Supporting Information

Influence of Equatorial CH···O Interactions on Secondary Kinetic Isotope Effects for Methyl Transfer

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Supporting Information

Contents

Computational details ........................................ 2
References ......................................................... 4
Table S1. Z-matrix template for TS cage complexes ........... 5
Table S2. Optimised parameters for cage transition structures ... 6
Note on Table S2 ................................................. 6
Table S3. Z-matrix template for RS cage complexes ........... 7
Table S4. Optimised parameters for cage reactant structures ... 8
Notes on Table S4 ................................................ 8
Table S5. B3LYP/aug-cc-pVDZ optimised energies for RS and TS structures (total energies in hartree, relative energies in kJ mol\(^{-1}\)) ........................................ 9
Notes on Table S5 ................................................ 9
Table S6. Vibrational wavenumbers (cm\(^{-1}\)) for symmetric and \textit{antisymmetric} (italics) axial C-O bond stretching in transition structures of methyl cation in constrained water cages ........................................ 10
Notes on Table S6 ................................................. 10
Table S7. Imaginary vibrational wavenumbers (cm\(^{-1}\)) for motions of constrained cage water molecules. Vibrations in brackets correspond to the heavier isotopologue, vibrations in regular type to the TS, and in bold to the RS ........................................ 11
Notes on Table S7 ................................................ 11
Table S8. B3LYP/aug-cc-pVDZ average CH-bond stretching force constants (aJ Å\(^{-2}\)) for RS and TS. ........................................ 14
Notes on Table S8 ................................................ 14
Table S9. B3LYP/aug-cc-pVDZ isotopic partition function ratios, \(2^\circ\) \(\alpha\)-D\(_3\) isotope effects for transfer of methyl cation from vacuum to the center of the constrained water cage with \(r_{eq} = 3.0\) Å at 298 K and isotope effect factors. ........................................ 16
Notes on Table S9 ................................................ 16
Table S10. B3LYP/aug-cc-pVDZ isotopic partition function ratios, \(2^\circ\) \(\alpha\)-D\(_3\) isotope effects for insertion of symmetric axial structures [H\(_2\)O…CH\(_3^+\)...OH\(_2\)] from vacuum to the center of the constrained three-water equatorial cage at 298 K and isotope effect factors. ........................................ 17
Notes on Table S10 ................................................ 17
Table S11. B3LYP/aug-cc-pVDZ isotopic partition function ratios and factors for RS and TS, and KIEs, for methyl transfer within a constrained superheavy cage with \(r_{ax} = 2.04\) Å. ........................................ 18
Notes on Table S11. .............................................. 18
Computational Methods

Constrained geometry optimizations and analytical second-derivative calculations of Hessians were performed by means of the Gaussian09 program (revision A.02). The B3LYP density functional was used with the aug-cc-PVDZ basis set, a method previously identified as performing well for a harmonic vibrational frequencies, leading to reliable estimates of isotope effects. Residual translational and rotational contributions to Hessian elements (punch=derivatives) were removed by a projection method and equilibrium and/or kinetic isotope effects at 298.15 K were determined within the rigid-rotor/harmonic approximation without scaling of vibrational frequencies, which satisfied the Teller-Redlich product rule; tunneling was treated by means of Bell’s model applied to the imaginary frequency for motion along the reaction coordinate.

The conventional transition-state theory treatment of KIEs with the Born-Oppenheimer, rigid-rotor and harmonic oscillator approximations (and neglecting tunnelling and transmission-factor contributions) considers the rate-constant ratio \( k/k' \) (where the prime denotes the rate constant for the heavier isotopologue) as the product of three factors (eq. 1) involving translational, rotational and vibrational partition functions for the isotopologous RS and TS species. The first is the mass and moments-of-inertia factor (MMI), where \( |I| \) is the determinant of the moment-of-inertia tensor (i.e. the product of the three principal moments of inertia) of a non-linear \( N \)-atomic molecule of molecular mass \( M \); rotational symmetry factors are omitted here since they are all equal to unity for the applications to be presented below. The second is the Boltzmann excitational (EXC) factor corresponding to the relative populations of the higher vibrational quantum states, and the third is the zero-point energy (ZPE). EXC involves a product, and ZPE a summation, over \( 3N-6 \) and \( 3N-7 \) real vibrational frequencies of RS and TS, respectively, where \( u = hcv/k_BT \) with frequency \( (s^{-1}) \) replaced by wavenumber \( v \) (cm\(^{-1}\)) and \( h, k_B, c \) and \( T \) are the Planck and Boltzmann constants, the velocity of light and the absolute temperature. Inspection of the forms of the MMI, EXC and ZPE factors shows that the KIE may be rewritten simply as a quotient of isotopic partition function ratios (IPFRs) for RS and TS (eq. 2).

\[
k/k' = \left( \frac{|I|}{I_{RS}} \right)^{\frac{1}{2}} \left( \frac{M}{M_{RS}} \right)^{\frac{1}{2}} \left( \frac{M}{M_{TS}} \right)^{\frac{1}{2}} \gamma_1 \gamma_2 3^{N-6} \prod_{i=1}^{3N-6} \left[ \frac{1 - \exp(-u_i)}{1 - \exp(-u'_i)} \frac{\exp(u_i/2)}{\exp(u'_i/2)} \right]_{RS}^{\frac{1}{2}}
\]

\[
KIE = MMI \times EXC \times ZPE
\]

\[
k/k' = \frac{f_{RS}}{f_{TS}}
\]

