Chemoton 2.0: Exploration of Chemical Reaction Networks

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Supporting Information

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### S1 Test Reactions

Table S1: Reference reactions that we probed for in the test runs.

| Reaction | Ref. |
|----------|------|
| 1.1 $\text{H}_2\text{B}^-\text{NH}_2 + \text{H}_2\text{B}^-\text{NH}_2 \rightarrow \text{H}_2\text{N}^+\text{B}^-\text{NH}_2\text{H}^-\text{H}_2$ | 1, 2 |
| 1.2 $\text{H}_2\text{B}^-\text{NH}_2 + \text{H}_2\text{B}^-\text{NH}_2 \rightarrow \text{H}_3\text{N}^-\text{B}^-\text{NH}_2\text{H}^-\text{H}$ | 1, 2 |
| 1.3 $\text{H}_2\text{B}^-\text{NH}_2 + \text{H}_2\text{B}^-\text{NH}_2 \rightarrow \text{H}_2\text{N}^+\text{B}^-\text{NH}_2\text{H}^-\text{H}_2$ | 1, 2 |
| 2.1 $\text{H}_2\text{B}^-\text{NH}_2 + \text{H}_3\text{B}^-\text{NH}_3 \rightarrow \text{H}_3\text{N}^-\text{B}^-\text{NH}_2\text{H}^+\text{H}_2$ | 1, 2 |
| 2.2 $\text{H}_2\text{B}^-\text{NH}_2 + \text{H}_3\text{B}^-\text{NH}_3 \rightarrow \text{H}_2\text{B}^-\text{H}^-\text{BH}^+\text{H}_2 + \text{NH}_3$ | 1, 2 |
| 2.3 $\text{H}_2\text{B}^-\text{NH}_2 + \text{H}_3\text{B}^-\text{NH}_3 \rightarrow \text{H}_2\text{B}^-\text{NH}_2 + \text{H}_2\text{B}^-\text{NH}_2 + \text{H}_2$ | 1, 2 |
| 2.4 $\text{H}_2\text{B}^-\text{NH}_2 + \text{H}_3\text{B}^-\text{NH}_3 \rightarrow \text{H}_3\text{B}^-\text{H}^-\text{BH}^+\text{H}_2\text{NH}_3$ | 1, 2 |
| 2.5 $\text{H}_2\text{B}^-\text{NH}_2 + \text{H}_3\text{B}^-\text{NH}_3 \rightarrow \text{H}_2\text{N}^+\text{B}^-\text{NH}_2\text{H}^-\text{H}_2\text{H}^+\text{NH}_3$ | 1, 2 |
| 3.1 $\text{OH} + \text{H}_2\text{C}^-\text{O} \rightarrow \text{O}^-\text{H}^-\text{C}^-\text{OH}$ | 1, 2 |
| 3.2 $\text{OH} + \text{H}_2\text{C}^-\text{O} \rightarrow \text{H}^+\text{H}^-\text{C}^-\text{OH}$ | 1, 2 |
| 3.3 $\text{OH} + \text{H}_2\text{C}^-\text{O} \rightarrow \text{H}^-\text{C}^-\text{OH}^-\text{H}$ | 1, 2 |
| 3.4 $\text{OH} + \text{H}_2\text{C}^-\text{O} \rightarrow \text{HO}^-\text{C}^-\text{H}$ | 1, 2 |
| 3.5 $\text{OH} + \text{H}_2\text{C}^-\text{O} \rightarrow \text{HO}^-\text{C}^-\text{OH}$ | 1, 2 |
| 3.6 $\text{OH} + \text{H}_2\text{C}^-\text{O} \rightarrow \text{HO}^-\text{C}^-\text{O}$ | 1, 2 |
| 3.7 $\text{OH} + \text{H}_2\text{C}^-\text{O} \rightarrow \text{OH}^- + \text{O}=\text{C}=$ | 1, 2 |
| Equation | Reaction | References |
|----------|----------|------------|
| 3.8 | $\text{OH} + H\text{H}_2\text{O} \rightarrow \text{HO}_\text{H}_2\text{O}$ | 1, 2 |
| 3.9 | $\text{OH} + H\text{H}_2\text{O} \rightarrow \text{HO}_\text{H}_2\text{O}$ | 1, 2 |
| 4.1 | $\text{O}_\text{C}_\text{F}_3 + \text{NH}_3 \rightarrow \text{H}_2\text{N}_\text{NH}_2 + \text{HO}_\text{C}_\text{F}_3$ | 1, 2 |
| 4.2 | $\text{O}_\text{C}_\text{F}_3 + \text{NH}_3 \rightarrow \text{HO}_\text{C}_\text{F}_3 \text{NH}_2$ | 1, 2 |
| 5.1 | $\text{H} \rightarrow \text{HO}_\text{H}$ | 1, 2 |
| 6.1 | $\text{H} \rightarrow \text{H}_2 + \text{H}_2$ | 1, 2 |
| 7.1 | $\text{F}_3\text{C}_\text{F}_\text{F} \rightarrow \text{F}_3\text{C}_\text{F}_\text{F}$ | 1, 2 |
| 7.2 | $\text{F}_3\text{C}_\text{F}_\text{F} \rightarrow \text{F}_3\text{C}_\text{F}_\text{F}$ | 1, 2 |
| 8.1 | $\text{H}_\text{O} + \text{NH}_3 \rightarrow \text{H}_2\text{N}_\text{O}$ | 1, 2 |
| 8.2 | $\text{H}_\text{O} + \text{NH}_3 \rightarrow \text{HO}_\text{NH}_2$ | 1, 2 |
| 9.1 | $\text{H}_\text{O} \rightarrow \text{C}=\text{O} + \text{H}_2$ | 1, 2 |
| 10.1 | $\text{OH} \rightarrow \text{C}$ | 1, 2 |
| 10.2 | $\text{OH} \rightarrow \text{HO}$ | 1, 2 |
| 10.3 | $\text{OH} \rightarrow \text{H}_2\text{H}$ | 1, 2 |
| 10.4 | $\text{OH} \rightarrow \text{H}_3\text{C}_\text{H}_\text{H}$ | 1, 2 |
| 10.5 | $\text{OH} \rightarrow \text{H}_2\text{O} + \text{C}=\text{C}$ | 1, 2 |
| 10.6 | $\text{OH} \rightarrow \text{H}_\text{H}$ | 1, 2 |
| 11.1 | $\text{OH} + \text{H}_2\text{O} \rightarrow \text{HO}_\text{H}_2\text{O}$ | 1, 2 |
11.2 \[ \text{HO} + \text{H}_2\text{O} \rightarrow \text{H}_2\text{O} \] 1, 2

