# Transition-State Structure for the Quintessential $\mathrm{S}_{\mathrm{N}} 2$ Reaction of a Carbohydrate: The Reaction of $\alpha$ Glucopyranosyl Fluoride with Azide Ion in Water. 

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## Supporting Information

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Materials. $\mathrm{D}-\left(1-{ }^{13} \mathrm{C}\right)$ Glucose was purchased from Omicron Biochemicals Inc. $\mathrm{D}-\left(1-{ }^{2} \mathrm{H}\right) \mathrm{Glucose}, \mathrm{D}-(2-$ $\left.{ }^{2} \mathrm{H}\right)$ glucose, $\mathrm{D}-\left(5-{ }^{2} \mathrm{H}\right)$ glucose and $\mathrm{D}-\left(5-{ }^{18} \mathrm{O}\right)$ glucose were made according to literature procedures. ${ }^{1}$ Labeled and unlabeled $\alpha$-glucopyranosyl fluorides ( $\alpha \mathrm{GluF}$ ) were prepared from the corresponding 1,2,3,4,6-penta-O-acetyl-glucopyranose in two steps using a known procedure. ${ }^{2}$ All aGluFs were recrystallized and had sharp melting points as well as ${ }^{1} \mathrm{H}$ NMR ( $500 \mathrm{MHz} ; \mathrm{D}_{2} \mathrm{O}$ ) and ${ }^{13} \mathrm{C}$ NMR ( 125 MHz ; $\mathrm{D}_{2} \mathrm{O}$ ) spectra consistent with the isotopic substitution. Sodium azide was purified by recrystallization from $\mathrm{H}_{2} \mathrm{O}$.

## Measurement of kinetic isotope effects by ${ }^{19} \mathrm{~F}$ NMR spectroscopy

KIEs were determined via ${ }^{19} \mathrm{~F}$ NMR spectroscopy on a Bruker AVANCE III 500 MHz spectrometer. Briefly, samples were prepared in new 5 mm NMR tubes by addition of unlabeled $\alpha$ GluF ( $\sim 1.5 \mathrm{mg}$ ), a labeled $\alpha G \operatorname{luF}(\sim 1.5 \mathrm{mg}), \mathrm{D}_{2} \mathrm{O}(15 \mu \mathrm{~L})$, trifluoroacetic acid ( $1.5 \mu \mathrm{~L}$ ), and an aqueous solution of 0.2 M sodium succinate and 2.0 M sodium azide at $\mathrm{pH} 6.0(650 \mu \mathrm{~L})$. An initial NMR spectrum was recorded with the sample temperature maintained at 323 K . Quantitative proton-decoupled ${ }^{19} \mathrm{~F}$ NMR spectrum for the $\alpha^{2}{ }^{2} \mathrm{H}$ KIE experiments were acquired using either gated (runs 1-6) or inverse-gated pulse sequences (run 7). The $1-{ }^{13} \mathrm{C}$ KIE values were obtained either indirectly (run 2) via competition between $2-{ }^{2} \mathrm{H}$ aGluF and $1-{ }^{13} \mathrm{C}$ aGluF or directly (runs $1 \& 3$ ) using unlabeled $\alpha$ GluF and $1-{ }^{13} \mathrm{C}$ aGluF. Spectra consisting 100 scans (acquisition time of 0.7 s ) were recorded with a recycle delay of 11 s between scans ( 20 min per spectrum). The baseline was corrected to remove baseline distortions that are typically associated with ${ }^{19} \mathrm{~F}$ spectra using the Whittaker Smoother method found in MestReNova version 6.2. The ${ }^{19} \mathrm{~F}$ signals corresponding to the internal standard trifluoroacetic acid and $\alpha \mathrm{GluF}$ were -76.55 ppm and -151.07 ppm , respectively.

## Measurement of kinetic isotope effects using the 'quasi-racemate' method

The change in optical rotation at 405 nm of a buffered solution in 1 dm path length jacketed cell was monitored using a Perkin-Elmer 341 polarimeter at $50^{\circ} \mathrm{C}$. Water thermostatted to $50.0 \pm 0.1^{\circ} \mathrm{C}$ was passed through the cell jacket. Solutions of 6.0 mg of each enantiomer in 1.2 mL of 0.2 M sodium succinate ( pH 6.0 ) and 2.0 M sodium azide were used. Experimental time courses of optical rotation
for each isotopic quasi-racemate were fitted to equation 3 using the nonlinear least squares fitting routine in the computer program Prism version 5.0.

The optical rotation change for complete reaction for the light isotopologue $(A)$ was measured in separate experiments. Solutions containing $\sim 6.0 \mathrm{mg}$ of $\alpha-L-g l u c o p y r a n o s y l$ fluoride in 1.2 mL of 0.2 M sodium succinate ( pH 6.0 ) and 2.0 M sodium azide were used.