It is common to replace MMI in eq. 1 by an equivalent factor containing only vibrational frequencies. According to the Teller-Redlich product rule, the masses and moments of inertia for a pair of isotopologues are related to the vibrational frequencies: the equality expressed by eq. 3 assumes separability of translational and rotational motions from vibrational motions within the harmonic approximation. Substituting the vibrational product VP for each of RS and for TS in eq. 1,
the KIE may be written as eq. 4, the Bigeleisen equation, where VPR is the vibrational product ratio. Two points should be noted: (i) the product of ratios of atomic masses \( m \) that appears eq. 3 vanishes from the KIE because it is identical for both RS and TS; (ii) it is conventional to consider the ratio of imaginary transition frequencies for the TS as a separate factor, so that (in eq. 5) the VPR and EXC products and the ZPE summation are all taken over \( 3N - 7 \) real TS frequencies.

\[
\prod_{i}^{3N-6} \frac{v'_i}{v_i} = \text{VP} = \text{MI} = \left[ \begin{bmatrix} I' \\ I \end{bmatrix} \right]^{1/2} \left[ \begin{bmatrix} M' \\ M \end{bmatrix} \prod_{j}^{N} \frac{m'_j}{m_j} \right]^{1/2} \tag{3}
\]

\[
k/k' = (v_t / v'_t) \times \text{VPR} \times \text{EXC} \times \text{ZPE} \tag{4}
\]

\[
\text{VPR} = \prod_{i}^{3N-6} \frac{v'_i}{v_i} / \prod_{i}^{3N-7} \frac{v'_i}{v_i} \tag{5}
\]

Use of the Bigeleisen equation enables the determination of KIEs from normal-mode frequencies without the need to consider the MMI factor explicitly. However, there is practical merit in separately determining the vibrational product and mass-moment-of-inertia terms for a pair of isotopologues, rather than relying upon their equality: the requirement for VP and MI to be equal in value provides a strict test for the correctness of the vibrational frequency calculations. If these two terms are not equal to a satisfactory number of decimal places, it is a sure indication that something is wrong, often (in our experience) with the definition of internal coordinates used in the projection method for removing residual components of translational and rotational motion from the Hessian.

We prefer to evaluate IPFRs for each RS or TS species separately and then to evaluate kinetic isotope effects (KIEs) by means of eq. 2 or equilibrium isotope effects (EIEs) by the analogous eq. 6, where PS refers to a minimum-energy product structure.

\[
K/K' = f_{RS} / f_{PS} \tag{6}
\]

Within the inherent assumption of separability in this treatment of KIEs, the quantum correction \( \Gamma_z / \Gamma_z' \) for motion along the transition vector may be approximated by Bell’s expression\(^9\) for an inverted parabola, eq. 7; this quantum correction is applied routinely to a transition frequency in evaluation of the IPFR for isotopologous TSs.

\[
\frac{\Gamma_z}{\Gamma_z'} = \frac{v_z \sin(u_i'/2)}{v_z' \sin(u_i/2)} \tag{7}
\]
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Table S1. Z-matrix template for TS cage complexes.

|   |   |   |   |
|---|---|---|---|
| C |   |   |   |
| X | 1 | c_1 |   |
| X | 2 | c_1 | 1 | c_90 |
| H | 1 | v_CH | 2 | c_90 | 3 | c_0 |
| H | 1 | v_CH | 2 | c_90 | 3 | c_120 |
| H | 1 | v_CH | 2 | c_90 | 3 | -c_120 |
| O | 1 | c_Rax | 4 | c_90 | 3 | c_0 |
| X | 7 | c_1 | 8 | c_90 | 1 | c_180 |
| H | 7 | v_HOax | 9 | v_Aax | 8 | c_90 |
| H | 7 | v_HOax | 9 | v_Aax | 8 | -c_90 |
| O | 1 | c_Rax | 4 | c_90 | 3 | c_180 |
| X | 12 | c_1 | 1 | c_90 | 4 | c_0 |
| X | 12 | c_1 | 13 | c_90 | 1 | c_180 |
| H | 12 | v_HOax | 14 | v_Aax | 13 | c_90 |
| H | 12 | v_HOax | 14 | v_Aax | 13 | -c_90 |
| O | 1 | c_Req | 2 | c_90 | 3 | c_0 |
| X | 17 | c_1 | 1 | c_90 | 2 | c_0 |
| X | 17 | c_1 | 18 | c_90 | 1 | c_180 |
| H | 17 | v_HOeq | 19 | v_Aeq | 18 | c_90 |
| H | 17 | v_HOeq | 19 | v_Aeq | 18 | -c_90 |
| O | 1 | c_Req | 2 | c_90 | 3 | c_120 |
| X | 22 | c_1 | 1 | c_90 | 2 | c_0 |
| X | 22 | c_1 | 23 | c_90 | 1 | c_180 |
| H | 22 | v_HOeq | 24 | v_Aeq | 23 | c_90 |
| H | 22 | v_HOeq | 24 | v_Aeq | 23 | -c_90 |
| O | 1 | c_Req | 2 | c_90 | 3 | -c_120 |
| X | 27 | c_1 | 1 | c_90 | 2 | c_0 |
| X | 27 | c_1 | 28 | c_90 | 1 | c_180 |
| H | 27 | v_HOeq | 29 | v_Aeq | 28 | c_90 |
| H | 27 | v_HOeq | 29 | v_Aeq | 28 | -c_90 |

**Variables:**

v_CH 1.1014
v_HOax 0.9664
v_Aax 55.0
v_HOeq 0.9656
v_Aeq 54.74

**Constants:**

c_Rax 2.04
! this is \( r_{ax} \) in the paper

c_Req 3.0
! this is \( r_{eq} \) in the paper
c_0 0.0
c_1 1.0
c_90 90.0
c_120 120.0
c_180 180.0
## Table S2. Optimised parameters for cage transition structures.

