Supporting Information

Mechanistic insights on hydrazones synthesis: a combined theoretical and experimental study

Nissrine Al Assaad,[1,2] Alain Chamayou,[1] Rachel Calvet,[1,] * Manuel Pedrón,[2,] * Ilaria Ciofini,[2] Frédéric Labat.[2,] *

[1] Centre RAPSODEE (Recherche d'Albi en génie des Procédés des SOlides Divisés, de l'Energie et de l'Environnement), IMT Mines Albi, UMR CNRS 5302, Université de Toulouse, Campus Jarlard, Allée des Sciences, CEDEX 09, F-81013 Albi, France

[2] PSL University, Chimie ParisTech, CNRS, Institute of Chemistry for Life and Health Sciences, F-75005 Paris, France

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EXPERIMENTAL METHODS

HPLC measurements

To monitor the reaction kinetics, samples were collected at specific time intervals and analysed by High-Performance Liquid Chromatography (HPLC), from Agilent Technologies (model 1260 Infinity II). A reversed-phase Poroshell 120 EC-C18 column (4.6 x 100 mm, 4µm), purchased from Agilent Technologies, was employed for separation and analysis. The mobile phase consisted of a mixture of methanol (MeOH) and a phosphate buffer solution (pH = 7) maintained at a controlled temperature of 298.15 K. A multi-step hybrid elution method was employed, as detailed in **Table S 1**. The flow rate was maintained at 0.7 mL/min, and a 10 µL sample volume was injected. Detection of the analytes was carried out at a wavelength of 260 nm using a UV-Vis detector.

Prior to analysis, samples were diluted in a solvent mixture composed of MeOH, phosphate buffer, and acetone in a ratio of 40:35:25, respectively. Acetone was introduced into the dissolution medium to immediately quench the reaction between Isoniazid and Isophthalaldehyde after sampling. This large excess acetone reacts with Isoniazid, converting it into a product that is unreactive towards Isophthalaldehyde.

The HPLC system was calibrated using a set of six standards prepared from both commercially available reagents and synthesized products. Given the commercial unavailability of the monohydrazone and dihydrazone, these compounds were synthesized according to the procedure described below. These standards generated highly linear calibration curves with coefficient of determination (R^2) values ranging from 0.99992 to 0.99997.

Table S 1: HPLC elution method.

Time (min)	MeOH (%)	Phosphate Buffer (%)	Elution type
0-5	20	80	Isocratic
5-7	20-50	80-50	Linear gradient
7-17	50	50	Isocratic
17-19	50-20	50-80	Linear gradient
19-21	20	80	Isocratic

The monohydrazone was synthesized using an excess of isophthalaldehyde, with an isoniazid/isophthalaldehyde molar ratio of 1:2. The solvent employed is ethanol (EtOH)[7], and the mixture was refluxed for two hours. Upon completion of the reaction, the liquid reaction medium was concentrated under reduced pressure using a rotary evaporator. The resulting crude monohydrazone was purified through successive recrystallizations in a 3:7 EtOH/water mixture to eliminate any excess Isophthalaldehyde. To remove the dihydrazone by-product, additional purification was carried out using silica gel column chromatography with an eluent mixture[7] of ethyl acetate **(**EtOAc)/methanol (MeOH) in a ratio of 93:7.

Dihydrazone was synthesized in presence of an excess of isoniazid by refluxing a 2:1 molar ratio of isoniazid/isophthalaldehyde in EtOH for two hours. After removing the solvent under reduced pressure, the crude product was purified by successive recrystallizations from a 1:1 EtOH/H_2O mixture to remove unreacted isoniazid and any monohydrazone by-product, resulting in pure dihydrazone.

NMR Characterization

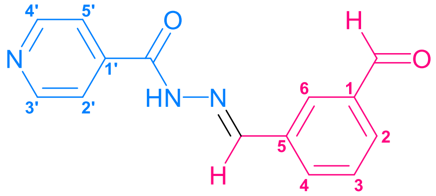
Monohydrazone

Chemical shifts (δ) are reported in parts per million (ppm), with signal multiplicities designated as singlet (s), doublet (d), and triplet (t). Coupling constants (J) are presented in hertz (Hz).

^{13}C NMR: δ 122.03 (2C, $C_{2'}$, $C_{5'}$), 128.27 (C_6), 130.26 (C_2), 131.31 (C_3), 133.4 (C_4), 135.5 (C_1), 137.15 (C_5), 140.79 ($C_{1'}$), 148.16 (C=N), 150.83 (2C, $C_{3'}$, $C_{4'}$), 162.27 (C=O), 193.45 (CH=O).

^{1}H NMR: δ 7.71 (1H, (t, $J = 7.6$), H_3), 7.85 (2H, (dd, $J = 6.1, 1.7$), $H_{2'}$, $H_{5'}$), 7.98 (1H, (d, $J = 7.6$), H_4), 8.06 (1H, d, $J = 7.7$), H_2), 8.29 (1H, s, N=CH), 8.57 (1H, s, H_6), 8.8 (2H, (dd, $J = 6.1, 1.7$), $H_{3'}$, $H_{4'}$), 10.09 (1H, s, CH=O), 12.22 (1H, s, NH).

MS m/z calculated for $C_{14}H_{11}N_3O_2$ [M+H$^+$]: 254.09, found: 254.0.



