O-Regioselective Synthesis with the Silver Salt Method

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ABSTRACT: The excellent O-regioselectivity of the glycosidation of the ambident 2-O-substituted 5-fluorouracil (5-FU) via the silver salt method is computationally investigated at the MP2/6-311++G(2d,p):DZP//B3LYP/6-31+G(d):DZP level of theory. The reactions studied are those between 1-bromo-1-deoxy-2,3,4,6-tetra-O-acyl-α-D-glucopyranose and the silver salts of 5-FU, 2-O-butyl-5-FU, and 2-O-benzyl-5-FU. Two pathways are considered as follows: (A) one where the silver and bromide ion do not interact, and (B) another where the silver and bromide ion interact in the transition states. Because the O-reaction barriers are much lower (by 13.3–22.2 kcal/mol) than N-reaction barriers in both pathways, the O-regioselectivity of the silver salt method can be satisfactorily explained by either path A or path B. Furthermore, path B, where Ag and Br interact consistently, has lower activation barriers than the corresponding path A (by 6.8–17.4 kcal/mol) in both N- and O-reactions. This computational result can be attributed to the following reasons: (1) the speeding-up effect in Koenigs−Knorr reactions due to the addition of silver carbonate into the reaction mixture; (2) the halogens being pulled away by silver ions from halides, as proposed by Kornblum and co-workers; and (3) the oxocarbenium ion involvement in the glycosidation reactions. The large energy difference between N- and O-transition states originates from the association between Ag and N−(O−) of the ambident unit (−N3=C4=O4) that shows significant covalent character so that the O-reaction transition states of the silver salt method benefit from favorable ionic interaction (C−···O−) and favorable covalent interaction (Ag−···N). These two favorable interactions are in agreement with the hard and soft acids and bases principle; the former is a hard−hard interaction and the latter is a soft−soft interaction.

INTRODUCTION

Uracil is one of the four bases found in RNA, and it metabolizes into thymine (5-methyl-uracil) in DNA. The replacement of S-H in uracil by fluorine introduced the novel property of 5-fluorouracil (5-FU) as an anticancer drug through irreversible inhibition of thymidylate synthase.1–3 Although 5-FU has high antitumor activity, its therapeutic index is low due to its side effects. Many new 5-FU derivatives, e.g., the glycosides of 5-FU, were synthesized to develop more effective and more selective drugs.4–6 These glycosides are deemed promising as both sugar and 5-FU units are well-known biologically important compounds.

The silver salt method is used to synthesize O-glycosides of 5-FU or 2-O-substituted 5-FU (Scheme 1), in which the protected (by acetyl groups) and activated (by Br) reacting glucose 1 are α-anomers and the products 3 are β-anomers. This method has also been successfully applied to synthesize glycosides of other sugars, e.g., xylose, methyl glucuronate, and galactose.5–7,8

The silver salt method is based upon the well-known Koenigs−Knorr reaction (Scheme 2), wherein silver carbonate is added to the substitution reaction of a glycosyl halide with an alcohol to synthesize a glycoside. It is observed that the silver carbonate accelerates the rate of the reaction. However, because an equivalent amount of silver salt is typically needed, the silver (or other heavy metal) salts are more appropriately referred to as “promoter” or “coactivator” rather than catalyst. In the silver salt method, the 2-O-alkyl 5-FU is directly converted into the corresponding silver salt. The silver salt of the 2-O-substituted 5-FU acts as a glycosyl acceptor that reacts in nonpolar solvents (usually xylene mixture) with a glycosyl donor, a protected sugar with a leaving group (usually Br) at its anomeric center, to form a glycoside. The reactions are heterogeneous and yield the O-glycoside products (33.2−54.3% yield).5,8

The more-than-a-century old Koenigs−Knorr reaction is still widely used and continuously modified in pursuit of more effective syntheses of glycosides.9–10 The silver salt method also plays an important role in the reactivity of ambient nucleophiles, as the silver salt method provides the opposite regioselectivity to methods involving the alkali salts or anions of ambient nucleophiles.11–14 In late 1960s and early 1970s, Tieckelmann and co-workers investigated alkylations of heterocyclic ambident anions.11 For the alkylation of 2-pyridone salts, the control of the alkylation site was achieved by manipulation of a few simple variables. Alkylation was 95−97% on a nitrogen atom in the reaction of the sodium salt of 2-
The mechanistic studies on the reactivity of ambident nucleophiles have been very active in the past 60 years. In 1955, Kornblum and co-workers studied the reaction of silver nitrite with alkyl halides and suggested that the silver salt method gave products with the O4/N3 alklylation ratio of approximately 5:1, although the overall yield was only 20–30%. Significantly, steric influence was observed to increase alkylation at the O4 position at the expense of alkylation at N3. In another study on the alkylation of 5-carboxethoxy- and 5-nitro-2-pyridone salts, Tieckelmann et al. found that the substitution of silver salts in DMF was a homogeneous reaction that yielded both the N- and O-alkylated products, whereas the corresponding reaction in hexane and benzene was heterogeneous and resulted in O-alkylation exclusively. In agreement with the work of Brower et al., Tieckelmann concluded that the silver salt method consistently obtained the O product (with reaction at the hard site on N/O-ambident nucleophiles). Mayr et al. also used alkali salts and the silver salt of these anions to study the product ratios. In most cases, the reactions happened at the soft site of the ambident nucleophiles, even in cases where one of the reactants was a hard carbocation. After reviewing experimental results on ambident reactivity, Mayr and co-workers found that the HSAB principle was wrong in about 50% of the cases and subsequently suggested that the HSA principle be totally discarded for the study of reactivity of ambident nucleophiles. However, the silver salt method consistently obtained the O product (with reaction at the hard site on N/O-ambident nucleophiles). Over the years, Mayr and co-workers explained that the O-regioselectivity was due to the blockage of N-attack through Ag coordination with N-site, but Ayers and co-workers showed that the HSAB theory could still be used to rationalize ambident reactivity, as proven by simple chemical potential derivations.