| Rax / Å | Req / Å | CH / Å | HOax / Å | Aax / ° | HOeq / Å | Aeq / ° | HCOax / ° |
|---------|---------|--------|----------|---------|----------|---------|-----------|
| 2.04    | 3.0     | 1.08499| 0.96469  | 54.6395 | 0.96596  | 52.277  | 90.0      |
|         | 3.5     | 1.08817| 0.96528  | 54.7945 | 0.96552  | 52.300  | 90.0      |
|         | 3.75    | 1.08750| 0.96554  | 54.806  | 0.96551  | 52.2795 | 90.0      |
|         | 4.0     | 1.08667| 0.96576  | 54.800  | 0.96553  | 52.251  | 90.0      |
| 2.525   | 3.0     | 1.09642| 0.96467  | 53.7425 | 0.96575  | 52.4315 | 90.0      |
|         | 3.5     | 1.09693| 0.96498  | 53.9960 | 0.96542  | 52.3712 | 90.0      |
|         | 3.75    | 1.09561| 0.96515  | 54.0535 | 0.96544  | 52.3275 | 90.0      |
|         | 4.0     | 1.09436| 0.96530  | 54.0862 | 0.96547  | 52.2835 | 90.0      |
| 3.0     | 3.0     | 1.10304| 0.96505  | 52.9624 | 0.96574  | 52.5279 | 90.0      |
|         | 3.5     | 1.10206| 0.96519  | 53.1986 | 0.96541  | 52.4223 | 90.0      |
|         | 3.75    | 1.10038| 0.96528  | 53.2690 | 0.96543  | 52.364  | 90.0      |
|         | 4.0     | 1.09890| 0.96536  | 53.3171 | 0.96546  | 52.3084 | 90.0      |

**Note on Table S2:**
The main text refers to values of \( r_{ax} = 2.0, 2.5 \) and \( 3.0 \) Å. In fact the precise values used in this study were \( r_{ax} = 2.04, 2.525 \) and \( 3.0 \) Å. The former two values are a legacy from an earlier published study on methyl cation within a continuum solvation model.\(^{10}\) \( 2.04 \) Å is the PCM default radius for a carbon atom within the UFF cavity model, and \( 2.525 \) Å is the default radius for a \( \text{CH}_3 \) group within the UA0 cavity model.
Table S3. Z-matrix template for RS cage complexes.

\[
\begin{array}{cccc}
\text{O} & 1 & v_{\text{CO}} & \\
\text{C} & 2 & v_{\text{CH}} & 1 & v_{\text{OCH}} \\
\text{H} & 2 & v_{\text{CH}} & 1 & v_{\text{OCH}} & 3 & c_{120} \\
\text{H} & 2 & v_{\text{CH}} & 1 & v_{\text{OCH}} & 3 & -c_{120} \\
\text{H} & 1 & v_{\text{HOax}} & 2 & c_{\text{Aax}} & 3 & c_{90} \\
\text{H} & 1 & v_{\text{HOax}} & 2 & c_{\text{Aax}} & 3 & -c_{90} \\
\text{O} & 1 & c_{\text{OO}} & 6 & c_{\text{Aax}} & 2 & c_{0} \\
\text{H} & 8 & v_{\text{HOax}} & 2 & c_{\text{Aax}} & 3 & c_{90} \\
\text{H} & 8 & v_{\text{HOax}} & 2 & c_{\text{Aax}} & 3 & -c_{90} \\
\text{X} & 1 & c_{\text{Rax}} & 6 & c_{\text{Aax}} & 2 & c_{0} \\
\text{O} & 11 & c_{\text{Req}} & 1 & c_{90} & 3 & c_{0} \\
\text{H} & 12 & c_{\text{HOeq}} & 11 & c_{\text{Aeq}} & 1 & c_{90} \\
\text{H} & 12 & c_{\text{HOeq}} & 11 & c_{\text{Aeq}} & 1 & -c_{90} \\
\text{O} & 11 & c_{\text{Req}} & 1 & c_{90} & 3 & c_{120} \\
\text{H} & 15 & c_{\text{HOeq}} & 11 & c_{\text{Aeq}} & 1 & c_{90} \\
\text{H} & 15 & c_{\text{HOeq}} & 11 & c_{\text{Aeq}} & 1 & -c_{90} \\
\text{O} & 11 & c_{\text{Req}} & 1 & c_{90} & 3 & -c_{120} \\
\text{H} & 18 & c_{\text{HOeq}} & 11 & c_{\text{Aeq}} & 1 & c_{90} \\
\text{H} & 18 & c_{\text{HOeq}} & 11 & c_{\text{Aeq}} & 1 & -c_{90} \\
\end{array}
\]

Variables:
\[
v_{\text{CO}} 1.56677 \\
v_{\text{CH}} 1.08504 \\
v_{\text{HCax}} 102.0
\]

Constants:
\[
c_{\text{OO}} 4.08 \quad \text{! this is } r_{ax} \times 2 \\
c_{\text{Rax}} 2.04 \quad \text{! this is } r_{ax} \text{ in the paper} \\
c_{\text{Req}} 3.0 \quad \text{! this is } r_{eq} \text{ in the paper} \\
c_{\text{HOax}} 0.96469 \\
c_{\text{Aax}} 125.361 \\
c_{\text{HOeq}} 0.96596 \\
c_{\text{Aeq}} 127.723 \\
c_{0} 0.0 \\
c_{90} 90.0 \\
c_{120} 120.0
\]
**Table S4.** Optimised parameters for cage reactant structures.