Scheme S 1: Monohydrazone structure with atom numbering for NMR characterization.

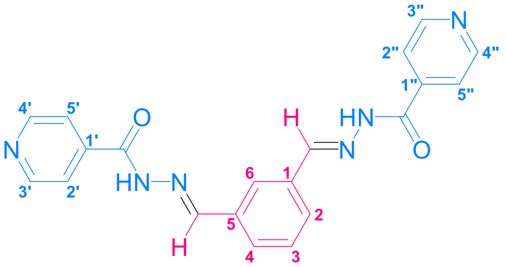
Dihydrazone

Chemical shifts (δ) are reported in parts per million (ppm), with signal multiplicities designated as singlet (s), doublet (d), and triplet (t). Coupling constants (J) are presented in hertz (Hz).

^{13}C NMR: δ 122.03 (4C, $C_{2'}$, $C_{5'}$, $C_{2''}$, $C_{5''}$), 125.56 (C_6), 129.79 (C_3), 130 (2C, C_2, C_4), 135.19 (2C, C_1, C_5), 140,88 (2C, C=N, C=N), 148.81 (2C, $C_{1'}$, $C_{1''}$), 150.84 (4C, $C_{3'}$, $C_{4'}$, $C_{3''}$, $C_{4''}$), 162.24 (2C, C=O, C=O).

^{1}H NMR: δ 7.59 (1H, (t, $J = 7.7$), H_3), 7.82 (2H, (dd, $J = 7.7, 1.8$), H_2, H_4), 7.85 (4H, (d, $J = 6.1$), $H_{2'}$, $H_{5'}$, $H_{2''}$, $H_{5''}$), 8.17 (1H, s, H_6), 8.54 (2H, s, N=CH, N=CH), 8.81 (4H, (d, $J = 4.8$), $H_{3'}$, $H_{4'}$, $H_{3''}$, $H_{4''}$), 12,17 (2H, S, NH, NH).

MS m/z calculated for $C_{20}H_{16}N_6O_2$ [M+H$^+$]: 372.13, found: 372.1.



Scheme S 2: Dihydrazone structure with atom numbering for NMR characterization.

Experimental Operating Conditions

Due to the limited solubility of isoniazid in acetonitrile at concentrations above 1.7 g/L, this initial concentration (C = 0.0124 mol/L) was used across both protic and aprotic solvent experiments to allow for consistent comparative analysis.

The reaction kinetics in both solvent systems were monitored over 7 hours at a controlled temperature of 298.15 K. Prior to initiating the reaction, each reactant was separately dissolved in the solvent and maintained at 298.15 K. First, isophthalaldehyde was introduced into the reactor. Then, using a dropping funnel, isoniazid was added to the isophthalaldehyde solution over approximately 45 seconds, at equimolar concentrations (C = 0.0124 mol/L) while stirring at 500 rpm. Ten samples, each representing 1% of the total volume, were collected at predetermined intervals: every 30 minutes for the first 2 hours, followed by hourly sampling over the remaining 5 hours. Each experiment was repeated three times, and the reported results represent the average of these three trials.

Kinetic Model

Kinetic modelling of the reaction is conducted to determine the kinetic constant and the activation energy obtained experimentally. The rate laws describing the consumption of reactants and formation of products in the competitive consecutive reaction [15], are expressed as follows:

$$\mathrm{A + B} \xrightarrow{\mathrm{k_1}} \mathrm{C + W}$$

$$\mathrm{B + C} \xrightarrow{\mathrm{k_2}} \mathrm{D + W}$$

Scheme S 3: Representation of the competitive consecutive reaction system.

$$-\frac{dC_A}{dt} = k_1 \times C_A \times C_B \tag{Eq. 1}$$

$$-\frac{dC_B}{dt} = k_1 \times C_A \times C_B + k_2 \times C_C \times C_B \tag{Eq. 2}$$

$$\frac{dC_C}{dt} = k_1 \times C_A \times C_B - k_2 \times C_C \times C_B \tag{Eq. 3}$$

$$\frac{dC_D}{dt} = k_2 \times C_C \times C_B \tag{Eq. 4}$$

$$\frac{dC_W}{dt} = k_1 \times C_A \times C_B + k_2 \times C_C \times C_B \tag{Eq. 5}$$

Where C_W is water concentration in mol.L^{-1} at time t, and k_1 and k_2 are the kinetic constants for monohydrazone and dihydrazone formation, respectively.

However, since water was identified as both a product and a catalyst of the reaction, the model above has been modified to incorporate it as an auto-catalyst, as shown below:

$$\mathrm{A + B + W} \xrightarrow{k'_1} \mathrm{C + 2W}$$

$$\mathrm{B + C + W} \xrightarrow{k'_2} \mathrm{D + 2W}$$

Scheme S 4: The competitive consecutive reaction system with the water as auto-catalyst.