11.3 \[ \text{HO} + \text{H}_2\text{O} \rightarrow \text{HO} + \text{H}_2\text{O} \] 1, 2

11.4 \[ \text{HO} + \text{H}_2\text{O} \rightarrow \text{HO} + \text{H}_2\text{O} \] 1, 2

11.5 \[ \text{HO} + \text{H}_2\text{O} \rightarrow \text{HO} + \text{H}_2\text{O} \] 1, 2

12.1 \[ \text{HO} + \text{H}_2\text{O} \rightarrow \text{HO} \] 1, 2

12.2 \[ \text{HO} + \text{H}_2\text{O} \rightarrow \text{HO} + \text{H}_2\text{O} \] 1, 2

12.3 \[ \text{HO} + \text{H}_2\text{O} \rightarrow \text{HO} + \text{H}_2\text{O} \] 1, 2

13.1 \[ \text{NH} \rightarrow \text{H}_2\text{NH} \] 1, 2

13.2 \[ \text{NH} \rightarrow \text{H}_2\text{NH} \] 1, 2

13.3 \[ \text{NH} \rightarrow \text{H}_2\text{NH} \] 1, 2

13.4 \[ \text{NH} \rightarrow \text{H}_2\text{NH} \] 1, 2

13.5 \[ \text{NH} \rightarrow \text{H}_2\text{NH} \] 1, 2

14.1 \[ \text{P} \rightarrow \text{P} \] 1, 2

15.1 \[ \text{H} \rightarrow \text{H} \] 1, 2

16.1 \[ \text{H} + \text{H}_2\text{SiH} \rightarrow \text{H}_2\text{SiH} \] 1, 2

17.1 \[ \text{O} + \text{Cl}_2 \rightarrow \text{Cl}_2 + \text{O} \] 1, 2

18.1 \[ \text{OH} \rightarrow \text{H}_2\text{O} \] 1, 2

19.1 \[ \text{HO} + \text{H}_2\text{O} \rightarrow \text{HO} \] 1, 2

20.1 \[ \text{H} \rightarrow \text{H} \] 1, 2
\[
\begin{align*}
26.1 & \quad \text{\ce{\text{O} + HO\text{O}_2 -> OO\text{H}}} \\
26.2 & \quad \text{\ce{\text{O} + HO\text{O}_2 -> O\text{H}O\text{H}}} \\
26.3 & \quad \text{\ce{\text{O} + HO\text{O}_2 -> O\text{H}O\text{H}}} \\
27.1 & \quad \text{\ce{\text{[structures]}}} \quad \text{\ce{\text{[structures]}}} \\
27.2 & \quad \text{\ce{\text{[structures]}}} \quad \text{\ce{\text{[structures]}}} \\
28.1 & \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}} \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}} \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}}}} \\
28.2 & \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}} \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}} \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}}}} \\
28.3 & \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}} \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}} \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}}}} \\
28.4 & \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}} \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}} \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}}}} \\
28.5 & \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}} \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}} \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}}}} \\
28.6 & \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}} \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}} \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}}}} \\
28.7 & \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}} \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}} \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}}}} \\
28.8 & \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}} \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}} \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}}}} \\
28.9 & \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}} \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}} \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}}}} \\
28.10 & \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}} \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}} \quad \text{\ce{\text{H\text{O}_2\text{O}_2\text{H}}}}} \\
\end{align*}
\]
28.27 \( \text{H}_3\text{C}-\text{O}-\text{OH} \rightarrow \text{O}+\text{H}_2\text{O} \)

28.28 \( \text{H}_3\text{C}-\text{O}-\text{OH} \rightarrow \text{HO}-\text{O} \)

28.29 \( \text{H}_3\text{C}-\text{O}-\text{OH} \rightarrow \text{H}_2\text{O} \)

28.30 \( \text{H}_3\text{C}-\text{O}-\text{OH} \rightarrow \text{O}+\text{H}_2 \)

28.31 \( \text{H}_3\text{C}-\text{O}-\text{OH} \rightarrow \text{H}_2\text{O}+\text{H}_2 \)

28.32 \( \text{H}_3\text{C}-\text{O}-\text{OH} \rightarrow \text{HO}+\text{H}_2 \)

28.33 \( \text{H}_3\text{C}-\text{O}-\text{OH} \rightarrow \text{H}_2\text{O}+\text{H}_2 \)

28.34 \( \text{H}_3\text{C}-\text{O}-\text{OH} \rightarrow \text{H}_2\text{O}+\text{HO} \)

28.35 \( \text{H}_3\text{C}-\text{O}-\text{OH} \rightarrow \text{H}_2\text{O}+\text{HO} \)

28.36 \( \text{H}_3\text{C}-\text{O}-\text{OH} \rightarrow \text{H}_2\text{O}+\text{HO} \)