| RaX / Å | Req / Å | CH / Å | HoAx / Å | CoHax / ° | HoEq / Å | CoHeq / ° | HCoAx / ° |
|---------|---------|--------|----------|-----------|----------|-----------|-----------|
| 2.04    | 3.0     | 1.08609 | 0.96469  | 125.361   | 0.96596  | 127.723   | 102.249   |
|         | 3.5     | 1.09039 | 0.96469  | 125.361   | 0.96596  | 127.723   | 102.825   |
|         | 3.75    | 1.09010 | 0.96469  | 125.361   | 0.96596  | 127.723   | 103.174   |
|         | 4.0     | 1.08959 | 0.96469  | 125.361   | 0.96596  | 127.723   | 103.428   |
| 2.525   | 3.0     | 1.09287 | 0.96469  | 125.361   | 0.96596  | 127.723   | 103.831   |
|         | 3.5     | 1.09420 | 0.96469  | 125.361   | 0.96596  | 127.723   | 104.185   |
|         | 3.75    | 1.09359 | 0.96469  | 125.361   | 0.96596  | 127.723   | 104.375   |
|         | 4.0     | 1.09289 | 0.96469  | 125.361   | 0.96596  | 127.723   | 104.552   |
| 3.0     | 3.0     | 1.09513 | 0.96469  | 125.361   | 0.96596  | 127.723   | 104.472   |
|         | 3.5     | 1.09452 | 0.96469  | 125.361   | 0.96596  | 127.723   | 104.631   |
|         | 3.75    | 1.09384 | 0.96469  | 125.361   | 0.96596  | 127.723   | 104.713   |
|         | 4.0     | 1.09322 | 0.96469  | 125.361   | 0.96596  | 127.723   | 104.811   |

**Note on Table S4:**
The main text refers to values of $r_{ax} = 2.0$, 2.5 and 3.0 Å. In fact the precise values used in this study were $r_{ax} = 2.04$, 2.525 and 3.0 Å. The former two values are a legacy from an earlier published study on methyl cation within a continuum solvation model: $^{10}$ 2.04 Å is the PCM default radius for a carbon atom within the UFF cavity model, and 2.525 Å is the default radius for a CH$_3$ group within the UA0 cavity model.
Table S5. B3LYP/aug-cc-pVDZ optimised energies for RS and TS structures (total energies in hartree, relative energies in kJ mol\(^{-1}\)).

| \(r_{\text{eq}} / \text{Å}\) | \(r_{\text{ax}} / \text{Å}\) | 3.0 | 3.5 | 3.75 | 4.0 | \(\infty\) |
|-----------------|----------------|-----|-----|------|-----|--------|
| 2.04            | \(E_{\text{RS}}\) | -421.86098 | -421.86284 | -421.85963 | -421.85637 | -192.49373 |
|                 | \(E_{\text{TS}}\) | -421.85431 | -421.85515 | -421.85132 | -421.84755 | -192.48296 |
|                 | \(\Delta E^\ddagger\) | 17.5 | 20.2 | 21.8 | 23.2 | 28.3   |
| 2.525           | \(E_{\text{RS}}\) | -421.85795 | -421.85585 | -421.85265 | -421.84965 | -192.48948 |
|                 | \(E_{\text{TS}}\) | -421.83256 | -421.82884 | -421.82388 | -421.81939 | -192.45370 |
|                 | \(\Delta E^\ddagger\) | 66.6 | 70.9 | 75.5 | 79.4 | 93.9   |
| 3.0             | \(E_{\text{RS}}\) | -421.85239 | -421.84793 | -421.84511 | -421.84261 | -192.48528 |
|                 | \(E_{\text{TS}}\) | -421.81262 | -421.80504 | -421.79898 | -421.79371 | -192.42612 |
|                 | \(\Delta E^\ddagger\) | 104 | 113 | 121 | 128 | 155   |

Notes on Table S5:

\(\Delta E^\ddagger\) is the barrier height for methyl transfer between axial waters within the constrained cage, either with the three equatorial waters present (\(r_{\text{eq}} = 3.0, 3.5, 3.75\) and 4.0 Å) or without them (\(r_{\text{eq}} = \infty\)). On the one hand, the value of this barrier increases steeply as the methyl-transfer distance (\(= 2 \times r_{\text{ax}}\)) increases; this may be rationalized simply in terms of the Principle of Least Nuclear Motion, as has been noted previously.\(^{11}\) On the other hand, the value of this barrier decreases as the CH…O distance (\(r_{\text{eq}}\)) decreases. This reflects a differential between the RS and TS energies for interaction between the each of the symmetric axial structures \([\text{H}_2\text{O}…\text{CH}_3^+…\text{OH}_2]\) and the three equatorial water molecules which serves to stabilize the TS more effectively for shorter, stronger CH…O hydrogen-bonding interactions. (These interactions give rise to catalysis within the constrained cage model.)
Table S6. Vibrational wavenumbers (cm$^{-1}$) for symmetric and *antisymmetric* (italics) axial C-O bond stretching in transition structures of methyl cation in constrained water cages.

| $r_{ax}$ / Å  | $r_{eq}$ / Å |
|----------------|---------------|
|               | 3.0           | 3.5           | 3.75          | 4.0           | $\infty$ |
| CH$_3$ CD$_3$  | 258           | 260           | 259           | 260           | 263       | 262       |
| CH$_3$ CD$_3$  | 357           | 355           | 363           | 361           | 367       | 366       |
| CH$_3$ CD$_3$  | 82            | 85            | 84            | 83            | 78        | 78        |
| CH$_3$ CD$_3$  | 258           | 259           | 273           | 264           | 276       | 267       |
| CH$_3$ CD$_3$  | 92            | 98            | 99            | 99            | 97        | 97        |
| CH$_3$ CD$_3$  | 190           | 181           | 197           | 188           | 202       | 192       |
| CH$_3$ CD$_3$  | 264           | 257           | 279           | 273           | 286       | 280       |
| CH$_3$ CD$_3$  | 291           | 285           |

**Superheavy cage** (all H atoms of “water” molecules have mass = 999):

| $r_{ax}$ / Å  | $r_{eq}$ / Å |
|----------------|---------------|
| 2.04           | 22            | 22            | 22            | 22            | 22        |
| A              | 264           | 257           | 279           | 273           | 286       | 280       |
| A              | 291           | 285           |

**Notes on Table S6:**

The antisymmetric stretching mode is the reaction-coordinate mode (or transition vector) for methyl transfer within the cage. Its frequency is imaginary (as expected) in all cases. Replacement of protium in CH$_3$ by deuterium in CD$_3$ leads to a diminution in magnitude of this frequency (as expected). An increase either in the value of $r_{eq}$ for a particular value of $r_{ax}$ or in the value of $r_{ax}$ for a particular value of $r_{eq}$ leads to an increase in the magnitude of this frequency, consistent with an increase in the barrier height $\Delta E^\dagger$ for methyl transfer (see Table S5).