$$-\frac{dC_A}{dt} = k'_1 \times C_A \times C_B \times C_W \tag{Eq. 6}$$

$$-\frac{dC_B}{dt} = k'_1 \times C_A \times C_B \times C_W + k'_2 \times C_C \times C_B \times C_W \tag{Eq. 7}$$

$$\frac{dC_C}{dt} = k'_1 \times C_A \times C_B \times C_W - k'_2 \times C_C \times C_B \times C_W \tag{Eq. 8}$$

$$\frac{dC_D}{dt} = k'_2 \times C_C \times C_B \times C_W \tag{Eq. 9}$$

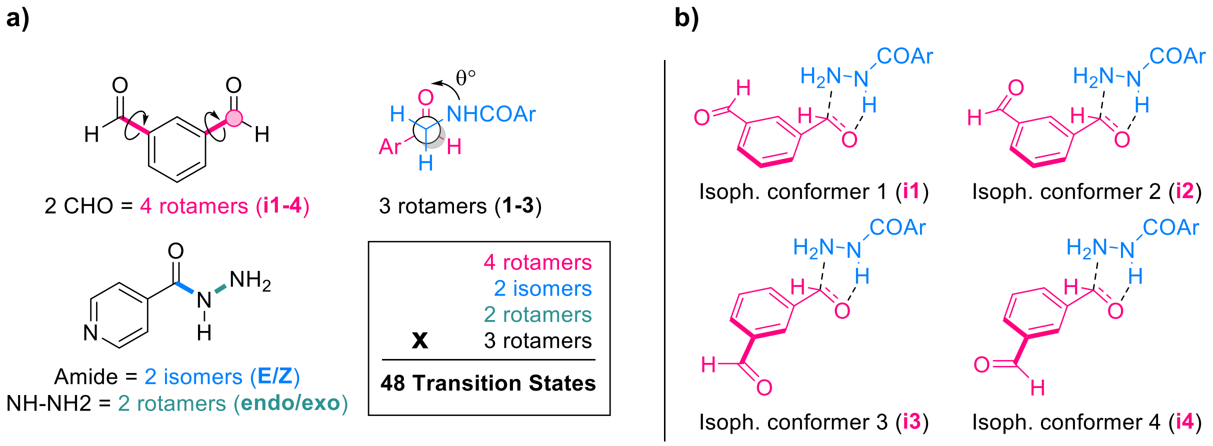
$$\begin{aligned}\frac{dC_W}{dt} = {} & -k'_1 \times C_A \times C_B \times C_W - k'_2 \times C_C \times C_B \times C_W + 2\,k'_1 \times C_A \times C_B \times C_W \\ & + 2\,k'_2 \times C_C \times C_B \times C_W\end{aligned} \tag{Eq. 10}$$

Where k_1' and k_2' are the kinetic constants for monohydrazone and dihydrazone formation, respectively, in presence of water as an auto-catalyst.

COMPUTATIONAL METHODS

TS1 Conformational Study

All possible conformers studied are depicted in **Scheme S 5**, **a**. Due to the symmetry plane of isophthalaldehyde, only 3 rotamers should be considered. However, the bond formation with the isoniazid breaks the inherent symmetry of the system, resulting in 4 different conformers to be considered (see **Scheme S 5**, **b**). Regarding isoniazid, both E/Z isomers of the amide group were considered, as well as the two different rotamers of the N-N bond. Finally, three starting θ angle rotamer geometries (60°, 180°, and -60°) were studied for the forming bond. Only N^{α}-O eclipsed conformations (θ ≈ 0°) could be located, resulting in a total of 16 TS with both E and Z conformations of the amide moiety.



Scheme S 5 : a) Possible conformers and rotamers of the starting materials considered for the formation of **TS1**. **b)** Conformers of the Isophthalaldehyde considered for TS1. Mirror-inverted geometries are displayed for clarity.

Similar to the condensation with hydrazines, no alkoxide intermediate could be located. IRC calculations demonstrated that the subsequent proton transfer occurs in a concerted matter, connecting **TS1-Z** directly to the first intermediate IN1-Z (**Figure S 1**, **a**). Relaxed scans from other geometries only revealed increase in energy, with no minima or TS observed (**Figure S 1, c**). The absence of this interaction is the main reason for not finding other θ rotamers different from θ ≈ 0°. Once the nucleophilic attack takes place, the initial conformation of the amide group leads to the E/Z configuration of the double bond in **IN1**, creating two different intermediates, **IN1-Z** and **IN1-E.** All TS leading to **IN1-E** were found to be less stable when compared to those leading to **IN1-Z** due to the lack of electronic conjugation caused by the steric hindrance between the pyridine and the terminal amino group in the E-configured amide (see **Figure S 1**, **a, b, d**). Therefore, while all the conformers of **TS1-Z** presented barriers between 20.5 and 22.0 kcal/mol, the range of all TS leading to **IN1-E** were higher, between 33.6 and 34.9 kcal/mol (see **Table S 2**). Same analysis can be also applied for the thermodynamic stability of the first intermediates (**Table S 4**).