28.37 \( \text{H}_3\text{C}-\text{O}-\text{OH} \rightarrow \text{H}_2\text{O}+\text{HO} \)

28.38 \( \text{H}_3\text{C}-\text{O}-\text{OH} \rightarrow \text{H}_2\text{O}+\text{HO} \)

28.39 \( \text{H}_3\text{C}-\text{O}-\text{OH} \rightarrow \text{H}_2\text{O}+\text{HO} \)

28.40 \( \text{H}_3\text{C}-\text{O}-\text{OH} \rightarrow \text{H}_2\text{O}+\text{HO} \)

28.41 \( \text{H}_3\text{C}-\text{O}-\text{OH} \rightarrow \text{H}_2\text{O}+\text{HO} \)

28.42 \( \text{H}_3\text{C}-\text{O}-\text{OH} \rightarrow \text{H}_2\text{O}+\text{HO} \)
28.43  $\text{O} - \text{CH} - \text{CH} - \text{OH} \rightarrow \text{HO} - \text{O} - \text{O} - \text{C} \quad 4, 5$

28.44  $\text{O} - \text{CH} - \text{CH} - \text{OH} \rightarrow \text{O} - \text{CH} - \text{CH} - \text{OH} + \text{H}_2 \quad 4, 5$

28.45  $\text{O} - \text{CH} - \text{CH} - \text{OH} \rightarrow \text{O} - \text{CH} - \text{CH} - \text{OH} + \text{H}_2\text{O} \quad 4, 5$

28.46  $\text{O} - \text{CH} - \text{CH} - \text{OH} \rightarrow \text{O} - \text{CH} - \text{CH} - \text{OH} + \text{H}_2\text{O} \quad 4, 5$

28.47  $\text{O} - \text{CH} - \text{CH} - \text{OH} \rightarrow \text{CO} + \text{HO} - \text{O} - \text{C} \quad 4, 5$

28.48  $\text{O} - \text{CH} - \text{CH} - \text{OH} \rightarrow \text{HO} - \text{O} - \text{C} + \text{H}_2\text{O} \quad 4, 5$

28.49  $\text{O} - \text{CH} - \text{CH} - \text{OH} \rightarrow \text{HO} - \text{O} - \text{C} + \text{H}_2\text{O} \quad 4, 5$

28.50  $\text{O} - \text{CH} - \text{CH} - \text{OH} \rightarrow \text{HO} - \text{O} - \text{C} + \text{H}_2\text{O} \quad 4, 5$

28.51  $\text{O} - \text{CH} - \text{CH} - \text{OH} \rightarrow \text{HO} - \text{O} - \text{C} + \text{H}_2\text{O} \quad 4, 5$

28.52  $\text{O} - \text{CH} - \text{CH} - \text{OH} \rightarrow \text{HO} - \text{O} - \text{C} + \text{H}_2\text{O} \quad 4, 5$

28.53  $\text{O} - \text{CH} - \text{CH} - \text{OH} \rightarrow \text{HO} - \text{O} - \text{C} + \text{H}_2\text{O} \quad 4, 5$

28.54  $\text{O} - \text{CH} - \text{CH} - \text{OH} \rightarrow \text{HO} - \text{O} - \text{C} + \text{H}_2\text{O} \quad 4, 5$

29.1  $\square \rightarrow \square \quad 6$

30.1  $\square \rightarrow \square \quad 6$

31.1  $\square \rightarrow \square \quad 6$

32.1  $\square \rightarrow \square \quad 6$

33.1  $\square \rightarrow \square \quad 6$

34.1  $\square \rightarrow \square \quad 6$
35.1 \[ \text{C}_5 \text{H}_6 + \text{H} \rightarrow \text{C}_6 \text{H}_{10} \]

36.1 \[ \text{C}_5 \text{H}_6 + \text{C}_5 \text{H}_{10} \rightarrow \text{C}_{10} \text{H}_{16} \]

37.1 \[ \text{H}_3 \text{C} = \text{CH} \text{C} = \text{CH} \rightarrow \text{C}_6 \text{H}_{10} \]

38.1 \[ \text{C}_5 \text{H}_{12} \rightarrow \text{C}_6 \text{H}_{10} \]

39.1 \[ \text{SH} + \text{I} \rightarrow \text{HI} + \text{S} \]

39.2 \[ \text{SH} + \text{I} \rightarrow \text{HI} + \text{S} + \text{CH}_4 \]

39.3 \[ \text{SH} + \text{I} \rightarrow \text{I} \text{SH} + \text{CH}_4 \]

40.1 \[ \text{C}_6 \text{H}_{5} \text{OH} + \text{H}_2 \text{SO}_4 \rightarrow \text{SO} + \text{C}_6 \text{H}_{5} \text{S} \text{O} \]

40.2 \[ \text{C}_6 \text{H}_{5} \text{C} = \text{O} + \text{H}_2 \text{SO}_4 \rightarrow \text{SO} + \text{C}_6 \text{H}_{5} \text{C} = \text{O} \]

40.3 \[ \text{C}_6 \text{H}_{5} \text{C} = \text{O} + \text{H}_2 \text{SO}_4 \rightarrow \text{SO} + \text{C}_6 \text{H}_{5} \text{C} = \text{O} \]

40.4 \[ \text{C}_6 \text{H}_{5} \text{C} = \text{O} + \text{H}_2 \text{SO}_4 \rightarrow \text{SO} + \text{C}_6 \text{H}_{5} \text{C} = \text{O} \]

41.1 \[ \text{O} \text{C} - \text{C} \text{O} - \text{C} \text{O} + \text{C}_3 \text{H}_6 \text{OH} \rightarrow \text{C}_6 \text{H}_{10} \text{O} \text{C} - \text{C} \text{O} - \text{C} \text{O} \]