The symmetric stretching frequency is insensitive to isotopic substitution in the methyl group because atomic motions of these atoms do not contribute to this normal mode of vibration. This frequency has a real value for $r_{ax} = 2.04$ Å but is imaginary for $r_{ax} = 2.525$ and 3.0 Å. However, it is important to recognise that these symmetric structures do not correspond to stationary points on the potential energy surface for the full unconstrained system: in particular, the gradient of the energy with respect to displacement in the symmetric stretching coordinate is not zero.

In the “superheavy” cage, all frequencies are lowered and the isotopically-sensitive modes of the methyl group are decoupled from those of the cage environment.
**Table S7.** Imaginary vibrational wavenumbers (cm\(^{-1}\)) for motions of constrained cage water molecules. (Regular font correspond to the TS and **bold to the RS.**)

| \( r_{ax} \) / Å | \( r_{eq} \) / Å |
|------------------|------------------|
|                  |                  |
| 3.0              |                  |
| 3.5              |                  |
| 3.75             |                  |
| 4.0              |                  |
| \( \infty \)     |                  |
| description      | CH\(_3\) CD\(_3\) | CH\(_3\) CD\(_3\) | CH\(_3\) CD\(_3\) | CH\(_3\) CD\(_3\) | CH\(_3\) CD\(_3\) | CH\(_3\) CD\(_3\) |
| ax-wag           | 418i 417i        | 419i 418i        | 416i 415i        | 412i 411i        | 369i 368i        |
|                  | **496i 496i**    | **496i 495i**    | **495i 495i**    | **495i 494i**    | **479i 478i**    |
|                  | 403i 403i        | 408i 408i        | 406i 405i        | 403i 402i        | 363i 362i        |
|                  | **295i 295i**    | **280i 279i**    | **274i 274i**    | **269i 269i**    | **137i 137i**    |
| ax-twist         | 146i 146i        | 122i 122i        | 113i 113i        | 105i 105i        | 82i 82i          |
|                  | **393i 393i**    | **422i 422i**    | **431i 431i**    | **438i 438i**    | **384i 364i**    |
| ax-twist         | 107i 107i        | 92i 92i          | 88i 88i          | 83i 83i          | 69i 62i          |
|                  | **54i 53i**      | **34i 34i**      | **48i 47i**      | **48i 47i**      | **48i 47i**      |
| ax-transln.      | 56i 55i          | 34i 34i          | 48i 47i          | 48i 47i          | 48i 47i          |
|                  | **61i 60i**      | **16i 16i**      | **35i 35i**      | **48i 47i**      | **48i 47i**      |
| eq-wag           | 38i 38i          | 27i 27i          | 42i 41i          | 48i 47i          | **48i 47i**      |
|                  | **39i 39i**      | **26i 26i**      | **40i 39i**      | **40i 39i**      | **40i 39i**      |
| eq-scissor        | 36i 34i          | 18i 18i          | 35i 35i          | 35i 35i          | 35i 35i          |
|                  | **34i 34i**      | **20i 20i**      | **34i 34i**      | **34i 34i**      | **34i 34i**      |
| flexing          | 32i 32i          | **22i 22i**      | **44i 44i**      | **46i 45i**      | **50i 50i**      |
| rotation         |                  |                  |                  |                  | **4i 4i**        |
| MI               | 21.44705286      | 21.48090880      | 21.50631983      | 21.50631983      | 21.50631983      |
| VP               | 21.45034410      | 21.48382664      | 21.49737106      | 21.50892768      | 21.50892768      |
| 16.25090291      | 21.44705287      | 21.48090880      | 21.49458279      | 21.50631972      | 21.50631972      |
| 16.32865153      | **21.45034411**  | **21.48382704**  | **21.49737148**  | **21.50892671**  | **21.50892671**  |

*Continued on next page...*
| $r_{ax}$ / Å | $r_{eq}$ / Å |
|--------------|--------------|
| 3.0          | 3.5          | 3.75        | 4.0  | $\infty$ |
| $\text{CH}_3$ | $\text{CD}_3$ | $\text{CH}_3$ | $\text{CD}_3$ | $\text{CH}_3$ | $\text{CD}_3$ | $\text{CH}_3$ | $\text{CD}_3$ |