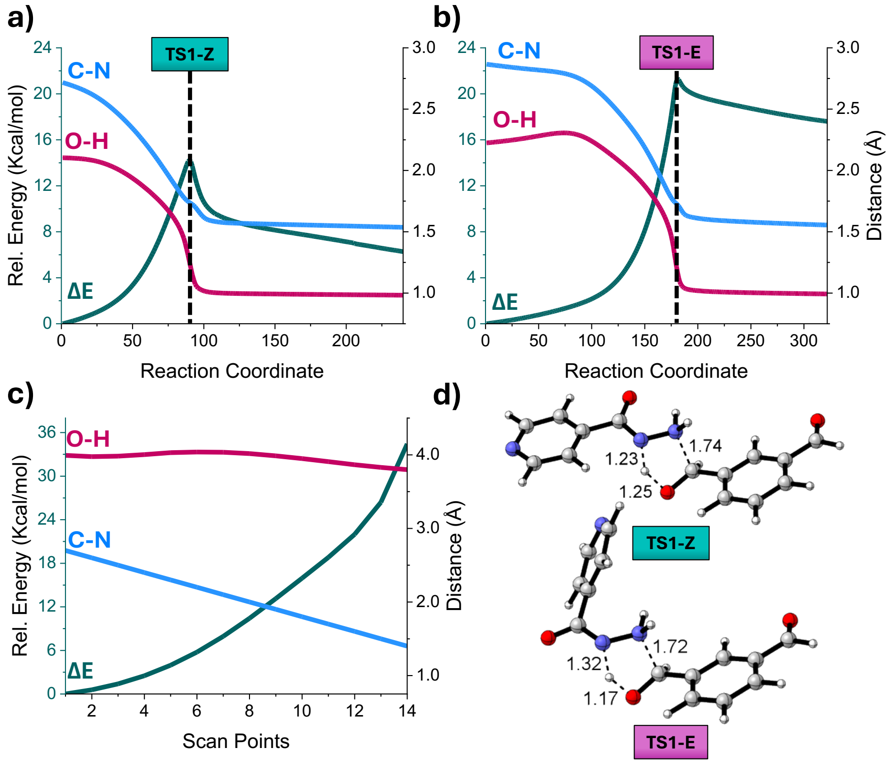


Figure S 1: **a)** Intrinsic Reaction Coordinate (IRC) of **TS1-Z** performed at PBE0/6-311+G(d,p) level. C-N and O-H distances are represented as blue and magenta continuous lines, respectively. Relative energy is depicted in dark green. The black dashed lines represent the TS position along the reaction coordinate. **b)** IRC of the lowest **IN1-E** forming TS (**TS1-E**) at the same level of theory. **c)** C-N forming bond scan starting from a non-eclipsed conformation. **d)** Optimized geometries of **TS1-Z** and **TS1-E** at the same level of theory.

Relative energies and first vibrational frequencies of all located **TS1** can be found in **Table S 2**. Colour code is relative to the conformers displayed in **Scheme S 5**. Since only conformers with θ = 0° could be located, no numeration for the 1-3 rotamers is included.

Gas Phase Relative Energies

Located encounter pairs for the reactants (denoted as **RE**) and first reaction intermediates (denoted and **IN1**) relative energies are collected in **Table S 3** and **Table S 4**, respectively.

Table S 2: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS1** regarding the nomenclature displayed in **Scheme S 5**.

TS1	ΔE	ΔE_0	ΔG	Freq
TS1_i1_Z_endo	17.9	17.0	21.4	-947.5
TS1_i2_Z_endo	17.2	16.3	20.7	-944.5
TS1_i3_Z_endo	18.6	17.7	22.0	-950.3
TS1_i4_Z_endo	17.8	16.9	21.3	-946.9
TS1_i1_Z_exo	17.5	16.6	20.9	-948.8
TS1_i2_Z_exo (TS1-Z)	**17.0**	**16.1**	**20.5**	**-939.7**
TS1_i3_Z_exo	18.0	17.1	21.3	-950.9

TS1_i4_Z_exo	17.3	16.4	20.8	-946.2
TS1_i1_E_endo	31.5	30.3	34.2	-708.6
TS1_i2_E_endo (TS1-E)	30.7	29.6	33.6	-729.7
TS1_i3_E_endo	32.0	30.7	34.5	-761.2
TS1_i4_E_endo	31.3	30.2	33.9	-691.8
TS1_i1_E_exo	31.3	30.1	34.2	-835.3
TS1_i2_E_exo	30.7	29.6	33.7	-814.3
TS1_i3_E_exo	32.1	30.8	34.9	-872.0
TS1_i4_E_exo	31.2	30.0	34.2	-837.9

Table S 3: Calculated relative energies (kcal/mol) for all the located conformers for **RE.**

RE	ΔE	ΔE_0	ΔG
RE_a1	0.8	0.7	0.8
RE_a2	0.0	0.0	0.1
RE_a3	0.1	0.1	0.0
RE_a4	0.8	0.7	0.8
RE_a5	0.1	0.1	0.0
RE_a6	0.0	0.0	0.0
RE_a7	0.1	0.1	0.0
RE_a8 (RE)	**0.1**	**0.1**	**0.0**

Table S 4: Calculated relative energies (kcal/mol) for all the located conformers for **IN1** regarding the nomenclature displayed in **Scheme S 5**.