Equation S1

$$
\begin{equation*}
\ln \left(\frac{k_{12}}{k_{13}}\right) \approx \ln \left(\frac{k_{12}}{k_{14}}\right) / 1.9 \tag{S1}
\end{equation*}
$$

Computational Analysis. Calculations for the reaction of $\alpha$-D-glucopyranosyl fluoride ( $\alpha$-GluF) with an azide ion were performed using Gaussian 09 and the B3LYP method with a $6-31 \mathrm{G}^{*}$ basis set. All structures were calculated at 323.15 K and with the polarizable continuum model (PCM) to account for solvent effects from water. A local minimum for the $\alpha$-GluF ground state structure was located by optimizing starting from several chair conformations. The differences between the optimized structures are subtle, that is they only varied in the geometric orientation of the hydroxyl substituents. An unconstrained transition state (TS) structure was located by extending the C-F bond to $3.5 \AA$ and positioning an azide ion, measured from the nucleophilic nitrogen atom, $3.5 \AA$ away from the anomeric center on the face opposite to the leaving group. This TS structure had one imaginary frequency; however, the calculated KIEs did not match the experimental values. Subsequently, the C-F and C-N bond distances were incrementally varied and constrained to locate TS structures that had one major imaginary frequency corresponding to a $\mathrm{S}_{\mathrm{N}} 2$ reaction coordinate. KIEs for each putative TS structure were calculated using ISOEFF98. Scale factors of 0.9614 were used for the B3LYP/6-31G* calculations.

Table S1: Individual Kinetic Isotope Effects for the Nucleophilic Substitution Reaction of $\alpha$-DGlucopyranosyl Fluoride with Azide Ion in Succinate Buffer (0.2 M at pH 6.0) Containing Sodium Azide (2 M) at $50^{\circ} \mathrm{C}$.

| Isotope | Run \# | KIE $\left({ }^{19} \mathrm{~F}\right.$ NMR) | KIE (Quasi-racemate) |
| :---: | :---: | :---: | :---: |
| D1 | 1 | $1.1845 \pm 0.0038$ |  |
| D1 | 2 | $1.1991 \pm 0.0055$ |  |
| D1 | 3 | $1.1905 \pm 0.0059$ |  |
| D1 | 4 | $1.1915 \pm 0.0063$ |  |
| D1 | 5 | $1.1888 \pm 0.0063$ |  |
| D1 | 6 | $1.1874 \pm 0.0038$ |  |
| D1 | 7 | $1.2010 \pm 0.0041$ |  |
| D2 | 1 | $1.0467 \pm 0.0031$ | $1.0493 \pm 0.0021$ |
| D2 | 2 | $1.0522 \pm 0.0019$ | $1.0508 \pm 0.0021$ |
| D2 | 3 | $1.0378 \pm 0.0016$ | $1.0328 \pm 0.0008$ |
| D2 | 4 |  | $1.0541 \pm 0.0009$ |
| D5 | 1 | $0.9829 \pm 0.0031$ |  |
| D5 | 2 | $0.9866 \pm 0.0027$ |  |
| D5 | 3 | $0.9901 \pm 0.0037$ |  |
| $1-{ }^{13} \mathrm{C}$ | 1 | $1.0270 \pm 0.0008$ | $1.030 \pm 0.0020$ |
| $1-{ }^{13} \mathrm{C}$ | 2 | $1.0281 \pm 0.0051$ | $1.021 \pm 0.0010$ |
| $1-{ }^{13} \mathrm{C}$ | 3 | $1.0170 \pm 0.0010$ | $1.016 \pm 0.0040$ |
| $5-{ }^{18} \mathrm{O}$ | 1 | $0.9818 \pm 0.0040$ |  |
| $5-{ }^{18} \mathrm{O}$ | 2 | $0.9816 \pm 0.0054$ |  |
| $5-{ }^{18} \mathrm{O}$ | 3 | $0.9805 \pm 0.0045$ |  |

Table S2: Cartesian coordinates for the starting material ( $\alpha$-GluF) calculated at the B3LYP/6-31G* level of theory.

| Atom | X | Y | Z |
| :---: | :---: | :---: | :---: |
| C | 1.574654 | -0.160428 | -0.610976 |
| C | 0.948351 | 0.993573 | 0.162441 |
| C | -0.574660 | 0.939146 | 0.027684 |
| C | -1.117343 | -0.426499 | 0.468296 |
| C | 0.911625 | -1.485065 | -0.194701 |
| H | 1.211084 | 0.882460 | 1.226509 |
| H | 1.369420 | -0.013464 | -1.680928 |
| H | -0.893956 | -0.580299 | 1.531918 |
| H | 1.263037 | -2.323188 | -0.803394 |
| H | -0.837943 | 1.098757 | -1.024369 |
| F | 1.277333 | -1.757595 | 1.130091 |
| O | -0.470572 | -1.462647 | -0.306722 |
| O | 2.970791 | -0.177749 | -0.357060 |
| H | 3.390014 | -0.743692 | -1.024917 |
| O | 1.442468 | 2.226031 | -0.341618 |
| H | 0.869551 | 2.904893 | 0.057120 |
| O | -1.087521 | 2.000012 | 0.838698 |
| H | -1.911941 | 2.316336 | 0.437887 |
| C | -2.618000 | -0.580322 | 0.273414 |
| H | -2.892634 | -1.618219 | 0.492329 |
| H | -3.125855 | 0.062261 | 1.006167 |
| O | -2.993821 | -0.205480 | -1.050618 |
| H | -3.575290 | -0.891266 | -1.407535 |

Sum of electronic and zero-point Energies = -711.176632 A.U.