| description | $\text{CH}_3$ | $\text{CD}_3$ | $\text{CH}_3$ | $\text{CD}_3$ | $\text{CH}_3$ | $\text{CD}_3$ | $\text{CH}_3$ | $\text{CD}_3$ |
|-------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| 2.525       | 348i 347i      | 384i 383i      | 394i 392i      | 399i 398i      | 390i 389i      | $\text{ax-wag}$ | $\text{ax-wag}$ | $\text{ax-wag}$ |
|             | 500i 499i      | 502i 501i      | 502i 501i      | 502i 501i      | 482i 481i      | $\text{ax-wag}$ | $\text{ax-wag}$ | $\text{ax-wag}$ |
|             | 342i 341i      | 380i 380i      | 389i 388i      | 394i 393i      | 376i 374i      | $\text{ax-twist}$ | $\text{ax-twist}$ | $\text{ax-twist}$ |
|             | 303i 303i      | 298i 298i      | 296i 296i      | 294i 294i      | 191i 191i      | $\text{eq-twist}$ | $\text{eq-twist}$ | $\text{eq-twist}$ |
|             | 123i 123i      | 101i 101i      | 93i 93i        | 85i 86i        | 60i 60i        | $\text{sym-stretch}$ | $\text{sym-stretch}$ | $\text{sym-stretch}$ |
|             | 48i 47i        | 48i 47i        | 48i 47i        | 48i 47i        | 48i 47i        | $\text{eq-stretch}$ | $\text{eq-stretch}$ | $\text{eq-stretch}$ |
|             | 85i 85i        | 72i 72i        | 70i 69i        | 68i 67i        | 43i 38i        | $\text{eq-stretch}$ | $\text{eq-stretch}$ | $\text{eq-stretch}$ |
|             | 416i 416i      | 442i 442i      | 451i 451i      | 457i 457i      | 402i 381i      | $\text{eq-stretch}$ | $\text{eq-stretch}$ | $\text{eq-stretch}$ |
|             | 73i 73i        | 34i 34i        | 60i 56i        | 56i 50i        | $\text{sym-stretch}$ | $\text{sym-stretch}$ | $\text{sym-stretch}$ | $\text{sym-stretch}$ |
|             | 57i 57i        | 54i 53i        | 54i 53i        | 51i 50i        | $\text{eq-stretch}$ | $\text{eq-stretch}$ | $\text{eq-stretch}$ | $\text{eq-stretch}$ |
|             | 52i 52i        | 59i 58i        | 48i 47i        | 51i 50i        | $\text{eq-stretch}$ | $\text{eq-stretch}$ | $\text{eq-stretch}$ | $\text{eq-stretch}$ |
|             | 49i 48i        | 54i 53i        | 46i 45i        | 45i 44i        | $\text{eq-stretch}$ | $\text{eq-stretch}$ | $\text{eq-stretch}$ | $\text{eq-stretch}$ |
|             | 29i 29i        | 40i 40i        | 28i 30i        | 39i 39i        | $\text{eq-stretch}$ | $\text{eq-stretch}$ | $\text{eq-stretch}$ | $\text{eq-stretch}$ |
| MI          | 21.45869210    | 21.48940694    | 21.50172858    | 21.51231609    | $\text{MI}$ | $\text{MI}$ | $\text{MI}$ | $\text{MI}$ |
| VP          | 21.45869201    | 21.48940646    | 21.50172858    | 21.51231604    | $\text{VP}$ | $\text{VP}$ | $\text{VP}$ | $\text{VP}$ |
|             | 21.43062013    | 21.46510757    | 21.47885354    | 21.49083006    | $\text{VP}$ | $\text{VP}$ | $\text{VP}$ | $\text{VP}$ |
|             | 21.43062012    | 21.46511162    | 21.47898918    | 21.49082882    | $\text{VP}$ | $\text{VP}$ | $\text{VP}$ | $\text{VP}$ |

Continued on next page...
Table S7, continued

| $r_{ax}$ / Å | $r_{eq}$ / Å |
|--------------|--------------|
|              | 3.0          | 3.5          | 3.75         | 4.0          | $\infty$   |
| description  | CH$_3$ CD$_3$| CH$_3$ CD$_3$| CH$_3$ CD$_3$| CH$_3$ CD$_3$| CH$_3$ CD$_3$| CH$_3$ CD$_3$|
| 3.0 wag      | 234i 233i   | 311i 310i    | 339i 336i    | 357i 356i    | 416i 415i   |
|              | 500i 499i   | 501i 501i    | 502i 501i    | 502i 501i    | 480i 497i   |
| wag          | 227i 227i   | 309i 309i    | 335i 335i    | 354i 353i    | 411i 408i   |
|              | 308i 308i   | 307i 307i    | 306i 306i    | 305i 305i    | 218i 218i   |
| twist        | 105i 105i   | 89i 89i      | 82i 82i      | 76i 76i      | 51i 51i     |
|              | 65i 65i     |             |             |             |             |
| twist        | 64i 63i     | 58i 58i      | 55i 55i      | 52i 52i      | 34i 31i     |
|              | 430i 429i   | 451i 451i    | 458i 458i    | 464i 464i    | 408i 386i   |
| sym-stretch  | 34i 34i     | 35i 35i      | 36i 36i      | 36i 36i      | 36i 36i     |
| eq-stretch   | 32i 32i     | 67i 66i      | 70i 68i      |             |             |
|              | 43i 43i     | 42i 39i      | 48i 47i      |             |             |
| eq-stretch   | 29i 28i     | 66i 65i      | 69i 67i      |             |             |
|              | 46i 46i     | 52i 51i      | 47i 47i      |             |             |
| eq-stretch   | 41i 41i     | 46i 46i      |             |             |             |
|              | 43i 43i     | 40i 40i      |             |             |             |
| flexing      | 29i 29i     | 16i 16i      | 16i 16i      | 17i 17i      |             |
|              | 19i 19i     |             |             |             |             |
| MI           | 21.46950873 | 21.49761555  | 21.50879727  | 21.51839000  |             |
| VP           | 21.46950873 | 21.49761553  | 21.50879728  | 21.51839001  |             |
|              | 21.38917652 | 21.42520186  | 21.43988590  | 21.45327838  |             |
|              | 16.34825736 |             |             |             |             |
|              | 21.38917704 | 21.42520188  | 21.43988594  | 21.45327900  |             |
|              | 16.34825736 |             |             |             |             |
Notes on Table S7.

Owing to the fact (mentioned above in the notes on Table S6) that neither the RS nor the TS structures correspond to stationary points on the potential energy surface for the full unconstrained system, and also because of the imposed symmetry, there are a number of additional modes associated with imaginary vibrational frequencies. Four of these are evident in the \( r_{\text{eq}} = \infty \) structures without the three equatorial waters, and involve in-phase and out-of-phase combinations of wagging and twisting of the axial water molecules. It is obvious that the CH\(_3\)OH\(_2^+\) fragment of the constrained RS structures is unstable with respect to displacement towards a pyramidalized sp\(^3\) O atom instead of the trigonal-planar geometry imposed by the constraints, and this instability is manifest in both the RS and TS cage structures. The constrained structures represent saddle points for inversion and torsion of the axial OH\(_2\) moieties. However, in practice these modes are almost insensitive to isotopic substitution in the methyl group and therefore do not affect the calculated KIEs.