IN1	ΔE	ΔE_0	ΔG
IN1_i1_Z_endo	9.1	11.2	15.4
IN1_i2_Z_endo	8.4	10.6	14.9
IN1_i3_Z_endo	9.8	11.9	16.1
IN1_i4_Z_endo	9.0	11.2	15.4
IN1_i1_Z_exo	7.4	9.7	14.0
IN1_i2_Z_exo	7.5	9.8	14.1
IN1_i3_Z_exo	7.6	9.9	14.1
IN1_i4_Z_exo (IN1-Z)	**7.3**	**9.6**	**13.9**

IN1_i1_E_endo	26.6	28.5	32.4
IN1_i2_E_endo	26.5	28.4	32.2
IN1_i3_E_endo	26.9	28.8	32.6
IN1_i4_E_endo	26.5	28.4	32.3
IN1_i1_E_exo	26.6	28.5	32.4
IN1_i2_E_exo	26.5	28.4	32.2
IN1_i3_E_exo	26.9	28.8	32.6
IN1_i4_E_exo	26.5	28.4	32.3

Relative energies for the next step via **TS2** and further **IN2** are collected in **Tables S 5 - 6**.

Table S 5: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS2** regarding the nomenclature displayed in **Scheme S 5**.

TS2	ΔE	ΔE_0	ΔG	Freq
TS2_i1_endo	14.1	13.6	18.0	-1067.6
TS2_i2_endo	14.1	13.6	17.8	-1062.2
TS2_i3_endo	14.1	13.6	18.1	-1091.8
TS2_i4_endo	14.1	13.6	17.8	-1066.3
TS2_i1_exo	9.6	9.4	13.9	-1079.1
TS2_i2_exo (TS2)	**9.5**	**9.3**	**13.9**	**-1079.5**
TS2_i3_exo	9.8	9.7	14.1	-1086.4
TS2_i4_exo	15.7	15.3	19.8	-1054.2

Table S 6: Calculated relative energies (kcal/mol) for all the located conformers for **IN2** regarding the nomenclature displayed in **Scheme S 5**.

IN2	ΔE	ΔE_0	ΔG
IN2_i1_endo	6.4	8.2	11.7
IN2_i2_endo	6.9	8.7	12.6
IN2_i3_endo	6.0	7.8	11.6
IN2_i4_endo	6.8	8.5	12.2
IN2_i1_exo	2.3	4.4	8.4
IN2_i2_exo (IN2)	**2.1**	**4.1**	**8.2**
IN2_i3_exo	2.7	4.7	8.7

IN2_i4_exo	2.3	4.3	8.3

From this point pathways a, b, and c can be followed. For pathway a, the first step consists of a dehydration to form a double C-N bond. Relative energies for all conformations of **TS3a** are collected in **Table S 7**. Since linear conformation of the isoniazid is preferred, no more endo/exo notation is relevant. Regarding the barriers, the formation of the E-hydrazone is preferred over the Z. Regarding so, all **IN3a_Z** were discarded. Relative energies for the corresponding intermediate, **IN3a_E**, can be seen in **Table S 8**. For clarity, after de dehydration, same i1-i4 notation was conserved to define the conformation of the recently formed C-N double bond.

Table S 7: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS3a** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5**.

TS3a	ΔE	ΔE_0	ΔG	Freq
TS3a_i1_E (TS3a)	54.0	51.0	55.3	-1788.2
TS3a_i2_E	54.3	51.3	55.5	-1810.6
TS3a_i3_E	54.0	51.0	55.3	-1774.3
TS3a_i4_E	54.1	51.1	55.4	-1791.4
TS3a_i1_Z	56.8	53.8	58.1	-1817.9
TS3a_i2_Z	56.3	53.3	57.7	-1814.4
TS3a_i3_Z	57.2	54.2	58.5	-1829.6
TS3a_i4_Z	56.7	53.6	57.9	-1818.7

Table S 8: Calculated relative energies (kcal/mol) for all the located conformers for **IN3a** regarding the nomenclature displayed for the isophthalaldehyde's conformation displayed in **Scheme S 5**, but being now between the aldehyde and the hydrazone groups.

IN3a	ΔE	ΔE_0	ΔG
IN3a_i1_E	2.3	1.6	5.1
IN3a_i2_E	2.0	1.3	4.8
IN3a_i3_E	-0.3	-1.1	1.8
IN3a_i4_E (IN3a)	-0.4	-1.2	1.6

Further steps to product formation relative energy through pathway a are displayed in **Table S 9 - 11**. For latest step (**TS5a**) the water assistance of the water molecule formed after dehydration is denotated as **-H2O**.

Table S 9: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS4a** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5** but being now between the aldehyde and the hydrazone groups.

TS4a	ΔE	$ΔE_0$	ΔG	Freq
TS4a_i1	32.3	29.1	30.0	-342.9
TS4a_i2 (TS4a)	**32.1**	**28.9**	**29.3**	**-337.3**
TS4a_i3	32.7	29.5	30.5	-341.1
TS4a_i4	32.3	29.1	30.0	-343.1

Table S 10: Calculated relative energies (kcal/mol) for all the located conformers for **IN4a** regarding the nomenclature displayed for the isophthalaldehyde's conformation displayed in **Scheme S 5**, but being now between the aldehyde and the hydrazone groups.

IN4a	ΔE	$ΔE_0$	ΔG
IN4a_i1	2.3	1.6	5.1
IN4a_i2 (IN4a)	**2.0**	**1.3**	**4.8**
IN4a_i3	2.9	2.2	5.6
IN4a_i4	2.2	1.5	5.0

Table S 11: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS5a** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5** but being now between the aldehyde and the hydrazone groups. -H2O suffix refer to the assistance of the water molecule generated after the dehydration.