Table S3: Cartesian coordinates for $\mathrm{TS}_{0}$ calculated at the B3LYP/6-31G* level of theory.

| Atom | X | Y | Z |
| :---: | :---: | :---: | :---: |
| C | -1.232313 | -0.849361 | -0.239472 |
| C | 0.055477 | -1.638599 | -0.436273 |
| C | 1.206861 | -0.631900 | -0.495653 |
| C | 1.272584 | 0.227009 | 0.771895 |
| C | -1.098690 | 0.130819 | 0.923759 |
| H | 0.187554 | -2.304703 | 0.419033 |
| H | -1.358508 | -0.260345 | -1.159719 |
| H | 1.382808 | -0.430636 | 1.636189 |
| H | -1.709746 | 0.037654 | 1.801054 |
| H | 1.051652 | 0.018081 | -1.365739 |
| F | -0.316054 | -1.358958 | 2.230376 |
| O | -0.000174 | 0.914020 | 0.974141 |
| O | -2.343816 | -1.709920 | -0.065475 |
| H | -3.128776 | -1.137058 | -0.103218 |
| O | -0.016690 | -2.354013 | -1.670895 |
| H | 0.899789 | -2.632071 | -1.843967 |
| O | 2.410645 | -1.391477 | -0.665543 |
| H | 3.045758 | -0.831111 | -1.138279 |
| C | 2.362481 | 1.277756 | 0.749626 |
| H | 2.232940 | 1.941155 | 1.616659 |
| H | 3.325339 | 0.759355 | 0.865956 |
| O | 2.316544 | 2.008149 | -0.475142 |
| H | 3.045462 | 2.647630 | -0.460622 |
| N | -2.431664 | 1.452942 | 0.273968 |
| N | -1.927767 | 2.087618 | -0.618438 |
| N | -1.420607 | 2.687190 | -1.478487 |

Imaginary Frequency = -478.214
Sum of electronic and zero-point Energies $=-875.429133$ A.U.

Table S4: Cartesian coordinates for $\mathrm{TS}_{1}$ calculated at the B3LYP/6-31G* level of theory.

| Atom | X | Y | Z |
| :---: | :---: | :---: | :---: |
| C | 0.98147 | 0.71864 | -0.36423 |
| C | -0.34389 | 1.47280 | -0.16335 |
| C | -1.53453 | 0.57254 | -0.48031 |
| C | -1.45416 | -0.66621 | 0.42707 |
| C | 0.88527 | -0.51713 | 0.49450 |
| H | -0.39467 | 1.72988 | 0.90512 |
| H | 1.07324 | 0.42949 | -1.42309 |
| H | -1.41103 | -0.31606 | 1.47256 |
| H | 0.98988 | -0.33177 | 1.56783 |
| H | -1.50669 | 0.27173 | -1.53490 |
| F | -0.31155 | 0.63779 | 2.68454 |
| O | -0.16584 | -1.32124 | 0.14817 |
| O | 2.07679 | 1.52099 | 0.04538 |
| H | 1.89693 | 2.40547 | -0.31835 |
| O | -0.28406 | 2.62102 | -1.01103 |
| H | -1.09993 | 3.12031 | -0.84100 |
| O | -2.71485 | 1.34008 | -0.21555 |
| H | -3.43307 | 0.96280 | -0.74694 |
| C | -2.55011 | -1.68261 | 0.20857 |
| H | -2.32317 | -2.58450 | 0.79500 |
| H | -3.48266 | -1.25276 | 0.60332 |
| O | -2.67285 | -1.98579 | -1.18135 |
| H | -3.40969 | -2.60876 | -1.27887 |
| N | 2.35756 | -1.71686 | 0.09873 |
| N | 3.33903 | -1.11650 | -0.30634 |
| N | 4.31582 | -0.64588 | -0.70380 |

Imaginary Frequency = -236.53, -27.37
Sum of electronic and zero-point Energies $=-875.427663$ A.U.

Figure S1. Fit of the data taken from Zhang et al., ${ }^{3}$ the line is the best non-linear least squares fit of the data to equation 2.


Figure S2: Unconstrained transition state model $\left(\mathrm{TS}_{0}\right)$ for the reaction of $\alpha$-glucopyranosyl fluoride with azide ion.


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