10
54.1 \[
\text{Cl} \quad + \quad \text{Pd} \quad \rightarrow \quad \text{Cl} \quad \text{Pd}
\]
3

55.1 \[
\text{H}_2\text{O} \quad + \quad \text{Pt} \quad \rightarrow \quad \text{Pt} \quad \text{Cl} \quad \text{H}_2\text{O}
\]
7, 8

56.1 \[
\text{H} \quad + \quad \text{Ni} \quad \rightarrow \quad \text{Ni} \quad \text{S} \quad \text{S} \quad \text{Ni}
\]
7, 9

57.1 \[
\text{H} \quad + \quad \text{Ir} \quad \rightarrow \quad \text{Ir} \quad \text{PH}_2
\]
7
S2 Detailed Exploration Settings

The molecular connectivity used for graph interpretation was determined from interatomic distances: Two atoms were considered to be bound if their distance had been below the sum of their covalent radii plus 0.4 Å. MOLASSEMBLER’s [19, 20] bond stereopermutators were instantiated on bonds that were detected based on the distance criterion and moreover had a Mayer bond order [21, 22] of more than 1.4. Additional settings used for structure optimizations of reference structures and elementary step trials are given in Table S2.

Table S2: Settings employed during structure optimizations and elementary step trial calculations. For further explanations consider the manuals and source codes of SCINE READUCT[23, 24] and PUFFIN.[25]

| Calculation Type          | Setting                      | Value                  |
|---------------------------|------------------------------|------------------------|
| Structure Optimization    | max_scf_iterations           | 1000                   |
|                           | convergence_max_iterations   | 1000                   |
|                           | convergence_step_max_coefficient | 2.0e-3              |
|                           | convergence_step_rms         | 1.0e-3                 |
|                           | convergence_gradient_max_coefficient | 2.0e-4            |
|                           | convergence_gradient_rms     | 1.0e-4                 |
|                           | convergence_delta_value      | 1.0e-6                 |
|                           | convergence_requirement      | 3                      |
|                           | bfgs_use_trust_radius        | True                   |
|                           | bfgs_trust_radius            | 0.2                    |
|                           | geoopt_coordinate_system     | cartesianWithoutRotTrans |
| Elementary Step Trial Calculation | max_scf_iterations           | 1000                   |
|                           | convergence_max_iterations   | 600                    |
|                           | nt_total_force_norm          | 0.1                    |
|                           | sd_factor                    | 1.0                    |
|                           | nt_use_micro_cycles          | True                   |
|                           | nt_fixed_number_of_micro_cycles | True               |
|                           | nt_number_of_micro_cycles    | 10                     |
|                           | nt_filter_passes             | 10                     |
| Transition State | convergence_max_iterations | 1000 |
|------------------|---------------------------|------|
|                  | convergence_step_max_coefficient | 2.0e-3 |
|                  | convergence_step_rms         | 1.0e-3 |
|                  | convergence_gradient_max_coefficient | 2.0e-4 |
|                  | convergence_gradient_rms      | 1.0e-4 |
|                  | convergence_requirement       | 3    |
|                  | convergence_delta_value       | 1e-6 |
| optimizer        | Bofill                      |      |
| bofill_trust_radius |                         | 0.2  |
| geoopt_coordinate_system | cartesianWithoutRotTrans |      |

| IRC              | convergence_max_iterations | 100  |
|------------------|---------------------------|------|
|                  | sd_factor                 | 0.2  |
|                  | sd_use_trust_radius       | True |
|                  | sd_trust_radius           | 0.05 |
|                  | sd_dynamic_multiplier     | 1.2  |
|                  | irc_initial_step_size     | 0.3  |
|                  | stop_on_error             | False|
|                  | convergence_step_max_coefficient | 2.0e-3 |
|                  | convergence_step_rms       | 1.0e-3 |
|                  | convergence_gradient_max_coefficient | 2.0e-4 |
|                  | convergence_gradient_rms    | 1.0e-4 |
|                  | convergence_delta_value     | 1.0e-6 |
| irc_coordinate_system | cartesianWithoutRotTrans |      |

| IRC Endpoint     | convergence_max_iterations | 1000 |
|------------------|---------------------------|------|
|                  | convergence_step_max_coefficient | 2.0e-3 |
|                  | convergence_step_rms         | 1.0e-3 |
|                  | convergence_gradient_max_coefficient | 2.0e-4 |
|                  | convergence_gradient_rms      | 1.0e-4 |
|                  | convergence_requirement       | 3    |
|                  | convergence_delta_value       | 1e-6 |
| bfgs_use_trust_radius | True                      |      |
| bfgs_trust_radius     | 0.2                        |      |

| Product Optimization | convergence_max_iterations | 1000 |
|----------------------|---------------------------|------|
|                      | convergence_step_max_coefficient | 2.0e-3 |
|                      | convergence_step_rms         | 1.0e-3 |
|                      | convergence_gradient_max_coefficient | 2.0e-4 |
|                      | convergence_gradient_rms      | 1.0e-4 |
|                      | convergence_requirement       | 3    |
|                      | convergence_delta_value       | 1e-6 |
| bfgs_use_trust_radius | True                      |      |
| bfgs_trust_radius     | 0.4                        |      |

| geoopt_coordinate_system | cartesianWithoutRotTrans |      |
**S3  Detailed Results**

Table S3: Found and missed reference reactions using different quantum chemical methods and algorithms in the elementary step search of Chemoton. Orange highlighting indicates that the structure optimization of the reference reactants or products was not successful, *e.g.*, resulting in the structure to dissociate into different molecules. Note that failures may be a consequence of the approximate structure model.