TS5a	ΔE	$ΔE_0$	ΔG	Freq
TS5a_i1	38.2	33.4	34.3	-1846.7
TS5a_i2 (TS5a)	**35.2**	**31.1**	**33.2**	**-1845.6**
TS5a_i3	38.5	33.7	35.0	-1843.7
TS5a_i4	37.8	33.6	36.4	-1853.0
TS5a_i1-H2O	12.0	7.6	12.1	-1507.3
TS5a_i2-H2O (TS5a-H2O)	**11.7**	**7.4**	**11.8**	**-1503.4**
TS5a_i3-H2O	12.5	8.1	12.4	-1508.0
TS5a_i4-H2O	11.9	7.6	12.0	-1507.5

Regarding pathway b, as for **TS3a**, **TS3b** can also dehydrate through E- and Z-TS, being again the E-isomer thermodynamically more stable than the Z (see **Table S 12**). However, since this is not the rate-limiting step, Z-hydrazides cannot be discarded yet. Both E- and Z-intermediates and further isomerization after dehydration relative energies are collected in **Table S 13 - 14**. As for pathway a, -H2O suffix stands for the assistance of the generated water molecule on a given TS.

Table S 12: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS3b** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5**.

TS3b	ΔE	ΔE_0	ΔG	Freq
TS3b_i1_E	23.4	21.8	26.7	-650.7
TS3b_i2_E (TS3b)	**23.1**	**21.5**	**26.5**	**-651.2**
TS3b_i3_E	23.7	22.0	26.9	-653.2
TS3b_i4_E	23.4	21.7	26.7	-649.2
TS3b_i1_Z	25.2	23.6	28.3	-670.4
TS3b_i2_Z	24.7	23.2	28.0	-630.0
TS3b_i3_Z	26.0	24.3	29.0	-679.4
TS3b_i4_Z	25.0	23.4	28.1	-667.9

Table S 13: Calculated relative energies (kcal/mol) for all the located conformers for **IN3b** regarding the nomenclature displayed for the isophthalaldehyde's conformation displayed in **Scheme S 5**, but being now between the aldehyde and the hydrazone groups.

IN3b	ΔE	ΔE_0	ΔG
IN3b_i1_E	-0.3	-0.5	2.9
IN3b_i2_E	-0.5	-0.7	2.7
IN3b_i3_E	0.2	-0.2	3.1
IN3b_i4_E (IN3b)	**-0.6**	**-0.8**	**2.6**
IN3b_i1_Z	-1.1	-1.3	1.8
IN3b_i2_Z	-1.4	-1.4	1.5
IN3b_i3_Z	-1.0	-1.1	2.5
IN3b_i4_Z	-1.3	-1.4	1.8

Table S 14: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS4b** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5** but being now between the aldehyde and the hydrazone groups. -H2O suffix refer to the assistance of the water molecule generated after the dehydration.

TS4b	ΔE	ΔE_0	ΔG	Freq
TS4b_i1_E (TS4b)	**58.1**	**53.3**	**55.9**	**-1970.6**
TS4b_i2_E	59.2	54.2	56.5	-1971.0
TS4b_i3_E	58.3	53.5	56.0	-1976.5
TS4b_i4_E	58.3	53.5	56.0	-1970.3

TS4b_i1_Z	63.1	58.2	60.7	-1968.1
TS4b_i2_Z	63.4	58.6	61.4	-1972.2
TS4b_i3_Z	63.6	58.7	61.1	-1970.2
TS4b_i4_Z	63.1	58.2	60.5	-1971.5
TS4b_i1_E-H2O	24.2	20.0	24.1	-1631.0
TS4b_i2_E-H2O	24.3	20.1	24.2	-1613.6
TS4b_i3_E-H2O	24.5	20.2	24.2	-1673.9
TS4b_i4_E-H2O (TS4b-H2O)	**24.2**	**19.9**	**24.1**	**-1626.8**
TS4b_i1_Z-H2O	30.8	26.7	31.4	-1656.7
TS4b_i2_Z-H2O	30.6	26.5	31.2	-1655.2
TS4b_i3_Z-H2O	31.1	26.9	31.6	-1651.1
TS4b_i4_Z-H2O	30.2	26.1	30.8	-1653.7

Pathways a and b can be equilibrated between **IN3a** and **IN3b** through **TSeq**. Relative energies of all conformers are collected in **Table S 15.**

Table S 15: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TSeq** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5** but being now between the aldehyde and the hydrazone groups.

TSeq	ΔE	ΔE_0	ΔG	Freq
TSeq_i1_E (TSeq)	**8.4**	**5.2**	**8.2**	**-1272.3**
TSeq_i2_E	8.6	5.4	8.3	-1272.4
TSeq_i3_E	8.9	5.6	8.6	-1278.8
TSeq_i4_E	8.4	5.2	8.2	-1270.8
TSeq_i1_Z	10.8	7.6	10.6	-1249.1
TSeq_i2_Z	10.5	7.4	10.4	-1248.0
TSeq_i3_Z	11.5	8.1	10.9	-1272.9
TSeq_i4_Z	10.3	7.2	10.3	-1244.6

Pathway c starts instead by the isomerization. Relative energies for all located conformers for this step are collected in **Table S 16**. **Table S 17 – 20** collect all the relative energies for the further steps following this pathway.

