**Supplementary Material**

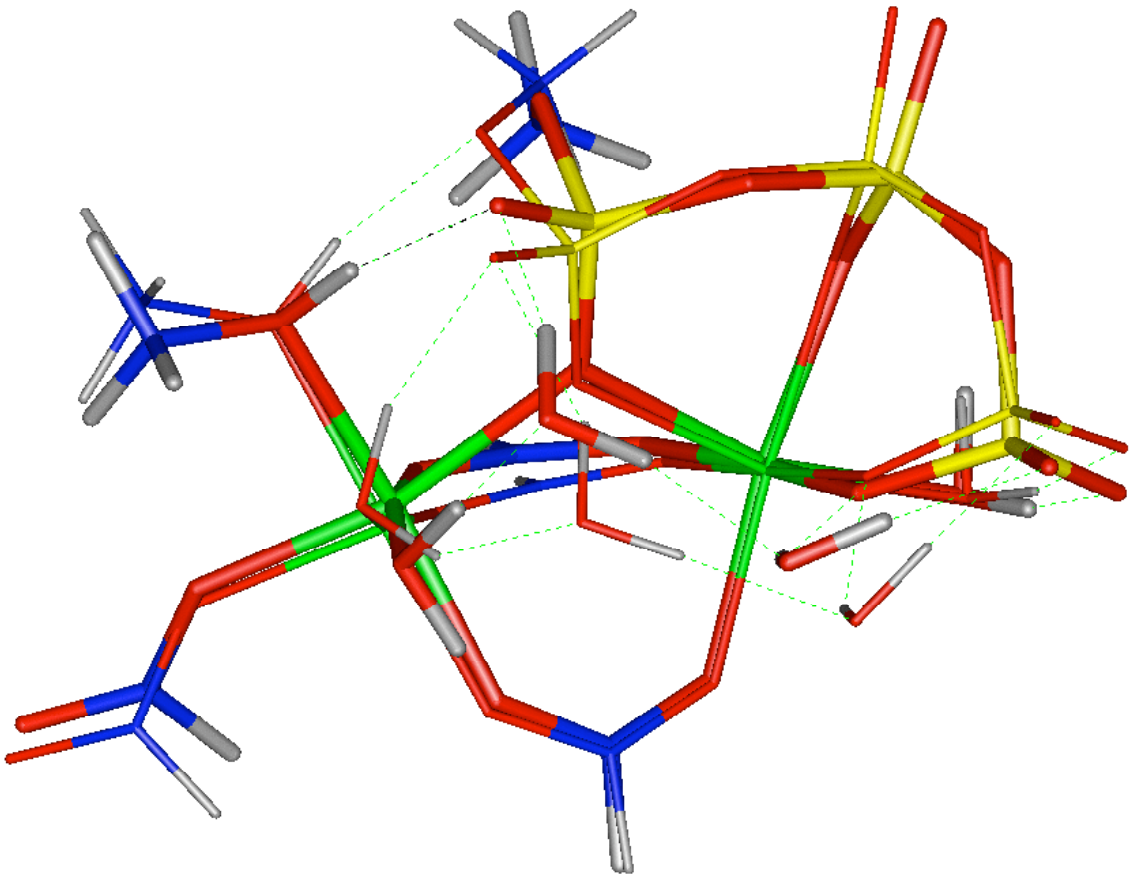


**Figure S1.** Overlap of **A** (thinner lines) and **B** (thicker lines).

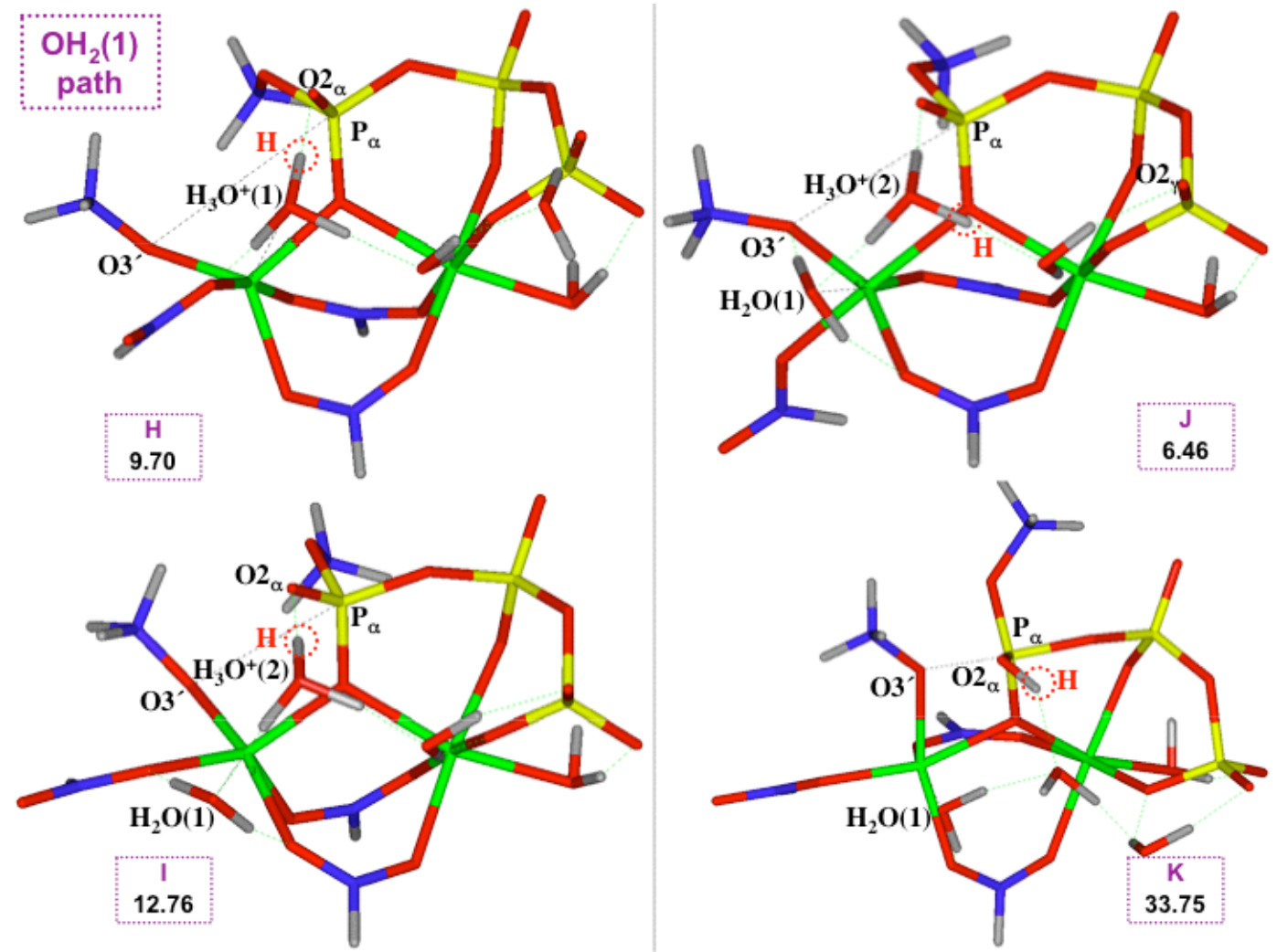



**Figure S2.** Intermediates on the $OH_2(1)$ pathway. Hydrogen bonds are the dashed green lines. Energies (in kcal/mol) are given at the B3LYP/6-31G(d,p) with respect to **A**.

**Table S1a**. Relative energies (kcal/mol) of the main intermediates (with two unbound waters) at different levels of theory and with different basis sets: HF/6–31G, B3LYP/6–31G.

| Molecule | Functional/Basis set | | | |
|---|---|---|---|---|
| | B3LYP | | HF | |
| | *6-31G(d,p) – G03* | *6-31G – G98* | *6-31G(d,p) – G03 (G98)* | *6-31G – G98* |
| A | **0.00** | ***0.00*** | **0.00 (0.00)** | **0.00** |
| B | **-0.87** | ***-1.11*** | **1.80 (1.83)** | **1.24** |
| C | **28.16** | ***12.14*** | **35.49 (35.30)** | **13.22** |
| D | **5.83** | ***2.21*** | **5.73 (5.73)** | **6.29** |
| E | **4.83** | ***6.00*** | **5.12 (5.11)** | **1.90** |
| F | **10.46** *(11.29*)* | *11.40** | **6.81 (9.87)** | **11.78** |
| G | **7.12** *(8.39*)* | *19.80** | **6.01 (7.47)** | **0.17** |

G03 – Gaussian 03
G98 – Gaussian 98
* no ZPE correction

**Table S1b**. Relative energies (kcal/mol) of the main intermediates at different levels of theory: HF/6–31G, B3LYP/6–31G.