In the cage structures with \( r_{\text{eq}} = 3.0, 3.5, 3.75 \) and 4.0 Å, some of the modes involving the axial waters are strongly coupled with motions of the equatorial waters and the brief descriptions given in the Table are rather approximate. Imaginary frequencies are associated with some displacements of the equatorial waters away from their constrained positions. When \( r_{\text{ax}} = 2.04 \) Å, the [H\(_2\)O…CH\(_3^+\)…OH\(_2\)] fragment has no room for lateral motion with respect to the equatorial waters, but for \( r_{\text{ax}} = 2.525 \) and 3.0 Å, combinations of CH…O hydrogen-bond stretching motions are associated with imaginary frequencies: these modes may also be considered as translations of [H\(_2\)O…CH\(_3^+\)…OH\(_2\)] within the equatorial plane. The important observation, however, is that in practice these modes are almost insensitive to isotopic substitution in the methyl group and therefore do not affect the calculated KIEs.

The quantities MI and VP represent the “masses & moments of inertia” and “vibrational product” terms appearing in eq.3. According to the Teller-Redlich Product Rule,\(^6\) these terms should be equal in value. The extent to which this is found to be true in practice provides a stern test of the correctness and internal consistency of the vibrational frequency calculations, and especially of the method employed to project out contaminating components of translation and rotation from the vibrational degrees of freedom. Inspection of the results presented in Table S7 shows agreement in all cases to the fourth decimal place, with the majority being to the seventh. This excellent agreement is achieved only if the vibrational products are evaluated by treating all the imaginary frequencies as if they were real. It also serves to confirm our view that the presence of imaginary frequencies associated with vibrational modes of the constrained water molecules does not have any material influence upon the values (or indeed the validity) of the calculated KIEs.
Table S8. B3LYP/aug-cc-pVDZ average CH-bond stretching force constants (aJ Å⁻²) for RS and TS.

| $r_{ax}$ / Å | $r_{eq}$ / Å | CH | CH | CH | CH |
|--------------|--------------|----|----|----|----|
| 3.0          | 3.0          | 5.467 | 5.496 | 5.518 | 5.540 | 5.600 |
| 3.5          | 5.620        | 5.633 | 5.654 | 5.730 |
| 3.75         | 5.633        | 5.654 | 5.730 |
| 4.0          | 5.654        | 5.730 |
| ∞            | 5.730        |

Notes on Table S8.

The environment of three methyl CH bonds within the constrained cage does not have strict 3-fold symmetry along the axial direction and so the individual CH stretching force constants are not quite equal. The values presented in the Table are averages of the individual values. For a particular value of $r_{ax}$, the value of the CH stretching force constant $F$ tends to diminish with decreasing $r_{eq}$, except for a slight upturn at $r_{eq} = 3.0$ Å for the shorter $r_{ax}$ distances. As $r_{ax}$ increases, the value of $F$ decreases for both RS and TS, but more rapidly for TS, for all values of $r_{eq}$. Consequently the difference $\Delta^\dagger$ between RS and TS changes from a positive number for $r_{ax} = 2.04$ Å (stiffer bond in TS) to a negative number for $r_{ax} = 2.525$ and 3.0 Å (looser bond in TS). The double difference $\Delta\Delta^\dagger$ (between $\Delta^\dagger$ values for each $r_{eq}$ distance and $r_{eq} = \infty$) becomes more negative, monotonically, as $r_{eq}$ decreases.
**Table S9.** B3LYP/aug-cc-pVDZ isotopic partition function ratios, $2^\circ \alpha$-D$_3$ isotope effects for transfer of methyl cation from vacuum to the center of the constrained water cage with $r_{eq} = 3.0$ Å at 298 K and isotope effect factors.

| $f_{\text{vacuum}}$(Me$^+$) | 20823 |
|--------------------------------|------|
| $r_{ax}$ / Å  | $f_{\text{complex}}$ | KIE | MMI | EXC | ZPE |
|----------------|----------------|-----|-----|-----|-----|
| 2.04           | 69189        | 0.301 | 3.536 | 0.727 | 0.117 |
| 2.525          | 32891        | 0.633 | 3.538 | 0.669 | 0.269 |
| 3.0            | 24213        | 0.860 | 3.540 | 0.607 | 0.401 |

**Notes on Table S9**

All hydrogen atoms have mass $m_H = 1$. Because each complex with the methyl cation in the center of the cage is a TS, these isotope effects are KIEs which include the quantum correction to the isotopic sensitivity of the transition frequency for methyl transfer. The normal MMI factor is almost constant. The inverse EXC and ZPE factors show opposite trends, but the latter dominates and is primarily responsible for the trend for a larger (more inverse) isotope effect with decreasing $r_{ax}$ distance.
Table S10. B3LYP/aug-cc-pVDZ isotopic partition function ratios, $2^\circ$ $\alpha$-D$_3$ isotope effects for insertion of symmetric axial structures [H$_2$O…CH$_3^+$…OH$_2$] from vacuum to the center of the constrained three-water equatorial cage at 298 K and isotope effect factors.