Table S 16: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS3c** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5**.

TS3c	ΔE	ΔE_0	ΔG	Freq

TS3c_i1	34.3	34.5	38.8	-352.7
TS3c_i2	34.3	34.6	38.8	-351.9
TS3c_i3	34.6	34.9	39.1	-352.6
TS3c_i4 (TS3c)	34.2	34.4	38.8	-352.5

Table S 17: Calculated relative energies (kcal/mol) for all the located conformers for **IN3c** regarding the nomenclature displayed for the isophthalaldehyde's conformation displayed in **Scheme S 5**.

IN3c	ΔE	ΔE_0	ΔG
IN3c_i1	7.6	9.2	13.5
IN3c_i2 (IN3c)	7.5	9.1	13.4
IN3c_i3	8.0	9.6	13.9
IN3c_i4	7.5	9.2	13.5

Table S 18: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS4c** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5**.

TS4c	ΔE	ΔE_0	ΔG	Freq
TS4c_i1	40.4	39.0	42.7	-1835.4
TS4c_i2 (TS4c)	39.9	38.6	42.4	-1833.1
TS4c_i3	40.7	39.3	43.0	-1836.7
TS4c_i4	40.3	38.9	42.7	-1835.7

Table S 19: Calculated relative energies (kcal/mol) for all the located conformers for **IN4c** regarding the nomenclature displayed for the isophthalaldehyde's conformation displayed in **Scheme S 5**.

IN4c	ΔE	ΔE_0	ΔG
IN4c_i1	-5.8	-3.6	0.9
IN4c_i2 (IN4c)	-6.2	-3.9	0.5
IN4c_i3	-5.1	-2.9	1.5
IN4c_i4	-5.9	-3.7	0.8

Table S 20: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS5c** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5**.

TS5c	ΔE	ΔE_0	ΔG	Freq
TS5c_i1 (TS5c)	46.4	44.6	49.4	-1576.8

TS5c_i2	46.8	45.0	49.8	-1577.7
TS5c_i3	46.6	44.8	49.4	-1576.7
TS5c_i4	46.5	44.8	49.5	-1578.2

Finally, relative energies regarding the first product of the reaction (**PR**) are collected in **Table S 21**.

Table S 21: Calculated relative energies (kcal/mol) for all the located conformers for **PR** regarding the nomenclature displayed for the isophthalaldehyde's conformation displayed in **Scheme S 5**.

PR	ΔE	ΔE_0	ΔG
PR_i1	-6.0	-6.7	-3.6
PR _i2 (PR)	**-6.3**	**-7.0**	**-3.9**
PR _i3	-5.5	-6.3	-3.2
PR _i4	-6.1	-6.8	-3.7

The comparison between competing pathways a and b, with and without water assistance, is depicted in **Figure S 2**, where the greater stabilization of pathway b with the water assistance can be seen. This is a consequence of the higher ring strain released when transitioning from a 3-membered cycle to a 5-membered one (**TS4b**), compared to the four-to-six member increase in **TS5a**. Based on these results, pathway a will be the preferred route in dry solvents, where the availability of water molecules is limited. Pathway b could be followed in some situations in which water is more abundant, but as discussed in the main text, if a sufficient water molecules are present, other pathways may be followed (see subsequent models).

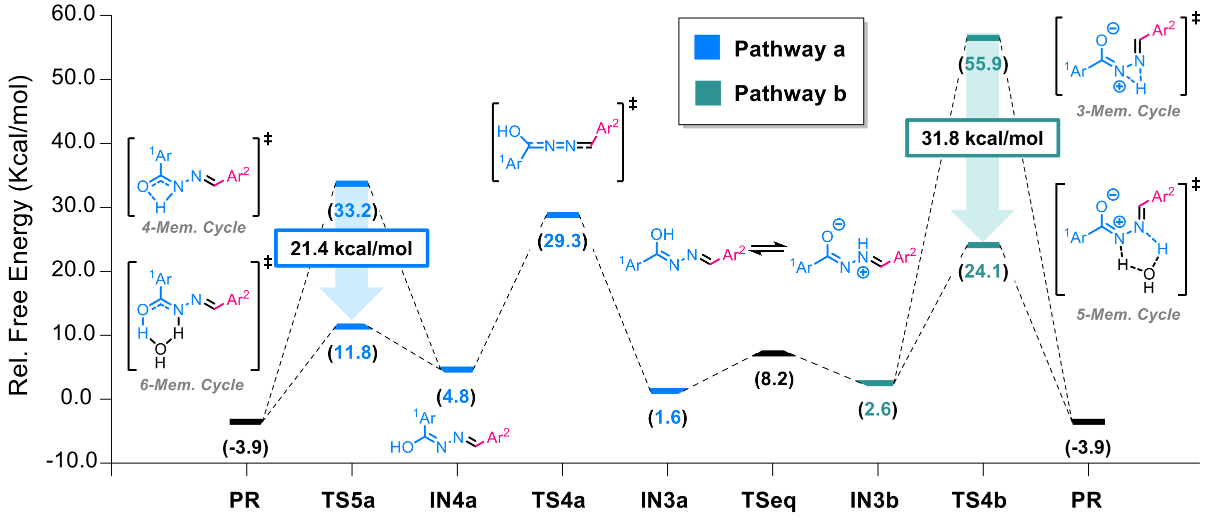


Figure S 2: Comparison of the energy profile and the stabilization with water-assistance of the two preferred pathways, pathways a (blue) and b (green) at PBE0/6-311+g(d,p) level of theory. With no assistance from the water molecule pathway a is the preferred route, while with assistance, pathway b becomes faster.