The oxocarbenium ions from sugars were also found to be biologically important. Amyes and Jencks experimentally determined the lifetime of the oxocarbenium ion of glucose in aqueous solution to be approximately $10^{-12}$ s.$^{19}$ Over the years, Woerpel and co-workers studied and proposed the involvement of oxocarbenium ions in the syntheses of glycosides.$^{20}$

The N-regioselectivity of the phase-transfer-catalysis method was investigated extensively in a previous publication.$^{21}$ In this article, we computationally investigated the reactivity of N- and O-ambident nucleophiles to account for the observed O-regioselectivity of the reactions between 1-bromo-1-deoxy-2,3,4,6-tetra-O-acetyl-glucopyranose (1) and 5-FU, 2-O-butyl-5-FU and 2-O-benzyl-5-FU (2a–c in Scheme 1). The 2-O-butyl-5-FU itself is an antitumor drug,$^{22}$ and the benzyl group of 2-O-benzyl-5-FU serves as a protecting group in the glycosidation reactions for it can be removed under H2/Pt-C at room temperature after the glycosides are synthesized.$^{23}$ The substituents are chosen according to their biological and chemical properties, and there are no detailed experimental results on their effect on the N/O product ratio. A second objective is to collaborate relevant aspects of silver salt methods, such as (1) the speeding-up effect of the Koenigs–Knorr reaction, (2) the involvement of oxocarbenium ions in the reactions, and (3) the HSAB principle. Two pathways were...
considered in the computational studies: (A) one without any interaction between Ag and Br and (B) the other wherein Ag and Br interacted in the transition states.

## RESULTS

The results are presented in the following order for reactions between 1 and all three silver salts of 5-FU (2a−c). First, the structures and energies of silver salts are shown. Second, two reaction pathways are considered: (A) one wherein the Ag and Br ions do not interact in the transition states and (B) another wherein the Ag and Br ions interact in the transition states. The structures and energies of all initial complexes, transition states, and products for the two pathways are presented. Without a substituent at O2, 2a is likely to use the ambident unit of −N1−C2=O2. Only path A is considered for reactions of 1 + 2a using the ambident unit N3−C4=O4 to make a comparison with reactions of 2-O-substituted 5-FU (2b and 2c). The density analysis results for 2a and 2b, as well as the atomic coordinates for all species, are provided as the Supporting Information.

### Reaction between 1 and the Silver Salt of 2a.

The negative charge of 5-FU anion 2a delocalizes among three atoms (O2, N3, and C4), and the three structures optimized at the B3LYP/6-31+G*−DZP level associate the Ag+ separately with O2, N3, and O4 (Figure 1). The expected interactions are shown by bond critical points (BCPs) between atomic pairs. Both 2a-Ag1 and 2a-Ag3 possess a second BCP separately between O4 and Ag and between F and Ag, indicating that Ag acts as a bridge in these two minima, but only the Ag−N and Ag−O have sizeable electron densities (0.09−0.10e) at the BCPs. In addition, the geometrical parameters of 2a-Ag1 are very close to those of the 5-FU anion, whereas 2a-Ag3 shows significant changes from 5-FU anion in geometry: the N3−C4 bond length decreases from 1.37 to 1.32 Å, whereas the C4−O4 bond length increases from 1.25 to 1.30 Å (Figure 1).

The 2a-Ag1 is the most stable structure, whereas 2a-Ag2 and 2a-Ag3 are significantly higher in Gibbs energy (by 39.1 and 26.0 kcal/mol, respectively, Table 1). Therefore, the structure with Ag−N3 association enhances the amide structure and provides the thermodynamic stability of the salt of 5-FU anion. Perron et al.24 and Tao et al.25 obtained crystal structures of the silver salt of succinimide to model the interaction between silver(I) and the uracil residue, wherein silver was attached to nitrogen. Only 2a-Ag1 is considered in following calculations.

The silver salt of 5-FU forms complexes with 1 primarily through the interaction between the silver ion and the acetyl oxygen on C3′ (Figure 2). The two optimized reactant complexes are overall similar, except for the conformation of the acetoxy group on C4′ and the orientation of fluorine on 5-FU: the N3 complex has a downward C4′ acetoxy group and an upward fluorine atom, whereas the O4 complex has an upward C4′ acetoxy group and a downward fluorine atom. The relative Gibbs energy of the N3 complex with respect to that of the O4 complex is about 5.0 kcal/mol at the MP2/6-311++G(2d,p):DZP/B3LYP/6-31+G*−DZP level of theory (Table 2). In two complexes, the distances for Ag···N3 and Ag···O (the carbonyl O of acetoxy group on C3′) are ∼2.02 and ∼2.06 Å, respectively, and BCPs are located between the associated atoms.

In the N3 transition state (TS), Ag+ moves away from N3 and comes closer to O4, enabling N3 to react with C1′ (Figure 2). In addition, Ag maintains the short distance with the acetoxy group on C3′ (2.06 Å), as it does in the initial complex (2.06 Å). In principle, the O4 transition state (TS) could be formed without losing Ag···N3 interactions in the O4 complex (Figure 2). However, the optimized O4 TS shows that the silver ion also moves away from N3 and locates between O2 (rAg−O2 = 2.07 Å) and the carbonyl oxygen of the acetoxy group on C4′ (rAg−O(=C) = 2.11 Å). In the meantime, O4 moves closer to and stays above the reaction center C1′ (Figure 2). The parameters around the C1′ reaction center are similar for the two transition states: (i) the sum of three angles around C1′ (ζH1C1′C2′ + ζH1C1′O′ + ζC2′C1′O′; note that the H on C1′ is not shown in Figure 2) were both 356°, indicating the near-planarity, (ii) the C1′−O5′ bond distances in N3 and O4 TS were relatively short (1.34 and 1.32 Å, respectively), (iii) both transition states are “loose,” that is, the C1′−N3 (C1′−O4) distance is 1.99 Å (1.91 Å), whereas the C2′−Br distances are 2.96 and 3.04 Å, respectively, and (iv) the ambient N3−C4=O4 group is also very similar in structure for both transition states: rC4−O4 = 1.36 Å for N3 TS and 1.35 Å for O4 TS, whereas rC4−O4 = 1.27 Å for both TS structures. Thus, it is

![Figure 1](image1.png)

**Figure 1.** Structures of the 5-FU anion (2a) and its three corresponding silver salts (2a-Ag1−3) optimized at the B3LYP/6-31+G*−DZP level. Bond distances (green) were in units of angstrom.