| # | Molecule | ΔE(kcal/mol) HF/6–31G | ΔE(kcal/mol) B3LYP/6–31G |
|---|---|---|---|
| 1 | **A** | 0.00 (–1.24) | 0.00 |
| 2 | **B** | 1.24 (0.00) | -1.11 |
| 3 | **C** | 13.22 (11.98) | 12.14 |
| 4 | **F** | 0.17 (–1.07) | 10.35 **(–34.7cm$^{-1}$) /11.40**** |
| 5 | **G** | 11.78 (10.54) | 19.80** |
| 6 | **D** | 1.90 (0.66) | 2.21 |
| 7 | **E** | 6.29 (5.05) | 6.00 |
| 1 | **A–no water** | 0.00 (–1.49) | 0.00 |
| 2 | **B–no water** | 1.49 (0.00) | 0.66 |
| 3 | **C–no water** | 13.90 (12.41) | 16.12 |
| 4 | **F–no water** | –9.82 (–11.21) | –0.33 |
| 5 | **G–no water** | 7.42 (5.93) | * |
| 6 | **D–no water** | 4.95 (4.46) | 6.22 |
| 7 | **E–no water** | 11.90 (10.41) | 12.99 |

* not converged. ** no ZPE.

**Table S2.** Relative energies, at the B3LYP/6-31G(d,p) level, in kcal/mol, along with a brief description of the key structural changes that occur to the complexes with two unbound waters (**A**, **B**, **C**), when the proton is moved from O3´ to O(D256–0), O(D256–90), O(D190) and O(D192) (alternative mechanisms).

| Molecule | O3´ | O(256–0) | O(256–90) | O(190) | O(192) |
|---|---|---|---|---|---|
| **A** | **0.00** | *33.37** D256–$H^+$•••H($CH_3$)–O3´ Clash of hydrogen atoms. D256-H leaves $Mg^{2+}_{cat}$ | *27.97** D256-$H^+$ leaves $Mg^{2+}_{cat}$, and has no significant interactions with other residues | *33.43** D256–$H^+$•••D190. D256-$H^+$ leaves $Mg^{2+}_{cat}$ | *14.36** D256–$H^+$•••D192. D256-$H^+$ leaves $Mg^{2+}_{cat}$ |
| **B** | **-0.87** | **–3.92** D256–$H^+$•••O3´ Hydrogen bond. D256-H leaves $Mg^{2+}_{cat}$ | **25.90** D256 and $H_2O$ leave $Mg^{2+}_{cat}$ | **6.87** D256–$H^+$•••D190. D256-$H^+$ leaves $Mg^{2+}_{cat}$ | **15.05** D256–$H^+$•••D192. D256-$H^+$ leaves $Mg^{2+}_{cat}$ |
| **C** | **27.97** | *35.71** D256-$H^+$•••OH2(1). Both leave $Mg^{2+}_{cat}$. O3´–$P_\alpha$ bond breaks | **–4.14** D256•••$H^+$–O3´. D256 leaves $Mg^{2+}_{cat}$. O3´–$P_\alpha$ bond breaks | **8.21** D190–$H^+$•••D256. D190-$H^+$ leaves $Mg^{2+}_{cat}$. O3´–$P_\alpha$ bond breaks | **6.58** D192–$H^+$•••D256. D190-$H^+$ leaves $Mg^{2+}_{cat}$. O3´–$P_\alpha$ bond breaks |

* Not fully converged, thus no ZPE included.

**Table S3a.** Relative energies (kcal/mol) of the protonated complexes with two unbound water molecules (example: D-H$^{d}$ is the protonated complex of D, where the proton is place on the $^{d}$ site described in Figure 1), at the HF/6–31G level.