| $r_{eq}$ / Å | $r_{ax}$ / Å | $f_{\text{complex}}$ | EIE   | MMI   | EXC   | ZPE   |
|--------------|--------------|----------------------|-------|-------|-------|-------|
| 3.0          | 2.04         | 69189                | 0.844 | 1.320 | 0.909 | 0.702 |
| 2.525        | 32891        | 0.931                | 1.319 | 0.976 | 0.723 |
| 3.0          | 24213        | 0.993                | 1.319 | 1.039 | 0.724 |
| 3.5          | 2.04         | 61558                | 0.948 | 1.322 | 0.888 | 0.806 |
| 2.525        | 31643        | 0.967                | 1.321 | 0.931 | 0.786 |
| 3.0          | 24366        | 0.987                | 1.321 | 0.980 | 0.762 |
| 3.75         | 2.04         | 59969                | 0.974 | 1.323 | 0.866 | 0.848 |
| 2.525        | 31074        | 0.985                | 1.321 | 0.900 | 0.828 |
| 3.0          | 24172        | 0.995                | 1.321 | 0.941 | 0.800 |
| 4.0          | 2.04         | 59233                | 0.986 | 1.323 | 0.846 | 0.878 |
| 2.525        | 30790        | 0.994                | 1.322 | 0.873 | 0.861 |
| 3.0          | 24046        | 1.000                | 1.322 | 0.904 | 0.837 |
| $\infty$     | 2.04         | 58381                |       |       |       |       |
| 2.525        | 30608        |                      |       |       |       |       |
| 3.0          | 24052        |                      |       |       |       |       |

Notes on Table S10

All hydrogen atoms have mass $m_H = 1$. Because each symmetric axial structure [H$_2$O…CH$_3^+$…OH$_2$] is a TS both with and without the equatorial waters, each isotope effect for transfer into the cage is an EIE. However, the IPFR ($f_{\text{complex}}$) for each structure includes a quantum correction on the transition frequency for methyl transfer which (approximately) cancels in the ratio EIE = $f(\infty)$ / $f(r_{eq})$. The normal MMI factor is almost constant. For each value of $r_{ax}$ the EXC becomes less inverse as $r_{eq}$ decreases but the ZPE factor becomes more inverse and dominates the trend in the EIE. Some of these data are presented graphically in Figure 2 of the paper.
**Table S11.** B3LYP/aug-cc-pVDZ isotopic partition function ratios and factors for RS and TS, and KIEs, for methyl transfer within a constrained superheavy cage with \( r_{\text{ax}} = 2.04 \text{ Å}. \)

|       | RS \( r_{\text{eq}} / \text{Å} \) |       | TS \( r_{\text{eq}} / \text{Å} \) |       | KIE \( r_{\text{eq}} / \text{Å} \) |
|-------|---------------------------------|-------|---------------------------------|-------|---------------------------------|
|       | 3.0 | 3.5 | 3.75 | 4.0 | 3.0 | 3.5 | 3.75 | 4.0 | 3.0 | 3.5 | 3.75 | 4.0 |
| \( D_3 \) | | | | | | | | | | | | |
| IPFR  | 274385 | 23668 | 22907 | 22359 | 23617 | 20761 | 20183 | 19944 | 1.160 | 1.140 | 1.135 | 1.121 |
| QC     | 0.336 | 0.332 | 0.331 | 0.331 | 0.347 | 0.342 | 0.342 | 0.342 | 0.969 | 0.969 | 0.968 | 0.969 |
| MMI    | 1.466 | 1.502 | 1.545 | 1.566 | 1.385 | 1.426 | 1.461 | 1.496 | 1.058 | 1.053 | 1.057 | 1.047 |
| ZPE    | 55581 | 47517 | 44835 | 43132 | 49343 | 42669 | 40561 | 39166 | 1.126 | 1.114 | 1.105 | 1.101 |
| \( T_3 \) | | | | | | | | | | | | |
| IPFR  | 4534493 | 3728891 | 3574577 | 3459265 | 3526567 | 2975164 | 2869461 | 2827638 | 1.126 | 1.235 | 1.267 | 1.223 |
| QC     | 0.352 | 0.350 | 0.349 | 0.358 | 0.357 | 0.355 | 0.355 | 0.355 | 0.985 | 0.985 | 0.984 | 1.008 |
| MMI    | 2.010 | 2.101 | 2.196 | 2.234 | 1.836 | 1.933 | 2.009 | 2.082 | 1.095 | 1.087 | 1.093 | 1.073 |
| ZPE    | 6411169 | 5077315 | 4660873 | 4341584 | 5409525 | 4362471 | 4051919 | 3852361 | 1.185 | 1.164 | 1.150 | 1.127 |
| \(^{13}\text{C}\) | | | | | | | | | | | | |
| IPFR  | 1.258 | 1.256 | 1.257 | 1.258 | 1.187 | 1.182 | 1.181 | 1.180 | 1.060 | 1.064 | 1.065 | 1.066 |
| QC     | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 |
| MMI    | 1.000 | 1.000 | 1.053 | 1.054 | 1.030 | 1.036 | 1.037 | 1.037 | 1.015 | 1.015 | 1.015 | 1.016 |
| ZPE    | 1.204 | 1.194 | 1.194 | 1.194 | 1.158 | 1.147 | 1.145 | 1.145 | 1.039 | 1.042 | 1.042 | 1.043 |
| \(^{14}\text{C}\) | | | | | | | | | | | | |
| IPFR  | 1.545 | 1.540 | 1.542 | 1.540 | 1.383 | 1.371 | 1.369 | 1.368 | 1.117 | 1.123 | 1.126 | 1.126 |
| QC     | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 |
| MMI    | 1.091 | 1.104 | 1.107 | 1.105 | 1.060 | 1.072 | 1.074 | 1.074 | 1.029 | 1.029 | 1.030 | 1.028 |
| ZPE    | 1.416 | 1.395 | 1.393 | 1.393 | 1.317 | 1.292 | 1.288 | 1.288 | 1.075 | 1.080 | 1.081 | 1.082 |
Notes on Table S11.

Hydrogen atoms on “water” molecules have mass $m_H = 999$; hydrogen atoms on methyl group have $m_H = 1$. Quantum corrections on transition frequencies are included in the IPFRs for TSs. The quantum corrections (QC) on the KIEs are all very close to unity, indicating the relative insignificance of tunneling in these model methyl transfer reactions. Some of these data are presented graphically in Figure 3 of the paper.