| species compared                  | B3LYP/6-31+G*:DZP | MP06-2a/6-311+G(3d2p):DZP | MP2/6-311+G(2d,p):DZP |
|----------------------------------|--------------------|-----------------------------|------------------------|
|                                  | E_btot             | G_btot                     | G_btot                 |
| 2a-Ag2−2a-Ag1                   | 36.1               | −0.8                        | −1.5                   |
| 2a-Ag3−2a-Ag1                   | 22.3               | −0.5                        | −0.7                   |

\*Single-point energies were calculated at the B3LYP/6-31+G* optimized geometry. \*Thermal and solvation corrections were obtained from the B3LYP/6-31+G* frequency calculation and then added onto the MP2/6-311+G(2d,p):B3LYP/6-31+G* single-point electronic energy to obtain G_btot values, respectively. The G_btot values in bold were used in the discussion.
not surprising that the energies also turned out to be similar for N3 TS and O4 TS (the N3 TS is only 1.4 kcal/mol higher in Gibbs energy when compared with O4 TS) (Table 2).

In the N3 product and O4 product, the C1′−N3 bond and C1′−O4 bond are separately formed between the sugar ring and the ambident N3−C4==O4 group. The N3−C4==O4 geometrical parameters are markedly different between the two products: \( r_{C4-N3} = 1.41 \text{ Å} \) and \( r_{C4-O4} = 1.23 \text{ Å} \) in the N product, as opposed to \( r_{C4-N3} = 1.31 \text{ Å} \) and \( r_{C4-O4} = 1.32 \text{ Å} \) in the O product. The relative G (N3− minus O4−) value was \(-22.9 \text{ kcal/mol}\) (Table 2 and Figure 2).

It turned out that the significant energy and parameter changes occur only when Ag′ associated with different centers of the ambident N3−C4==O4 group. In the case of the silver salt of 2a, the structure 2a-Ag1 (with Ag···N3 bond) was 26 kcal/mol lower in energy than the structure 2a-Ag3 (with Ag···O4 bond). For the reaction transition states, both N- and O-transition states lost Ag···N3 association. Coincidently, two transition states are close in energy (N TS is 1.4 kcal/mol higher than O TS). In the products, the C1′−N3 bond and C1′−O4 bond are formal covalent bonds between C1′ and the ambident centers of the N3−C4==O4 unit so that the association with Ag′ was only a secondary interaction. Overall, the Gibbs activation energies for N- and O-reactions are similar: \( \Delta G^\ddagger_{N} = 43.4 \text{ kcal/mol} \) and \( \Delta G^\ddagger_{O} = 47.0 \text{ kcal/mol} \) (Table 3).

**Reaction between 1 and the Silver Salt of 2b.** The negative charges in 2-O-butyl-5-FU anion 2b delocalize between N3 and O4, and two structures 2b-Ag1 and 2b-Ag2 attach their Ag′ separately to N3 and O4 (Figure 3). The BCPs are also located between Ag···O3 in 2b-Ag1 and between Ag···F in 2b-Ag2, resulting in bridged structures in both cases. However, these secondary Ag···O3 and Ag···F associations are much weaker than the primary ones, as verified by the electron densities at the BCPs that are only one-third to one-half of those primary associations (Table S3c). The association of Ag strongly affects geometrical parameters of the N3−C4==O4 ambident unit (\( r_{CN} = 1.39 \text{ Å} \) and \( r_{CO} = 1.25 \text{ Å} \) in 2b anion; \( r_{CN} = 1.38 \text{ Å} \) and \( r_{CO} = 1.26 \text{ Å} \) in 2b-Ag1; and \( r_{CN} = 1.34 \text{ Å} \) and \( r_{CO} = 1.30 \text{ Å} \) in 2b-Ag2; Figure 3). The 2b-Ag1 (with the Ag···N3 bond) was 20.4 kcal/mol lower in Gibbs energy than 2b-Ag2 (with the Ag···O3 bond) (Table 4). Again, only 2b-Ag1 is considered as a reactant in the subsequent calculations.

The silver and bromine ions will not interact when they are on the opposite sides of the sugar ring (path A, Figure 4). The silver salt of 2b retains its basic structure of 2b-Ag1 after it forms the reactant complex with 1. The silver ion attaches to the nitrogen in the 2b anion and also interacts with an oxygen atom in the acetoxyl group at C3′. The structural parameters for the two complexes are similar; however, there is a 6.9 kcal/mol difference in Gibbs energy between the two reactant complexes (Table 2). This difference can be attributed to the different conformations associated with the orientation of the acetoxyl group on C4′ and the n-butyl group in 2b (Figure 4).

Two transition states are located in pathway A, both of which have an imaginary frequency of i327 cm\(^{-1}\), but independently...
lead to the N-glycoside and the O-glycoside. In the transition states, the N- (or O-) center attacks the anomeric carbon C1’ and expels Br from the opposite side of C1’. The two transition states have very similar structural parameters for the sugar unit and show Sn2 characteristics: (1) C1’–Br is approximately 3.0 Å and C1’–N3 (or C1’–O4) is 1.95 Å (or 1.85 Å); (2) the anomeric C1’ has a near-planar structure (the sums of the three angles around C1’ = HCl’ C2’ + HCl’ O + ∠C2’C1’O are 354°–355°); (3) the Hirshfeld charges also show that the ring oxygen has a relatively small negative charge (−0.12e), whereas C1’ has a relatively small positive charge (0.19–0.20e). As expected, most of the negative charge is found on the Br ion (≈−0.70e). The main difference between the two TS structures lies in the long-distance interactions between Ag+ and the ambient −N3–C4=O4 unit: (1) in the N3-reaction transition state, the C1’−N3 interaction is coupled with a Ag+–O4 bond; (2) in the O4-reaction transition state, the C1’−O4 interaction is coupled with a Ag–N3 bond. Although the atomic distances for the coupled interactions are similar (1.85–2.09 Å), the Ag–N3 and Ag–O4 interactions share more

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more “exploded” (looser) than transition states in pathway A wherein Ag and Br did not interact: The C1′···O and C1′···N distances are in the range 2.57–2.70 Å, and the C1′···Br distances are in the range 3.33–3.63 Å, but the Ag···Br distances are relatively short (2.397–2.431 Å). Thus, both oxocarbenium ion 4 and AgBr molecule are developed to give a character of 4 + 2b + AgBr with two unique features in these transition states: (1) the oxocarbenium ion 4 does not have the neighboring-participation group from acetoxoy group on C2’; (2) the Ag end of AgBr still attaches to one of the ambient centers. Although Ag···Br distances are short in the transition states, the Ag···N and Ag···O distances are even shorter (2.016–2.055 Å). At the MP2/6-311++G(2d,p):DZP//B3LYP/6-31+G*:DZP level of theory, the Ag···N3 or Ag···O4 interactions share more electrons at the BCPs (0.11e) compared with the Ag···Br bond (~0.08e). The O TS with Ag···N3 association is 15.4 kcal/mol lower than the N TS with Ag···O4 association.