| # | File name | ΔE (kcal) |
|---|---|---|
| 1 | D–H$^{d}$ | **0.00** |
| 2 | E–H$^{d}$ | **0.00** |
| 3 | C´–H$^{d}$ | **0.05** |
| 4 | F–H$^{b}$–0 | **6.29** |
| 5 | B–H$^{b}$–0 | **9.63** |
| 6 | A–H$^{b}$–0 | **9.96** |
| 7 | F–H$^{d}$ | **10.09** |
| 8 | D–H$^{c}$ | **10.82** |
| 9 | B–H$^{b}$–90 | **11.16** |
| 10 | C˝–H$^{b}$–0 | **11.19** |
| 11 | C–H$^{d}$ | **11.86** |
| 12 | A–H$^{b}$–90 | **11.92** |
| 13 | D–H$^{b}$–90 | **12.30** |
| 14 | D–H$^{b}$–0 | **12.31** |
| 15 | F–H$^{c}$ | **13.67** |
| 16 | B–H$^{d}$ | **15.13** |
| 17 | B–H$^{a}$ | **15.91** |
| 18 | B–H$^{c}$ | **16.21** |
| 19 | A–H$^{d}$ | **16.79** |
| 20 | A–H$^{a}$ | **16.82** |
| 21 | C–H$^{b}$–0 | **17.20** |
| 22 | C´–H$^{b}$–90 | **17.20** |
| 23 | D–H$^{a}$ | **18.54** |
| 24 | A–H$^{c}$ | **18.67** |
| 25 | G–H$^{b}$–90 | **20.27** |
| 26 | C´–H$^{c}$ | **20.43** |
| 27 | G–H$^{b}$–0 | **21.02** |
| 28 | C˝–H$^{a}$ | **22.03** |
| 29 | F–H$^{b}$–90 | **23.43** |
| 30 | E–H$^{b}$–0 | **24.80** |
| 31 | C–H$^{b}$–90 | **24.86** |
| 32 | C´–H$^{b}$–0 | **24.86** |
| 33 | E–H$^{b}$–90 | **25.02** |
| 34 | C˝–H$^{d}$ | **25.29** |
| 35 | F–H$^{a}$ | **26.94** |
| 36 | C˝–H$^{c}$ | **27.87** |
| 37 | C–H$^{a}$ | **28.89** |
| 38 | E–H$^{a}$ | **29.00** |
| 39 | C´–H$^{a}$ | **29.43** |
| 40 | G–H$^{a}$ | **32.92** |
| 41 | C˝–H$^{b}$–90 | **34.29** |
| 42 | G–H$^{c}$ | **35.89** |
| 43 | C–H$^{c}$ | **100.85** |
| 44 | E–H$^{c}$ | * |
| 45 | G–H$^{d}$ | * |
| 46 | A–H$^{g}$ | **–15.00** |
| 47 | B–H$^{b}$ | **–12.90** (–33.0 cm$^{-1}$) |
| 48 | C–H$^{b}$ | **–8.84** |
| 49 | C–H$^{g}$ | **–6.06** |

* no convergence

**Table S3b.** Relative energies (kcal/mol) of the protonated complexes without unbound water molecules (example: B(no water)-H$^{c}$ is the protonated complex of B(no water), where the proton is place on the [c] site described in Figure 1), at the HF/6–31G level.

| # | File name | ΔE (kcal) |
|---|---|---|
| 1 | B(no water)–H$^{c}$ | **0.00** |
| 2 | E(no water)–H$^{c}$ | **1.07** |
| 3 | C(no water)–H$^{d}$ | **2.28** |
| 4 | C˝(no water)–H$^{c}$ | **2.45** |
| 5 | C(no water)–H$^{c}$ | **3.71** |
| 6 | C˝(no water)–H$^{d}$ | **4.55** |
| 7 | C´(no water)–H$^{d}$ | **5.88** |
| 8 | C´(no water)–H$^{c}$ | **7.89** |
| 9 | B(no water)–H$^{b}$–0 | **8.26** |
| 10 | A(no water)–H$^{c}$ | **8.50** |
| 11 | B(no water)–H$^{b}$–90 | **9.32** |
| 12 | F(no water)–H$^{c}$ | **10.26** |
| 13 | F(no water)–H$^{d}$ | **12.14** |
| 14 | G(no water)–H$^{d}$ | **14.15** |
| 15 | C(no water)–H$^{b}$–0 | **15.69** |
| 16 | B(no water)–H$^{d}$ | **16.84** |
| 17 | F(no water)–H$^{b}$–90 | **18.35** |
| 18 | G(no water)–H$^{b}$–90 | **18.80** |
| 19 | B(no water)–H$^{a}$ | **19.36** |
| 20 | F(no water)–H$^{b}$–0 | **19.61** |
| 21 | G(no water)–H$^{b}$–0 | **19.70** |
| 22 | C´(no water)–H$^{b}$–90 | **20.38** |
| 23 | C´(no water)–H$^{b}$–0 | **20.38** |
| 24 | C(no water)–H$^{b}$–90 | **20.38** |
| 25 | D(no water)–H$^{d}$ | **21.70** |
| 26 | F(no water)–H$^{a}$ | **23.28** |
| 27 | C(no water)–H$^{a}$ | **23.50** |
| 28 | G(no water)–H$^{a}$ | **24.10** |
| 29 | C´(no water)–H$^{a}$ | **24.46** |
| 30 | A(no water)–H$^{b}$–0 | **25.28** |
| 31 | G(no water)–H$^{c}$ | **25.50** |
| 32 | A(no water)–H$^{b}$–90 | **25.56** |
| 33 | D(no water)–H$^{b}$–90 | **28.98** |
| 34 | D(no water)–H$^{b}$–0 | **28.98** |
| 35 | A(no water)–H$^{d}$ | **30.21** |
| 36 | A(no water)–H$^{a}$ | **31.52** |
| 37 | D(no water)–H$^{a}$ | **35.22** |
| 38 | C˝(no water)–H$^{b}$–90 | **37.16** |
| 39 | C˝(no water)–H$^{b}$–0 | **37.16** |
| 40 | D(no water)–H$^{c}$ | **38.53** |
| 41 | C˝(no water)–H$^{a}$ | **45.21** |
| 42 | E(no water)–H$^{b}$–0 | **45.85** |
| 43 | E(no water)–H$^{b}$–90 | **46.40** |
| 44 | E(no water)–H$^{d}$ | **46.59** |
| 45 | E(no water)–H$^{a}$ | **52.38** |
| 46 | A(no water)–H$^{g}$ | **–9.35** |
| 47 | B(no water)–H$^{b}$ | **–3.80** |
| 48 | C(no water)–H$^{g}$ | **3.83** |
| 49 | C(no water)–H$^{b}$ | **17.95** |