|    | GFN2 | DFTB3 |
|----|------|-------|
|    | NT1  | NT2   | NT2  |
| 1.1| ✓    | ✓     | –    |
| 1.2| ✓    | ✓     | –    |
| 1.3| ✓    | ✓     | –    |
| 2.1| ✓    | ✓     | –    |
| 2.2| ✓    | ✓     | –    |
| 2.3| ✓    | ✓     | –    |
| 2.4| ×    | ×     | –    |
| 2.5| ×    | ×     | –    |
| 3.1| ✓    | ×     | ×    |
| 3.2| ✓    | ✓     | ×    |
| 3.3| ✓    | ✓     | ✓    |
| 3.4| ✓    | ✓     | ✓    |
| 3.5| ×    | ✓     | ✓    |
| 3.6| ✓    | ✓     | ✓    |
| 3.7| ✓    | ✓     | ✓    |
| 3.8| ×    | ×     | ×    |
| 3.9| ✓    | ✓     | ✓    |
| 4.1| ✓    | ✓     | –    |
| 4.2| ✓    | ✓     | –    |
| 5.1| ✓    | ✓     | ✓    |
| 6.1| ✓    | ✓     | ✓    |
| 7.1| ✓    | ✓     | –    |
| 7.2| ✓    | ✓     | –    |
| 8.1| ✓    | ×     | ×    |
| 8.2| ✓    | ✓     | ✓    |
| 9.1| ✓    | ✓     | ✓    |
| 10.1| ✓   | ✓     | ✓     |
| 10.2| ✓   | ✓     | ✓     |
| 10.3| ✓   | ✓     | ✓     |
| 10.4| ✓   | ✓     | ✓     |
| 10.5| ✓ | ✓     | ✓     |
| 10.6| ✓ | ✓     | ✓     |
| 11.1| ✓ | ✓     | ×     |
| 11.2| ✓ | ✓     | ×     |
| 11.3| ✓  | ×     | ✓     |
| 11.4| × | ×     | ×     |
| 11.5| × | ×     | ×     |
| 12.1| ✓ | ✓     | ✓     |
| 12.2| ✓ | ✓     | ✓     |
| 12.3| ✓ | ✓     | ✓     |
| 13.1| ✓ | ✓     | ✓     |
| 13.2| ✓ | ✓     | ×     |
| 13.3| ✓ | ✓     | ✓     |
| 13.4| ✓ | ✓     | ✓     |
| 13.5| ✓ | ✓     | ✓     |
| 14.1| ✓ | ✓     | ✓     |
| 15.1| ✓ | ✓     | ✓     |
| 16.1| ✓ | ✓     | –    |
| 17.1| ✓ | ✓     | –    |
| 18.1| ✓ | ✓     | ✓     |
| 19.1| ✓ | ✓     | ✓     |
| 20.1| ✓ | ✓     | ✓     |
| 21.1| ✓ | ✓     | ✓     |
| 21.2| ✓ | ✓     | ×     |
| 21.3| ✓ | ✓     | ✓     |
| 21.4| ✓ | ✓     | ✓     |
| 21.5| ✓ | ✓     | ✓     |
| 21.6| × | ×     | ×     |
|   | GFN2 | DFTB3 |
|---|------|-------|
| NT1 | NT2 | NT2 |
| 21.7 | ✓  | ✓  | × |
| 21.8 | ✓  | ✓  | × |
| 21.9 | ✓  | ✓  | ✓ |
| 21.10 | ✓  | ✓  | ✓ |
| 22.1 | ✓  | ✓  | ✓ |
| 23.1 | ×  | ✓  | × |
| 24.1 | ✓  | ×  | – |
| 24.2 | ✓  | ✓  | – |
| 24.3 | ✓  | ✓  | – |
| 25.1 | ×  | ✓  | ✓ |
| 25.2 | ×  | ✓  | ✓ |
| 25.3 | ✓  | ✓  | ✓ |
| 25.4 | ✓  | ✓  | ✓ |
| 26.1 | ✓  | ✓  | ✓ |
| 26.2 | ×  | ×  | ✓ |
| 26.3 | ✓  | ✓  | ✓ |
| 27.1 | ✓  | ✓  | ✓ |
| 27.2 | ✓  | ✓  | ✓ |
| 28.1 | ✓  | ✓  | ✓ |
| 28.2 | ✓  | ✓  | ✓ |
| 28.3 | ×  | ×  | × |
| 28.4 | ✓  | ✓  | ✓ |
| 28.5 | ✓  | ✓  | ✓ |
| 28.6 | ✓  | ✓  | ✓ |
| 28.7 | ✓  | ✓  | ✓ |