The C–N3 or C–O4 bonds are fully formed covalent bonds in the products (Figure 5), which are much stronger than the Ag···N3 or Ag···O4 interactions. The N3 product is an amide, and the O4 product is an imidate. The free energy of the N-glycoside is 6.3 kcal/mol higher than that of the O4-glycoside at the MP2/6-311++G(2d,p):DZP//B3LYP/6-31+G*:DZP level of theory.

For the reaction kinetics, the activation barriers in pathway B for the N-reaction and O-reaction are 29.8 and 10.7 kcal/mol, respectively, and the corresponding activation barriers in pathway A are 47.2 and 27.6 kcal/mol, respectively (Table 3). One could describe such a reaction in pathway B as being “prompted” by Ag···Br interactions as opposed to pathway A.

**Reaction between 1 and the Silver Salt of 2c.** Again, the negative charges in 2-0-benzy1-S-FU anion 2c delocalize onto N3 and O4, and the geometry optimization of the silver salt of 2c yields two stable structures (Figure 6). In 2c-Ag1, the silver ion attaches to N3 and bends slightly toward O2 but the BCP is not located between Ag and N3. In 2c-Ag2, the silver ion attaches to O4 and bends toward fluorine. A BCP is found between Ag and F, giving this second minimum a ringlike feature (Figure 6 and Table 5). The association of Ag with either N3 or O4 center of the N3–C4=O=O4 ambident unit influences the stability of silver salts. The 2c-Ag1 with the Ag···N3 bond, in particular, was ~20.6 kcal/mol lower in Gibb’s free energy than that of 2c-Ag2 with the Ag···O4 bond (Table 5). Once again, only 2c-Ag1 is considered in the subsequent calculations.

Two pathways are considered for 1 + 2c + Ag⁺ reactions: (A) a pathway wherein the silver and bromide ions are non-interacting (Figure 7) and (B) the other pathway wherein the silver and bromide ions are interacting (Figure 8).

In path A that has noninteracting Ag and Br ions, Ag⁺ is stabilized by interactions with the carbonyl oxygen on the

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**Table 4. Relative Electronic Energies and Gibbs Free Energies (kcal/mol) between the Silver Salts of the 2-O-butyl-5-FU Anion in Figure 4**

| species compared | B3LYP/6-31+G*:DZP | M06-2x/6-311++G(3d3l2p):DZP | MP2/6-311++G(2d,p):DZP | MP2/6-311++G(2d,p):DZP |
|------------------|-------------------|-----------------------------|------------------------|------------------------|
|                  | $E_{elec}$ | $G_{elec}$ | $G_{elec}^{Gibbs}$ | $E_{elec}$ | $G_{elec}$ | $G_{elec}^{Gibbs}$ |
| 2b-Ag1–2b-Ag2    | −15.9       | −0.3         | 2.3              | −19.0       | −20.1       | −20.4           | −17.8           |

“Single-point energies were calculated at the B3LYP/6-31+G* optimized geometry. "Thermal and solvation corrections were obtained from the B3LYP/6-31+G* frequency calculation and then added onto the MP2/6-311++G(2d,p)/B3LYP/6-31+G* single-point electronic energy to obtain $G_{elec}^{Gibbs}$ values, respectively. The $G_{elec}^{Gibbs}$ values in bold were used in the discussion.”

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acetoxy group on C3’ or C2’, whereas Br− is positioned far away from Ag+ on the opposite side of the sugar ring (Figure 7). This arrangement is seen in all reaction intermediates, namely, in the initial reactant complexes, transition states, and products for both N- and O-reactions.

Both N3- and O4-reactant complexes of path A possess short Ag···N3 bond lengths (2.03 and 2.02 Å, respectively). Furthermore, the Ag···O (carbonyl oxygen on C2’ acetoxy group) bond length is 2.11 Å in the N3-reactant complex and 2.05 Å in the O4-reactant complex (Figure 7). These results suggest that the silver ion acts as a bridge to form initial complexes. The free energy of the N-reactant complex is 8.8 kcal/mol higher than that of the O complex (Table 2 and Figure 7), and the conformational difference of the acetoxy and benzyl groups is most likely responsible for this energy difference.

In the N3-TS structure of path A, the silver ion loses Ag···N3 interaction but establishes two new Ag···O interactions with (i) the carbonyl oxygen of the C3’ acetoxy group and (ii) O4 of 5-FU to facilitate the optimal orientation for N3 to attack C1’ and expel Br−. In the O4 TS structure, the Ag···N3 and Ag···O (carbonyl oxygen of the C3’ acetoxy group) associations from the reactant complex are preserved, and O4 of 5-FU is found to be in closer proximity to C1’. In addition, the C1’−Br bond length of both N3 and O4 transition states increases to ~3.0 Å as Br− continues with its departure. The Ag···N3 interaction possesses the largest electron density at the BCP of 0.107 e, when compared with the electron density at the Ag···O4 bond (~0.083e) and at the partially formed C1’−N3 and C1’−O4 bonds (0.085e and 0.093e, respectively). The electron density at the BCPs of the C1’−Br bonds in both N3 and O4 TS structures is even smaller (~0.020e) (Table 7). The N3 TS structure (without the Ag···N3 bond) is 22.1 kcal/mol higher in free energy than the O4 TS (with the Ag···N3 bond) (Table 2 and Figure 7).