**Table S4a.** Relative energies (kcal/mol) of the doubly protonated complexes with two unbound water molecules (example: A–$H^aH^c$ is the doubly protonated complex of A, in which protons are placed on the [a] and [c] sites described in Figure 1), at the HF/6–31G level.

| # | File Name | ΔE (kcal) |
|---|---|---|
| 1 | A–$H^aH^c$ | **27.49** |
| 2 | A–$H^{b(0)}H^c$ | **24.26** |
| | | |
| 3 | B–$H^aH^c$ | **20.51** |
| 4 | B–$H^{b(0)}H^c$ | **58.19** |
| | | |
| 5 | C´–$H^aH^c$ | **15.58** |
| 6 | C´–$H^{b(0)}H^c$ | **36.37** |
| | | |
| 7 | D–$H^aH^c$ | **8.64** |
| 8 | D–$H^{b(0)}H^c$ | **0.00** |
| | | |
| 9 | E–$H^aH^c$ | **8.65** |
| 10 | E–$H^{b(0)}H^c$ | **13.88** |
| | | |
| 11 | C–$H^aH^c$ | * |
| 12 | C–$H^{b(0)}H^c$ | **36.36** |
| | | |
| 13 | F–$H^aH^c$ | **33.58** |
| 14 | F–$H^{b(0)}H^c$ | **27.17** |
| | | |
| 15 | G–$H^aH^c$ | **30.33** |
| 16 | G–$H^{b(0)}H^c$ | **26.99** |
| | | |
| 17 | C˝–$H^aH^c$ | * |
| 18 | C˝–$H^{b(0)}H^c$ | **8.60** |

* no convergence

**Table S4b.** Relative energies (kcal/mol) of the doubly protonated complexes with two unbound water molecules (example: A(no water)–$H^aH^c$ is the doubly protonated complex of A(no water), in which protons are placed on the [a] and [c] sites described in Figure 1), at the HF/6–31G level.

| # | File Name | ΔE (kcal) |
|---|---|---|
| 1 | A(no water)–$H^aH^c$ | **14.18** |
| 2 | A(no water)–$H^{b(0)}H^c$ | **16.75** |
| | | |
| 3 | F(no water)–$H^aH^c$ | **44.40** |
| 4 | F(no water)–$H^{b(0)}H^c$ | **29.09** |
| | | |
| 5 | G(no water)–$H^aH^c$ | * |
| 6 | G(no water)–$H^{b(0)}H^c$ | * |
| | | |
| 7 | B(no water)–$H^aH^c$ | **20.54** |
| 8 | B(no water)–$H^{b(0)}H^c$ | **25.65** |
| | | |
| 9 | E(no water)–$H^aH^c$ | **25.22** |
| 10 | E(no water)–$H^{b(0)}H^c$ | **0.00** |
| | | |
| 11 | D(no water)–$H^aH^c$ | **25.01** |
| 12 | D(no water)–$H^{b(0)}H^c$ | **36.12** |
| | | |
| 13 | C´(no water)–$H^aH^c$ | **8.02** |
| 14 | C´(no water)–$H^{b(0)}H^c$ | **15.70** |
| | | |
| 15 | C˝(no water)–$H^aH^c$ | **23.71** |
| 16 | C˝(no water)–$H^{b(0)}H^c$ | **46.63** |
| | | |
| 17 | C(no water)–$H^aH^c$ | **24.06** |
| 18 | C(no water)–$H^{b(0)}H^c$ | **17.71** |

