaminase resistance	Enhanced uptake in pancreatic cancer stroma	[33,34]
Antimitotic	Docetaxel	Chemo-enzymatic glucose ester conjugate; water-soluble prodrug	52-fold solubility gain; cancer cell selective	[35,36]
PSMA-activated	G-202 (Mipsagargin)	Glucuronide prodrug of thapsigargin; activated by PSMA in prostate cancer vasculature	Solid tumour-specific vascular targeting	[8,37]

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