In both N3 and O4 products, the Ag and Br ions are still located on opposite sides of the sugar ring and the silver ion is still stabilized by the Ag···O (carbonyl oxygen of the C3’ acetoxy group) interaction but the N3 product forms a formal C−N bond and the O4 product forms a formal C−O bond, significantly affecting the structural parameters of the ambident unit (−N3−C4≡O4). The N3 product is 14.6 kcal/mol higher in Gibbs energy than the O4 product. It is possible that the steric effect contributes to the lower stability of the N product when compared to that of the O product.

In the path B wherein Ag and Br are allowed to interact, two complexes are obtained from properly oriented reactants (Figure 8). The Ag···O distances in the initial complexes are in the range 2.25−2.30 Å and both involve oxygen on the sugar ring (either the ring O between C5’ and C1’ or the O of the acetoxy group on C6’). The significant Gibbs energy difference between the two complexes is possibly due to different conformations of the benzyl group, as well as an electron-correlation effect (N complex is 11.3 kcal/mol lower than O complex).

The transition states of pathway B are “loose”: the C1’−N and C1’−O distances are in the range 2.61−2.68 Å, and the C1’−Br distances are in the range 3.25−3.75 Å, which lends
support to the possible formation of oxocarbenium ion 4. The Ag···Br distances are in the range 2.39–2.45 Å, which is in agreement with the formation of the AgBr molecule. The single imaginary frequencies are i26.1 and i51.1 cm⁻¹ for N TS and O TS, respectively. Again, two unique features are noticeable for the transition states: (1) the oxocarbenium ion does not have the neighboring-group participation from acetoxy group on C2', (2) the Ag end of AgBr attaches to either N- or O- of the ambident –N3–C4=O4 unit (2.02–2.08 Å). The O4 TS structure with the Ag···N3 interaction is 11.9 kcal/mol less in Gibbs energy than the N3-TS structure with the Ag···O4 interaction at the MP2/6-311+G(2d,p)/B3LYP/6-31+G* level of theory (Table 2 and Figure 8).

The AgBr unit still attaches to N3 in the O4 product (O4 in N3 product), but the Ag···N3 and Ag···O4 interactions are much weaker (i.e., electron density at the BCPs are 0.088e and 0.083e) than the newly formed C1'–N3 and C1'–O4 (i.e., electron densities at the BCPs are separately 0.250e and 0.246e, Table 8). The Gibbs free energy of the N product is 9.6 kcal/mol higher than that of the O product (Figure 8 and Table 2). This significant difference is once again possibly due to the steric effect that is more pronounced in the N product than in the O product.

The overall activation barriers in pathway B are 37.1 and 13.9 kcal/mol for the N-reaction and O-reaction (Table 3), respectively. These values are lower than those of the corresponding activation barriers in pathway A (43.9 and 30.6 kcal/mol, respectively). Once again, the interaction between Ag and Br increases reaction rates for both the N- and O-reactions in the case of 1 + 2c + Ag⁺.

### DISCUSSION

**Oxocarbenium Ion.** The free oxocarbenium ion 4 (carbocation) can be stabilized by two factors (Figure 9): (1) participation of the neighboring acetoxy group at C2'; (2) delocalization of the lone electron pairs on the ring oxygen to the cationic C1' center. Indeed, the optimized structure of 4 showed (1) an additional five-membered ring structure and (2) a rather short C1’–O bond (1.34 Å).
Efforts are made to investigate the neighboring-group participation, such as Figure 9 in the transition states (Figures S1 and S2). If oxocarbenium ion 4 exists in its most stable structure as in Figure 9, it can form oxocarbenium ion complexes with 2b-AgBr (or 2c-AgBr), then obtain the products via very shallow transition states. The optimized transition states do not have the five-membered ring; the C1′···O (carbonyl O of acetoxy group on C2′) distances are in the range 2.08–3.23 Å, and no BCPs were located for this interaction. The results indicate that the neighboring group (acetoxy group on C2′) can trap the oxocarbenium ion but the N3- or O4-reactions will still prevent the participation of the neighboring group. Such transition states are hard to locate on the potential energy surface for some reactions due to the

Table 5. Bond and Ring Critical Point Properties and the Laplacian$^a$ of the M06-2x/6-311++G(3df,2p) Electron Density Distribution for the 2c-Ag (cf. Figure 6)

| transition-state structure | bond critical point | ring critical point |
|----------------------------|---------------------|---------------------|
|                            | $\rho$ | $\nabla^2 \rho$ | $\rho$ | $\nabla^2 \rho$ | $\rho$ | $\nabla^2 \rho$ |
| 2c-Ag1                     | 0.108 | 0.567 | 0.099 | 0.668 | 0.027 | 0.11 | 0.017 | 0.076 |
| 2c-Ag2                     |        |        |        |        |        |        |        |        |

$^a$A less positive $\nabla^2 \rho$ value at a bond critical point indicated electron density accumulation, whereas a more positive $\nabla^2 \rho$ value at a bond critical point indicated electron density depletion.

Table 6. Relative Electronic Energies and Gibbs Free Energies (kcal/mol) between the Silver Salts of the 2-O-benzyl-5-FU Anion in Figure 6

| species compared | B3LYP/6-31+G* :DZP | M06-2x/6-311++G (3df,2p) :DZP$^a$ | MP2/6-311++G(2d,p) :DZP$^a$,$^b$ |
|------------------|----------------------|----------------------------------|----------------------------------|
| $^\dagger$2c-Ag2-2c-Ag1 | 14.6 | 1.3 | 0.2 | 19.1 | 19.4 | 20.6 | 19.6 |

$^a$Single-point energies were calculated at the B3LYP/6-31+G* optimized geometry. $^b$Thermal and solvation corrections were obtained from the B3LYP/6-31+G* frequency calculation and then added onto the MP2/6-311++G(2d,p)//B3LYP/6-31+G* single-point electronic energy to obtain $G^\text{m}$ and $G^\text{solv}$ values, respectively. The $G^\text{m}$ value in bold was discussed in the text.

Figure 7. B3LYP/6-31+G* :DZP structures of reactant complexes, transition states, and products for the reactions between 1 and the silver salt of 2c (Ag$^+$ and Br$^-$ were noninteracting). The typical color convention was used to represent carbon (gray), nitrogen (blue), oxygen (red), fluorine (cyan), bromine (dark red sphere), and silver (light blue sphere). Bond distances (green) were in angstrom, and the MP2/6-311++G(2d,p)//B3LYP/6-31+G* relative (N3- minus O4-) Gibbs energies were in kcal/mol.