* no convergence

**Table S5a.** Relative energies on the B–A pathway. The dihedral angle $P_{\alpha}$–$O1_{\alpha}$–$Mg_{cat}$–O3´ was varied in 24 steps, to capture the B–A transformation, using the B3LYP/6-31G(d,p) method.

| Point | E(kcal/mol) |
|---|---|
| B | -0.93 |
| 1 | -0.96 |
| 2 | -0.88 |
| 3 | -0.81 |
| 4 | -0.73 |
| 5 | -0.63 |
| 6 | -0.50 |
| 7 | -0.37 |
| 8 | -0.21 |
| 9 | -0.04 |
| 10 | 0.15 |
| 11 | 0.36 |
| 12 | 0.58 |
| 13 | 0.82 |
| 14 | 1.08 |
| 15 | 1.35 |
| 16 | 1.64 |
| 17 | 1.95 |
| 18 | 2.28 |
| 19 | 2.62 |
| 20 | 2.13 |
| 21 | 1.67 |
| 22 | 1.13 |
| 23 | 0.55 |
| A | 0.00 |

**Graph G1a.** A–B reaction coordinate, computed using the B3LYP/6-31G(d,p) method. The dihedral angle $P_{\alpha}$–$O1_{\alpha}$–$Mg_{cat}$–O3´ has been varied.

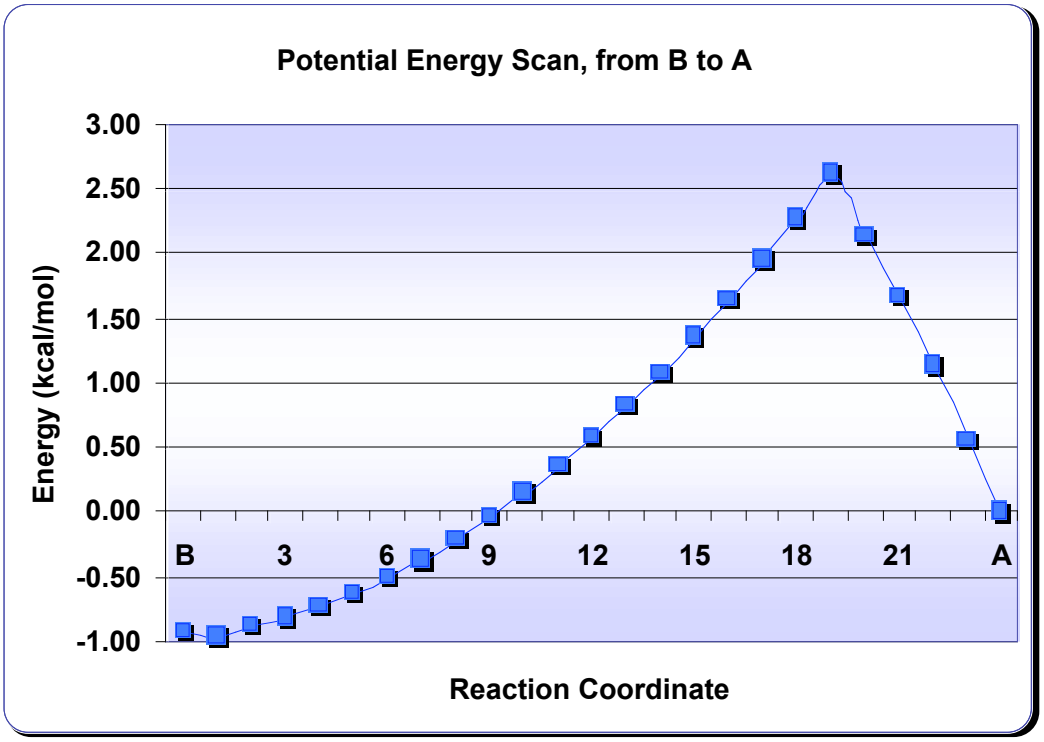
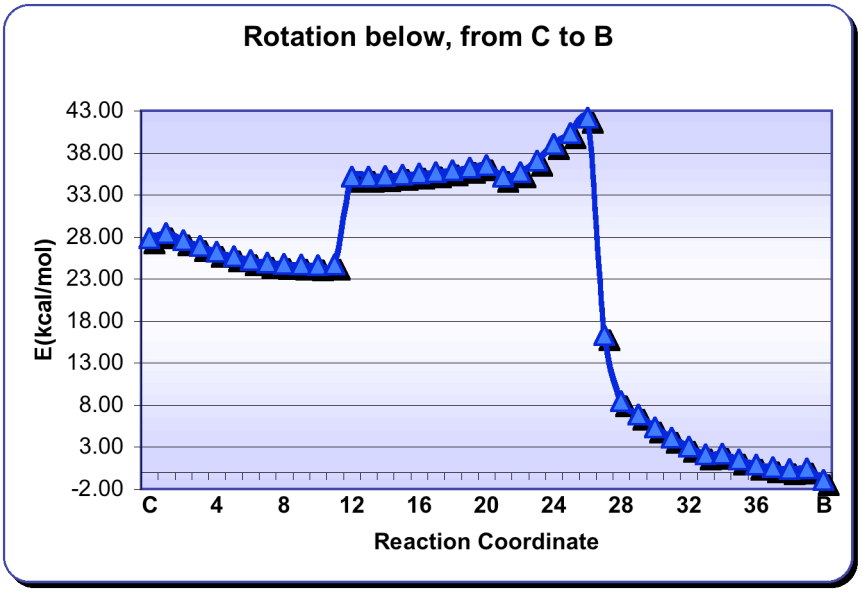