| 28.8 | ✓  | ✓  | × |
| 28.9 | ✓  | ✓  | × |
| 28.10 | ×  | ✓  | ✓ |
| 28.11 | ✓  | ✓  | ✓ |
| 28.12 | ×  | ✓  | ✓ |
| 28.13 | ✓  | ✓  | ✓ |
| 28.14 | ✓  | ✓  | ✓ |
| 28.15 | ✓  | ✓  | × |
| 28.16 | ×  | ✓  | × |
| 28.17 | ×  | ×  | × |
| 28.18 | ×  | ×  | × |
| 28.19 | ×  | ×  | × |
| 28.20 | ×  | ✓  | ✓ |
| 28.21 | ×  | ✓  | ✓ |
| 28.22 | ×  | ✓  | ✓ |
| 28.23 | ✓  | ✓  | ✓ |
| 28.24 | ×  | ✓  | ✓ |
| 28.25 | ×  | ×  | ✓ |
| 28.26 | ×  | ✓  | ✓ |
| 28.27 | ✓  | ✓  | × |
| 28.28 | ✓  | ✓  | ✓ |
| 28.29 | ✓  | ✓  | ✓ |
| 28.30 | ✓  | ✓  | ✓ |
| 28.31 | ✓  | ✓  | ✓ |
| 28.32 | ×  | ×  | × |
| 28.33 | ×  | ✓  | ✓ |
| 28.34 | ✓  | ✓  | ✓ |
| 28.35 | ×  | ×  | ✓ |
| 28.36 | ×  | ×  | ✓ |
| 28.37 | ✓  | ✓  | × |
| 28.38 | ✓  | ✓  | ✓ |
| 28.39 | ✓  | ✓  | ✓ |
| 28.40 | ×  | ✓  | ✓ |
| 28.41 | ×  | ✓  | ✓ |
| 28.42 | ✓  | ✓  | ✓ |
| 28.43 | ×  | ✓  | ✓ |
| 28.44 | ✓  | ✓  | ✓ |
| 28.45 | ×  | ✓  | ✓ |
| 28.46 | ✓  | ✓  | ✓ |
| 28.47 | ✓  | ✓  | ✓ |
| 28.48 | ✓  | ✓  | ✓ |
| 28.49 | ✓  | ✓  | × |
| 28.50 | ✓  | ✓  | ✓ |
| 28.51 | ✓  | ✓  | ✓ |
| 28.52 | ×  | ✓  | ✓ |
| 28.53 | ×  | ✓  | × |
| 28.54 | ✓  | ✓  | ✓ |
| 28.55 | ✓  | ✓  | ✓ |
| 29.1 | ✓  | ✓  | ✓ |
| 30.1 | ✓  | ✓  | ✓ |
|   | GFN2 | DFTB3 |
|---|------|-------|
|   | NT1  | NT2   |
| 31.1 | ✓    | ✓    | ✓    |
| 32.1 | ✓    | ✓    | ✓    |
| 33.1 | ✓    | ✓    | ✓    |
| 34.1 | ✓    | ✓    | ✓    |
| 35.1 | ✓    | ✓    | ✓    |
| 36.1 | ✓    | ✓    | ✓    |
| 37.1 | ✓    | ✓    | ✓    |
| 38.1 | ×    | ✓    | ✓    |
| 39.1 | ✓    | ✓    | ✓    |
| 39.2 | ✓    | ✓    | ✓    |
| 39.3 | ✓    | ✓    | ✓    |
| 40.1 | ✓    | ✓    | ✓    |
| 40.2 | ✓    | ✓    | ✓    |
| 40.3 | ✓    | ✓    | ✓    |
| 40.4 | ✓    | ✓    | ✓    |
| 41.1 | ×    | ×    | ×    |
| 42.1 | ✓    | ✓    | ✓    |
| 42.2 | ✓    | ✓    | ✓    |
| 42.3 | ×    | ✓    | ✓    |
| 42.4 | ×    | ×    | ×    |
| 42.5 | ×    | ✓    | ✓    |
| 43.1 | ✓    | ✓    | ✓    |
| 43.2 | ×    | ✓    | ✓    |
| 44.1 | ×    | ×    | ✓    |
| 45.1 | ×    | ×    | ✓    |
| 46.1 | ×    | ×    | ✓    |
| 47.1 | ×    | ×    | ✓    |
| 48.1 | ×    | ✓    | ✓    |
| 49.1 | ×    | ✓    | ✓    |
| 50.1 | ×    | ×    | ✓    |
| 51.1 | ✓    | ✓    | ✓    |
| 52.1 | ×    | ×    | ✓    |
| 53.1 | ×    | ✓    | ✓    |
| 54.1 | ×    | ×    | ✓    |
| 55.1 | ×    | ×    | ✓    |
| 55.2 | ✓    | ✓    | ✓    |
| 55.3 | ×    | ×    | ✓    |