$^\dagger$Subsequent to the B3LYP/6-31+G* :DZP frequency calculation, the temperature corrections for the MP2/6-311++G(2d,p)//B3LYP/6-31+G* single-point electronic energy were taken into account to obtain the $G^\text{m}$ and $G^\text{solv}$ values, respectively.

Efforts are made to investigate the neighboring-group participation, such as Figure 9 in the transition states (Figures S1 and S2). If oxocarbenium ion 4 exists in its most stable structure as in Figure 9, it can form oxocarbenium ion complexes with 2b-AgBr (or 2c-AgBr), then obtain the products via very shallow transition states. The optimized transition states do not have the five-membered ring; the C1′···O (carbonyl O of acetoxy group on C2′) distances are in the range 2.08–3.23 Å, and no BCPs were located for this interaction. The results indicate that the neighboring group (acetoxy group on C2′) can trap the oxocarbenium ion but the N3- or O4-reactions will still prevent the participation of the neighboring group. Such transition states are hard to locate on the potential energy surface for some reactions due to the
complication of methyl rotations and weak interactions, so the oxocarbenium ion complexes are used to estimate the activation barriers for $4 + 2\text{b-AgBr}$ (Figure S1), and the N3 TS structure for $4 + 2\text{c-AgBr}$ is obtained from the optimization at B3LYP/3-
21G level of theory (Figure S2). The reaction activation barriers are 30.7 and 12.2 kcal/mol for N3-reaction and O4-reaction in the case of \( 4 + 2b-AgBr \), respectively. These energies are slightly higher than those (29.8 and 10.7 kcal/mol, Figure 5 and Table 3) obtained for pathway B of \( 1 + 2b + Ag^+ \) reaction (with no participation of the acetoxy group on C2’). In the case of the \( 4 + 2c-AgBr \) reaction (Figure S2), the activation barriers are 55.3 and 10.1 kcal/mol for N3-reaction and O4-reaction, respectively. The former is overestimated because the transition-state structure is adopted from a lower-level optimization (B3LYP/3-21G). The activation barriers are 37.1 and 13.9 kcal/mol separately for N3-reaction and O4-reaction, respectively. From pathway B without the participation of the neighboring acetoxy group at C2’ (Figure 8 and Table 3). Although oxocarbenium ion 4 with its most stable form (Figure 9) leads to two important conclusions: (1) the N3-reactions are also less favorable than O4-reactions; (2) the product glycosides will be \( \beta \)-anomers, it is not required that oxocarbenium ion 4 is stabilized by neighboring-group participation in the transition states because these two conclusions are also satisfactorily explained by pathway B.

Two other reasons may also give argument against the involvement of the neighboring acetyl group (as in Figure 9) in the transition states: (1) the involvement of the acetoxy group in the transition states requires a conformational rearrangement of the acetoxy group (from an upward to a downward position on the ring) to form the oxocarbenium ion 4 in Figure 9; (2) there will be significant repulsion between the downward acetoxy group on C2’ and the leaving Br atom before the reactions reach the transition states. This reasoning suggests that the oxocarbenium ion 4 forms in the transition states of pathway B but does not rely on the neighboring acetoxy group participation, even though free oxocarbenium ion 4 is apparently stabilized by the neighboring-group participation effect (Figure 9).

Conformation, Steric, Electron-Correlation, Solvent, and Association Effects. The energies of N-reactant complexes are typically very similar to those of O-reactant complexes owing to the absence of strong interactions between the S-FU and sugar units. The strong interactions would have otherwise pulled the sugar unit closer to either the N3 or O4 center. This lack of strong interactions may explain why the free-energy differences between N complexes and O complexes are usually less than 8.0 kcal/mol. In some cases, conformation effects noticeably affect the Gibbs energy differences between the N complex and the O complex; the biggest difference of 11.3 kcal/mol was found between the N and O complexes for pathway B of the Ag–Br-interacting reaction (\( 1 + 2c + Ag^+ \)) (Table 2 and Figure 8).

The ambident unit in the N3 product with the C1’–N3 bond is an amide (\( -C1’-N3-C4==O4 \)), whereas the ambident unit in the O4 product with the C1’–O4 bond is an imidate (\( -C1’-O4-C4==N3=- \)). The amide product is generally more stable than the imidate product; however, the steric effects experienced by the N3 product can reverse the relative stability due to the more hindered nature of the two big units brought together by rather short C1’–N3 bonds (1.4–1.5 Å). Thus, the relative single-point energies of N products can be both negative and positive (\( -24.6-11.9 \) kcal/mol) when compared with O products at the MP2/6-311++G-(2d,p):DZP//B3LYP/6-31+G* level of theory. The biggest positive single-point energy difference between the N3 and the O4 products is 11.9 kcal/mol in the \( 1 + 2c + Ag^+ \) reaction (pathway A, without free-energy correction, Table 2).

Figure 10. (a) Electron density (the values from outmost to inner contours are 0.001, 0.002, 0.004, 0.008, 0.02, 0.04, 0.08, 0.2, 0.4, 0.8 au, ...), (b) Laplacian of the electron density (solid lines correspond to negative values, and dotted lines correspond to positive values) for N transition state of the (HN–CH==O)Ag + CH\(_4\)–F reaction optimized at the CCSD/aug-cc-pVDZ:DZP//MP2/6-31+G* level. The bond critical points (BCPs) are crossing points between bond paths and vector lines. Although this transition state shows an additional BCP between Ag and C, it is very close to the ring critical point, making this BCP insignificant.
At the B3LYP/6-31+G* level of theory, the free-energy corrections from total electronic energy are usually small (−1.7−3.0 kcal/mol) for the differences of complexes, transition states, and products, whereas the solvent effect corrections give similar contributions (−1.6−3.5 kcal/mol). The biggest solvent effect was found in the initial complexes for pathway B of 1 + 2c + Ag⁺ reactions, in which the solvent effect contributes 11.0 kcal/mol to the energy difference between the N complex and the O complex (Table 2). Interestingly, the biggest electron-correlation effect (−11.3 kcal/mol) was also found for the initial complexes for pathway B of 1 + 2c + Ag⁺ reaction (Table 2).