**Table S5b.** Relative energies on the C–B pathway, computed using the B3LYP/6-31G(d,p) method, performed in two steps. In series 1 (rotation above), the dihedral angle O5´–$P_\alpha$–$O2_\alpha$–H was varied from –90º to +90º, so that the proton passes on the same side with O5´, to capture the proton's rotation around the $O2_\alpha$–$P_\alpha$ bond, and the O3´–H distance was varied, to capture the proton shift from O3´ to $O2_\alpha$. In the second series (rotation below), the dihedral angle O5´–$P_\alpha$–$O2_\alpha$–H was varied from -90º to +90º, so that the proton passes on the same side with $OH_2$(2), to capture the proton's rotation around the $O2_\alpha$–$P_\alpha$ bond, and the O3´–H distance was varied, to capture the proton shift from O3´ to $O2_\alpha$.

| **Rotation above, from C to B** | |
|---|---|
| **C** | 27.84 |
| 1 | 27.94 |
| 2 | 28.27 |
| 3 | 28.80 |
| 4 | 29.50 |
| 5 | 30.36 |
| 6 | 31.36 |
| 7 | 32.46 |
| 8 | 33.64 |
| 9 | 34.85 |
| 10 | 36.08 |
| 11 | 37.28 |
| 12 | 38.40 |
| 13 | 39.43 |
| 14 | 40.34 |
| 15 | 41.13 |
| 16 | 41.77 |
| 17 | 42.26 |
| 18 | 42.83 |
| 19 | 42.81 |
| 20 | 42.85 |
| 21 | 42.76 |
| 22 | 42.56 |
| 23 | 42.24 |
| 24 | 41.82 |
| 25 | 41.32 |
| 26 | 40.75 |
| 27 | 40.14 |
| 28 | 39.49 |
| 29 | 38.83 |
| 30 | 38.15 |
| 31 | ***10.20*** |
| 32 | 8.43 |
| 33 | 6.83 |
| 34 | 5.36 |
| 35 | 4.08 |
| 36 | 3.01 |
| 37 | 2.09 |
| 38 | 2.20 |
| 39 | 1.48 |
| 40 | 0.93 |
| 41 | 0.57 |
| 42 | 0.37 |
| 43 | 0.42 |
| **B** | -0.93 |

| **Rotation below, from C to B** | |
|---|---|
| **C** | 27.84 |
| 1 | 28.45 |
| 2 | 27.62 |
| 3 | 26.90 |
| 4 | 26.26 |
| 5 | 25.71 |
| 6 | 25.26 |
| 7 | 24.95 |
| 8 | 24.75 |
| 9 | 24.66 |
| 10 | 24.65 |
| 11 | 24.68 |
| 12 | 35.12 |
| 13 | 35.15 |
| 14 | 35.23 |
| 15 | 35.34 |
| 16 | 35.50 |
| 17 | 35.70 |
| 18 | 35.93 |
| 19 | 36.19 |
| 20 | 36.48 |
| 21 | 35.12 |
| 22 | 35.65 |
| 23 | 37.07 |
| 24 | 39.06 |
| 25 | 40.34 |
| 26 | 42.17 |
| 27 | 16.33 |
| 28 | ***10.20*** |
| 29 | 8.43 |
| 30 | 6.83 |
| 31 | 5.36 |
| 32 | 4.08 |
| 33 | 3.01 |
| 34 | 2.09 |
| 35 | 2.20 |
| 36 | 1.48 |
| 37 | 0.93 |
| 38 | 0.57 |
| 39 | 0.37 |
| 40 | 0.42 |
| **B** | -0.93 |