|   | GFN2 | DFTB3 |
|---|------|-------|
|   | NT1  | NT2   |
| 56.1 | ×    | ×    | ✓    |
| 57.1 | ×    | ×    | ✓    |
| 58.1 | ✓    | ✓    | ✓    |
| 59.1 | ✓    | ✓    | ✓    |
| 60.1 | ×    | ×    | ✓    |
| 61.1 | ×    | ×    | ✓    |
| 62.1 | ×    | ✓    | ✓    |
| 63.1 | ×    | ×    | ✓    |
| 64.1 | ×    | ✓    | ✓    |
| 65.1 | ×    | ×    | ✓    |
| 66.1 | ✓    | ✓    | ✓    |
| 67.1 | ×    | ✓    | ✓    |
| 68.1 | ×    | ✓    | ✓    |
| 69.1 | ×    | ×    | ✓    |
| 69.2 | ×    | ×    | ✓    |

\[ \sum(✓) = 120 \quad 147 \quad 106 \]
Table S4: Total numbers of reactions found, elementary steps found and elementary step calculations during GFN2-based calculations. The elementary steps are not deduplicated. In the first column, the number of reactions used as reference is given. Note that many of the references given did not aim to list all possible reactions.

| # | Ref. | NT1 | NT2 | NT1 | NT2 | NT1 | NT2 |
|---|------|-----|-----|-----|-----|-----|-----|
| 1 | 3    | 6   | 9   | 140 | 97  | 530 | (26.4) |
| 2 | 5    | 12  | 15  | 222 | 179 | 1048 | (21.2) |
| 3 | 9    | 45  | 41  | 129 | 97  | 390 | (33.1) |
| 4 | 2    | 24  | 31  | 231 | 224 | 1596 | (14.5) |
| 5 | 1    | 3   | 7   | 19  | 226 | 102 | (18.6) |
| 6 | 1    | 1   | 2   | 3   | 452 | 193 | (1.6)  |
| 7 | 2    | 14  | 27  | 111 | 983 | 498 | (22.3) |
| 8 | 2    | 5   | 7   | 52  | 39  | 136 | (38.2) |
| 9 | 1    | 2   | 2   | 4   | 8   | 9   | (44.4) |
| 10| 6    | 30  | 75  | 334 | 6465 | 1782 | (18.7) |
| 11| 5    | 15  | 24  | 65  | 129 | 780 | (8.3)  |
| 12| 3    | 14  | 18  | 85  | 65  | 300 | (28.3) |
| 13| 5    | 14  | 21  | 239 | 2614 | 831 | (28.8) |
| 14| 1    | 31  | 34  | 416 | 315 | 1830 | (22.7) |
| 15| 1    | 6   | 11  | 35  | 662 | 324 | (10.8) |
| 16| 1    | 1   | 1   | 7   | 5   | 21  | (33.3) |
| 17| 1    | 3   | 4   | 14  | 46  | 25  | (56.0) |
| 18| 1    | 5   | 11  | 17  | 163 | 96  | (17.7) |
| 19| 1    | 9   | 8   | 59  | 42  | 657 | (9.0)  |
| 20| 1    | 35  | 76  | 733 | 17161 | 4458 | (16.4) |
| 21| 10   | 28  | 27  | 435 | 280 | 1830 | (23.8) |
| 22| 1    | 9   | 22  | 121 | 1124 | 519 | (23.3) |
| 23| 1    | 38  | 51  | 701 | 757 | 4186 | (16.7) |
| 24| 3    | 112 | 108 | 368 | 254 | 1378 | (26.7) |
| 25| 4    | 222 | 826 | 1643| 33395 | 12142 | (13.5) |
| 26| 3    | 126 | 137 | 846 | 1010 | 5886 | (14.4) |
| 27| 1    | 35  | 76  | 733 | 17161 | 4458 | (16.4) |
| 28| 54   | 54  | 158 | 225 | 4552 | 1228 | (18.3) |
| 29| 1    | 9   | 16  | 172 | 1767 | 489 | (35.2) |
| 30| 1    | 34  | 96  | 474 | 5518 | 2474 | (19.2) |
| 31| 1    | 47  | 187 | 1111| 9727 | 4396 | (25.3) |
| 32| 1    | 45  | 103 | 911 | 15577 | 4584 | (19.9) |
| 33| 1    | 40  | 103 | 581 | 5955 | 2391 | (24.3) |
| 34| 1    | 194 | 616 | 1469| 73115 | 18997 | (7.7) |
| 35| 1    | 58  | 53  | 705 | 387  | 2211 | (31.9) |
|   | Ref. | NT1 | NT2 | NT1 | NT2 | NT1 | NT2 |
|---|------|-----|-----|-----|-----|-----|-----|
| 36 | 1    | 190 | 127 | 1964| 1326| 7381| 7381|
| 37 | 1    | 56  | 203 | 1924| 73178| 14406| 434799|
| 38 | 1    | 29  | 155 | 91  | 3229 | 435 | 13701|
| 39 | 3    | 19  | 15  | 137 | 76   | 465 | 465  |
| 40 | 4    | 500 | 501 | 4547| 3646 | 23855| 23855|
| 41 | 1    | 13  | 24  | 62  | 128 | 32896| 32896|
| 42 | 5    | 285 | 236 | 1040| 701 | 434799| 434799|
| 43 | 2    | 183 | 184 | 598 | 528 | 5516| 5516|
| 44 | 1    | 56  | 42  | 267 | 199 | 49326| 49326|
| 45 | 1    | 7   | 8   | 388 | 117 | 1010 | 1010|
| 46 | 1    | 13  | 62  | 14  | 234 | 300 | 7671|
| 47 | 1    | 0   | 2   | 0   | 2   | 325 | 8641|
| 48 | 1    | 30  | 147 | 85  | 1669| 496 | 16204|
| 49 | 1    | 83  | 477 | 1324| 21856| 9496 | 241016|
| 50 | 1    | 31  | 75  | 107 | 1339| 378 | 10499|
| 51 | 1    | 112 | 108 | 445 | 671 | 4182 | 4182|
| 52 | 1    | 76  | 126 | 349 | 322 | 14145| 14145|
| 53 | 1    | 14  | 39  | 92  | 1152| 378 | 10499|
| 54 | 1    | 53  | 211 | 85  | 1787| 378 | 10499|
| 55 | 3    | 57  | 302 | 3959| 28254| 32510| 1017251|
| 56 | 1    | 64  | 316 | 88  | 1931| 630 | 22571|
| 57 | 1    | 17  | 53  | 25  | 463 | 378 | 10178|
| 58 | 1    | 38  | 180 | 59  | 1598| 406 | 11339|
| 59 | 1    | 23  | 100 | 48  | 1507| 276 | 7220 |
| 60 | 1    | 0   | 0   | 0   | 0   | 3   | 5   |
| 61 | 1    | 0   | 0   | 0   | 0   | 171 | 171 |
| 62 | 1    | 7   | 12  | 28  | 269 | 161 | 1898 |
| 63 | 1    | 0   | 1   | 0   | 3   | 136 | 136 |
| 64 | 1    | 1   | 2   | 20  | 17  | 300 | 300 |
| 65 | 1    | 0   | 0   | 0   | 0   | 3   | 3   |
| 66 | 1    | 1   | 2   | 18  | 8   | 120 | 120 |
| 67 | 1    | 78  | 331 | 860 | 17674| 5815| 128537|
| 68 | 1    | 27  | 106 | 54  | 552 | 276 | 6551 |
| 69 | 2    | 0   | 0   | 0   | 0   | 812 | 812 |

∑ 184 3443 7659 31542 354635 290976 (10.8) 3441120 (10.3)
Table S5: Comparison of the total number of reactions found, elementary steps found and elementary step calculations carried out during the calculations employing GFN2 and DFTB3, both with the NT2 algorithm. The elementary steps are not deduplicated. In the first column the number of reactions used as reference is given. Note that many of the references given did not aim to list all possible reactions.