The obvious association effect is demonstrated in the stability of the silver salts of 2-O-substituted 5-FU and the relative energies of N- and O-transition states. The association of Ag with N- or O- usually makes an energy difference in the range of 11.9−26.5 kcal/mol (Table 2) in these two situations, i.e., the association effect has the greatest impact on reaction kinetics among a variety of factors.

### Nature of the Association Effect

The silver ion was found to associate with the ambient N- and O-centers in initial complexes, transition states, and products. These associations have noticeable electron density at BCPs (0.05−0.111e) that is different from that of typical ionic bonds; these interactions also have positive Laplacian values at BCPs that are indicative of an electron density accumulation. Figure 10 shows the density contours and Laplacian plots of the N transition state for a model reaction (HN−CH=O)Ag + CH₃−F. It is clear that all long-distance interactions have positive Laplacian at the BCPs (Figure 10b) but Ag−O bond has the largest density at the BCP, judged from the contour values (Figure 10a).

The “exploded” (loose) nature of the transition states signifies the importance of the association effect. In pathway A wherein the Ag⁺ and Br⁻ ions do not interact, the partially formed C1′⋯N3 (1.96−1.99 Å) and C1′⋯O4 (1.85−1.91 Å) bonds are rather long and the atomic distances of the Ag−O4 (2.02−2.07 Å) and Ag−N3 (2.04 Å) interactions that accompanied these partially formed C1′⋯N3 and C1′⋯O4 bonds, respectively, are similar in length. Both Ag and C1′ are interacting with N3 (O4) but attaching to the opposite ends of the N3−C4=O unit in the transition states. In pathway B where the Ag⁺ and Br⁻ interact, both the oxocarbenium ion and AgBr molecule are nearly formed in the transition states. The atomic distances of Ag⋯O4 (2.02 Å) and Ag⋯N3 (2.07 Å) interactions remained around 2.0 Å, but the C1′⋯N3 or C1′⋯O4 distances increase to 2.61−2.68 Å. It is noticeable that the Ag⋯N3 and Ag⋯O4 distances were close to those in silver salt of 2-O-substituted 5-FU.

The stability of O4 TS structures can be attributed to two factors as follows: (1) the electrostatic interactions between C1′ and O4 and (2) the covalent interactions between Ag and N3. The fact that the anomer carbon C1′, N3, and O4 have charges in the ranges of 0.155−0.250e, −0.131e to −0.229e, and −0.195e to −0.362e, respectively (Tables S2b−S4b, S7 and 7), suggests that the electrostatic attractions are in favor of the C1′⋯O4 interactions over C1′⋯N3 interactions. Furthermore, because the electron densities at the BCPs were found to be higher in the Ag⋯N3 (0.096−0.107e) and Ag⋯O4 (0.087−0.099e) bonds than in the C1′⋯O4 (0.023−0.094e) and C1′⋯N3 bonds (0.020−0.086e) and the density at the BCP of Ag−Br bond is in between 0.071e and 0.080e (Tables S2c−S4c and 8), this suggests that covalent interactions exist between Ag and N3. Consequently, the O-reaction transition states have the strongest Ag⋯N3 associations amongst all of the long-distance associations, which in turn possess the strongest “amide” character in the ambient unit (N3−C4=O4) among all transition states.

### Reaction Mechanism of the Silver Salt Method

The theoretical results satisfactorily explained the O-regioselectivity in the synthesis of glycosides of 5-FU using the silver salt method (1 + 2b + Ag⁺ and 1 + 2c + Ag⁺), as the O-reaction barriers were calculated to be much lower (by 13.3−22.2 kcal/mol) than N-reaction barriers for both paths A and B. Although the blockage of N-site by Ag can also explain the O-regioselectivity, our results further support the well-known observations and advantages of silver salt methods: (1) the speeding-up effect due to the addition of silver carbonate in the Koenigs−Knorr reaction; (2) Kornblum and co-workers’ proposal on silver salt methods; (3) the involvement of the oxocarbenium ion in the synthesis of glycosides of 5-FU; and (4) the successful application of the HSAB principle in interpreting the silver salt method.

Path B effectively produces oxocarbenium ion in the transition states and possesses lower (by 6.8−16.9 kcal/mol) activation barriers than corresponding activation barriers of path A. The addition of Ag₂CO₃ could speed up the glycosidation reaction in the Koenigs−Knorr method, which can be attributed to the interaction between Ag and Br in path B. Because a stoichiometric amount of Ag₂CO₃ is usually needed, the one-on-one association more likely happens in the Koenigs−Knorr reactions.

In the alkylation with the silver salt method, Kornblum proposed that the silver pulled the halogen and enhanced the carbonium ion contribution to the transition state. The geometry parameters of transition states support the interpretation using Sₛ₁/Sₛ₂ borderline mechanism. The C1′⋯N3/O4 and C1′⋯Br distances are shorter in pathway A than in pathway B, and the oxocarbenium ions are effectively formed in the transition states of pathway B. Therefore, the transition states of pathway A have more Sₛ₂ characteristics and the transition states of pathway B have more Sₛ₁ characteristics. However, Sₛ₁/Sₛ₂ borderline mechanism only focuses on C1′ interactions and neglects the Ag interactions in the transition states. It is the association effect of Ag that significantly affects the energetics of transition states and in turn determines the O-regioselectivity in silver salt methods.

The Ag prefers the N site over O site of the ambient unit, which is supported by current calculations on all silver salts of 2-O-substituted 5-FU and by some reported crystal structures: (1) For silver salts of 2-substituted 5-FU, the structures with Ag−N3 bond have a large energy preference over those with Ag−O4 bond (by ~20 kcal/mol); (2) the crystal structure of the silver salt of succinimide showed Ag−N3 connection. These results are in perfect agreement with the HSAB principle: the Ag⋯N interaction is favorable soft−soft interaction and Ag⋯O interaction is less favorable soft−hard interaction. Our calculations further show that the O-reaction transition states benefit from two favorable factors: (1) the C1′⋯O ionic interaction and (2) the strong Ag⋯N covalent interaction. The results again appear to be in good accord with the hard soft acids and bases (HSAB) principle: (1) the C1′⋯O interaction is of ionic character, which is hard−hard interaction;
(2) the Ag···N interaction is of covalent character, which is soft–soft interaction.