**Graph G1b.** C–B potential energy surfaces, computed using the B3LYP/6-31G(d,p) method, performed in two steps. In series 1 (rotation above), the dihedral angle O5´–$P_\alpha$–$O2_\alpha$–H was varied from –90º to +90º, so that the proton passes on the same side with O5´, to capture the proton's rotation around the $O2_\alpha$–$P_\alpha$ bond, and the O3´–H distance was varied, to capture the proton shift from O3´ to $O2_\alpha$. In the second series (rotation below), the dihedral angle O5´–$P_\alpha$–$O2_\alpha$–H was varied from -90º to +90º, so that the proton passes on the same side with $OH_2$(2), to capture the proton's rotation around the $O2_\alpha$–$P_\alpha$ bond, and the O3´–H distance was varied, to capture the proton shift from O3´ to $O2_\alpha$.



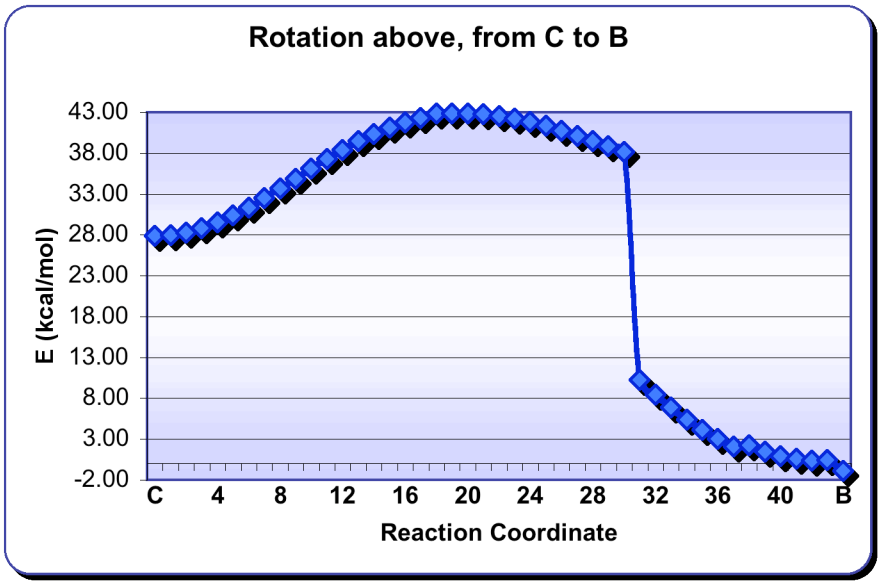



**Table S5c.** Relative energies, computed using the B3LYP/6-31G(d,p) method, on the D–C (β–) and F–C (γ–) pathways. In both series the $O2_{\beta}$–H…$O2_{\alpha}$, and $O2_{\gamma}$–H…$O2_{\alpha}$ distance, respectively, were varied, to capture the proton shift from $O2_{\beta}$ to $O2_{\alpha}$ (blue curve), and from $O2_{\gamma}$ to $O2_{\alpha}$ (green curve), respectively.

Beta Path

| | |
|---|---|
| **D** | 6.53 |
| 1 | 7.21 |
| 2 | 9.14 |
| 3 | 12.56 |
| 4 | 16.28 |
| 5 | 22.75 |
| 6 | 25.45 |
| 7 | 27.18 |
| 8 | 29.65 |
| 9 | 31.28 |
| 10 | 29.03 |
| **C** | 27.84 |

Gamma Path

| | |
|---|---|
| **F** | 11.08 |
| 1 | 12.36 |
| 2 | 15.40 |
| 3 | 19.41 |
| 5 | 23.11 |
| 6 | 26.58 |
| 7 | 29.52 |
| 8 | 31.92 |
| 9 | 33.86 |
| 10 | **37.14** |
| 11 | 35.56 |
| **C** | 27.84 |

**Graph G1c.** Relative energies, computed using the B3LYP/6-31G(d,p) method, on the D–C (β–) and F–C (γ–) pathways. In both series the $O2_{\beta}$–H…$O2_{\alpha}$, and $O2_{\gamma}$–H…$O2_{\alpha}$ distance, respectively, were varied, to capture the proton shift from $O2_{\beta}$ to $O2_{\alpha}$ (blue curve), and from $O2_{\gamma}$ to $O2_{\alpha}$ (green curve), respectively.