| #  | Ref. | GFN2 | DFTB3 | GFN2 | DFTB3 | # Elementary Step |
|----|------|------|-------|------|-------|--------------------|
|    |      |      |       |      |       | Trial (Success rate/%) |
| 3  | 9    | 41   | 44    | 97   | 102   | 390 (24.9) 390 (26.2) |
| 5  | 1    | 7    | 8     | 226  | 229   | 846 (26.7) 846 (27.1) |
| 6  | 1    | 2    | 4     | 452  | 215   | 1855 (24.4) 1855 (11.6) |
| 8  | 2    | 7    | 5     | 39   | 44    | 136 (28.7) 136 (32.4) |
| 9  | 1    | 2    | 2     | 8    | 8     | 27 (29.6) 27 (29.6) |
| 10 | 6    | 75   | 94    | 6465 | 6372  | 28755 (22.5) 28755 (22.2) |
| 11 | 5    | 24   | 19    | 129  | 77    | 780 (16.5) 780 (9.9) |
| 12 | 3    | 18   | 11    | 65   | 50    | 300 (21.7) 300 (16.7) |
| 13 | 5    | 21   | 29    | 2614 | 2302  | 11395 (22.9) 11395 (20.2) |
| 14 | 1    | 34   | 24    | 315  | 271   | 1830 (17.2) 1830 (14.8) |
| 15 | 1    | 11   | 25    | 662  | 438   | 3662 (18.1) 3662 (12.0) |
| 18 | 1    | 1    | 16    | 163  | 196   | 846 (19.3) 846 (23.2) |
| 19 | 1    | 8    | 6     | 42   | 26    | 657 (6.4) 657 (4.0) |
| 20 | 1    | 76   | 116   | 17161| 14723 | 92836 (18.5) 92836 (15.9) |
| 21 | 10   | 27   | 37    | 280  | 152   | 1830 (15.3) 1758 (8.6) |
| 22 | 1    | 22   | 50    | 1124 | 954   | 6669 (16.9) 6669 (14.3) |
| 23 | 1    | 51   | 32    | 757  | 741   | 4186 (18.1) 4186 (17.7) |
| 25 | 1    | 1    | 8     | 6    | 26    | 657 (6.4) 657 (4.0) |
| 26 | 3    | 137  | 151   | 1010 | 763   | 5886 (17.2) 5886 (13.0) |
| 27 | 2    | 585  | 517   | 6809 | 4646  | 72874 (9.3) 72874 (6.4) |
| 28 | 54   | 158  | 147   | 4552 | 3380  | 18491 (24.6) 18491 (18.3) |
| 29 | 1    | 16   | 34    | 1767 | 1222  | 6940 (25.5) 6940 (17.6) |
| 30 | 1    | 96   | 220   | 5518 | 4919  | 43147 (12.8) 43147 (11.4) |
| 31 | 1    | 187  | 394   | 9727 | 8565  | 92836 (10.5) 92836 (9.2) |
| 32 | 1    | 103  | 248   | 15577| 13469 | 89055 (17.5) 89055 (15.1) |
| 33 | 1    | 103  | 206   | 5955 | 5549  | 45059 (13.2) 45059 (12.3) |
| 34 | 1    | 616  | 1082  | 73115| 53819 | 487431 (15.0) 487431 (11.0) |
| 35 | 1    | 53   | 71    | 387  | 298   | 2211 (17.5) 2211 (13.5) |
| 36 | 1    | 127  | 221   | 1326 | 986   | 7381 (18.0) 7381 (13.4) |
| 37 | 1    | 203  | 655   | 73178| 51219 | 434799 (16.8) 434799 (11.8) |
| 38 | 1    | 155  | 141   | 3229 | 2385  | 13701 (23.6) 13701 (17.4) |
| 40 | 4    | 501  | 463   | 3646 | 2512  | 23855 (15.3) 23855 (10.5) |
| 41 | 1    | 24   | 61    | 128  | 1976  | 32896 (0.4) 32896 (6.0) |
| 42 | 5    | 236  | 312   | 701  | 601   | 3916 (17.9) 3916 (15.3) |
## Reactions

### Elementary Steps

| #  | Ref. | GFN2 | DFTB3 | GFN2 | DFTB3 | GFN2 | DFTB3 | Trials |
|----|------|------|-------|------|-------|------|-------|--------|
|    |      |      |       |      |       |      |       | (Success rate/%) |
| 43 | 2    | 184  | 160   | 528  | 470   | 5516 | (9.6) | 5565 (8.4) |
| 60 | 1    | 0    | 0     | 0    | 5     | (0.0) | 5 (0.0) |        |
| 61 | 1    | 0    | 0     | 0    | 0     | 171  | (0.0) | 171 (0.0) |
| 62 | 1    | 12   | 11    | 269  | 140   | 1898 | (14.2) | 1898 (7.4) |
| 63 | 1    | 1    | 2     | 3    | 5     | 136  | (2.2)  | 136 (3.7) |
| 64 | 1    | 2    | 2     | 17   | 5     | 300  | (5.7)  | 300 (1.7) |
| 65 | 1    | 0    | 0     | 0    | 0     | 3    | (0.0)  | 3 (0.0) |
| 66 | 1    | 2    | 1     | 8    | 2     | 120  | (6.7)  | 120 (1.7) |
| 67 | 1    | 331  | 382   | 17674 | 12495 | 128537 (13.8) | 128537 (9.7) |
| 68 | 1    | 106  | 116   | 552  | 607   | 6551 | (8.4)  | 6551 (9.3) |
| ∑  | 144  | 5201 | 7637  | 289670 | 227128 | 1985970 (14.6) | 1985947 (11.4) |
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