**CONCLUSIONS**

Because of the conformational flexibility, significant size of the substituent groups, the formation of complexes, and the impact of different reaction media, many factors affect the reaction kinetics: conformation effect, steric effect, electron-correlation effect, solvent effect, and association effect. The association effect has the greatest impact on reaction kinetics among a variety of factors.

The effect of 2-O-substitutional groups (in the order of no-substitution, butyl, and benzyl) is small, but the greatest hindering effect (the highest barrier) is found with the butyl group in the N-reaction, and the trend of increasing barriers is lower than the barriers of pathway A (by 6.8 kcal/mol) than N-reaction barriers in both path A and path B, the O-regioselectivity with the silver salt method is satisfactorily explained by either path A or path B.

The results of the barriers of pathway B (Ag and Br interact) being lower than the barriers of pathway A (by 6.8–16.9 kcal/mol) can further explain three points: (1) the speeding-up effect in Koenigs–Knorr reactions due to the addition of silver carbonate to the reaction mixture; (2) the halogens are pulled away by silver ion from halides; and (3) the oxocarbenium ion is involved in the glycosidation reactions but the neighboring acetyl group participation is not found in the transition states.

Kornblum and co-workers’ proposal of $\text{Sn}_1/\text{Sn}_2$ borderline mechanism focused on hard–hard interaction between C1′ and ambident NH=CH=O unit and neglected the soft–soft Ag···N interaction. The O-reaction transition states benefit from both hard–hard C1′···O interaction and soft–soft Ag···N interaction, and the soft–soft interaction is more important due to the significant covalent character of Ag···N(O-) interactions in the “loose” transition states.

The hard and soft acids and bases (HSAB) principle can be used to explain the stability of the transition states for the glycosidation reactions in the silver salt methods. The explanation that the Ag ion blocks the N-site agrees with experimental results; however, it is unable to provide information or insight on the kinetics of the reaction.

**COMPUTATIONAL METHODS**

Usually, the sugar ring in 1 adopts a chair form and the butyl group in 2 adopts zigzag conformers. This trend is also confirmed by conformational search using the MMFF94 force field$^{26}$ and the Global-MMX steric energy minimization program in PCMODEL.$^{27}$ In addition, the unit 2 is positioned properly through the Ag bridging between acetyl groups of 1 so that there is favorable interaction (or no interaction) between Ag and Br. The actual structures of initial complexes, transition states, and products are fully optimized using the Becke three-parameter Lee–Yang–Parr (B3LYP) functional$^{28}$ paired with two double-zeta basis sets: B3LYP/6-31+G*:DZP. The basis set notation denoted the use of People’s standard 6-31+G* basis set$^{29}$ for the C, H, N, O, F, and Br atoms and the DZP basis set for Ag.$^{30}$ The latter was obtained from the EMSL website.$^{31}$

The frequency calculations are also performed at the same level of theory to verify that each optimized structure is either a minimum with no imaginary frequency or a transition state with one imaginary frequency, i.e., first-order saddle point on the potential energy surface. The frequency calculations provide the thermal corrections to the Gibbs free energy ($G_{\text{emp}}$) that already incorporates the zero-point vibrational energy. The quadratic synchronous transit approach by Schlegel and co-workers$^{33}$ that requires a reactant and product as its input (QST2) or the reactant, the product, and an initial guess for the transition state as input (QST3) is used to optimize transition-state structures.

Single-point energies are additionally calculated using both density functional theory$^{34}$ and conventional ab initio techniques incorporating electron-correlation effects such as the Møller–Plesset second-order (MP2) perturbation theory. Specifically, single-point energies are evaluated using the M06-2X Minnesota global hybrid functional$^{35}$ with 6-311+G- (3df,2p) or 6-311++G(2d,p)$^{36}$ (for C, H, O, N, F, and Br) and DZP basis sets (for Ag). The double forward slash “//” in M06-2X/6-311++G(3df,2p):DZP//B3LYP/6-31+G*:DZP denotes the computation of the M06-2X/6-311++G(3df,2p):DZP energies of the structures optimized at the more cost-effective B3LYP/6-31+G*:DZP level. The M06 suite of functionals requires fine integration grids to obtain correct reaction energies,$^{38}$ so an ultrafine integration grid with 99 radial shells and 590 angular points per shell was used in the M06-2X calculations in this study. Single-point energies were further evaluated at the MP2/6-311++G(2d,p):DZP//B3LYP/6-31+G*:DZP level. The atomic charges are obtained from a Hirshfeld population analysis.$^{39}$

The SMD solvation model of Truhlar and co-workers$^{40}$ is used to obtain the corresponding reaction and activation free energies in xylene mixture (dielectric constant of 2.3879). Because geometrical parameters and energies of the conformers of the ionic test cases are not significantly impacted by the inclusion of solvents, the gas-phase free energies are utilized all throughout in assessing the preference for the O over the N product. Nevertheless, the solvated single-point free energies of the complex, transition state, and product are presented in all tables, alongside their gas-phase counterparts.

The density analysis was done within the framework of the quantum theory of atoms in molecules.$^{41,42}$ In this approach, a chemical bond was defined by a bond path through total density analysis rather than by an arbitrary line. Bond critical point (BCP) is a point on the bond path that has the minimal density on two directions and maximum density on one direction, i.e., it has a ranking of $(3,−1)$ in the topology of density. The density and the Laplacian of the density at the bond critical points (BCPs) indicate the magnitudes of shared electrons and bond characters, either by way of accumulating density (a negative number of Laplacian) or depleting density (a positive number of Laplacian).

All ab initio calculations are carried out with GAUSSIAN program packages.$^{43}$ Wavefunction files obtained from GAUSSIAN program are used for the density analysis AIMPAC$^{44}$ suite of programs.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b00361.
Additional tables for thermodynamic properties and density analysis results for these species; reaction 4 + 2b-Ag-Br (similar to pathway B but without the neighboring-group participation) (Figure S1); reaction 4 + 2c-Ag-Br (similar to pathway B but with the neighboring-group participation) (Figure S2); atom coordinates of all reactant complexes, transition states, and products (PDF).

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**Notes**

The authors declare no competing financial interest.

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