Implicit solvent model relative energies

Same analysis as reported for the gas phase calculations were performed applying implicit solvent effects (here water), using CPCM. Suffix -i denotates the implicit inclusion of the solvent. Relative energy data is collected in **Tables S 22 – 41**.

Table S 22: Calculated relative energies (kcal/mol) for all the located conformers for **RE-i.**

RE-i	ΔE	ΔE_0	ΔG
RE-i_a1	0.3	0.2	0.4
RE-i_a2	0.1	0.1	0.8
RE-i_a3	0.0	0.0	0.9
RE-i_a4	0.5	0.5	1.8
RE-i_a5	0.1	0.1	1.0
RE-i_a6	0.2	0.2	1.9
RE-i_a7 (RE-i)	**0.1**	**0.1**	**0.0**
RE-i_a8	0.3	0.2	0.4

Table S 23: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS1-i** regarding the nomenclature displayed in **Scheme S 5**.

TS1-i	ΔE	ΔE_0	ΔG	Freq
TS1-i_i1_Z_endo	14.9	14.4	19.2	-972.5
TS1-i_i2_Z_endo (TS1_Z-i)	**14.8**	**14.4**	**18.9**	-970.5
TS1-i_i3_Z_endo	14.9	14.4	19.2	-969.2
TS1-i_i4_Z_endo	14.8	14.4	19.0	-969.0
TS1-i_i1_Z_exo	15.0	14.5	19.2	-969.3
TS1-i_i2_Z_exo	15.0	14.4	19.0	-968.5
TS1-i_i3_Z_exo	15.0	14.6	19.3	-961.0
TS1-i_i4_Z_exo	14.9	14.4	19.0	-963.2
TS1-i_i1_E_endo	23.4	22.7	27.4	-983.7
TS1-i_i2_E_endo	23.3	22.7	27.5	-989.5
TS1-i_i3_E_endo	23.4	22.7	27.4	-989.6
TS1-i_i4_E_endo	23.4	22.7	27.2	-1002.2
TS1-i_i1_E_exo	23.4	22.7	27.2	-1002.2
TS1-i_i2_E_exo	23.4	22.7	27.4	-989.8

TS1-i_i3_E_exo	23.4	22.7	27.4	-983.7
TS1-i_i4_E_exo	23.3	22.7	27.5	-989.2

Table S 24: Calculated relative energies (kcal/mol) for all the located conformers for **IN1-i** regarding the nomenclature displayed in **Scheme S 5**.

IN1-i	ΔE	ΔE_0	ΔG
IN1-i_i1_Z_endo	5.5	8.1	12.4
IN1-i_i2_Z_endo	5.3	7.9	12.3
IN1-i_i3_Z_endo	5.4	7.9	12.2
IN1-i_i4_Z_endo	5.4	8.0	12.4
IN1-i_i1_Z_exo (IN1-Z-i)	5.2	7.7	11.8
IN1-i_i2_Z_exo	5.1	7.7	12.3
IN1-i_i3_Z_exo	5.1	7.7	12.1
IN1-i_i4_Z_exo	5.1	7.7	12.0
IN1-i_i1_E_endo	17.0	19.4	23.9
IN1-i_i2_E_endo	16.8	19.2	23.7
IN1-i_i3_E_endo	16.8	19.5	24.4
IN1-i_i4_E_endo	16.8	19.3	24.1
IN1-i_i1_E_exo	17.0	19.4	23.9
IN1-i_i2_E_exo	16.8	19.2	23.7
IN1-i_i3_E_exo	16.8	19.5	24.4
IN1-i_i4_E_exo	16.8	19.3	24.1

Table S 25: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS2-i** regarding the nomenclature displayed in **Scheme S 5**.

TS2-i	ΔE	ΔE_0	ΔG	Freq
TS2-i_i1_endo	13.3	12.7	17.3	-1237.5
TS2-i_i2_endo	13.2	12.7	17.2	-1237.4
TS2-i_i3_endo	13.3	12.7	17.1	-1235.3
TS2-i_i4_endo	13.2	12.7	17.2	-1235.4
TS2-i_i1_exo	10.6	10.4	15.3	-1229.9
TS2-i_i2_exo (TS2-i)	10.5	10.3	15.2	-1233.3

TS2-i_i3_exo	10.5	10.3	15.2	-1230.5
TS2-i_i4_exo	13.3	13.1	17.9	-1233.8

Table S 26: Calculated relative energies (kcal/mol) for all the located conformers for **IN2-i** regarding the nomenclature displayed in **Scheme S 5**.

IN2-i	ΔE	ΔE_0	ΔG
IN2-i_i1_endo	7.3	9.0	13.1
IN2-i_i2_endo	7.2	9.0	13.0
IN2-i_i3_endo	7.2	9.0	13.2
IN2-i_i4_endo	8.1	9.7	13.8
IN2-i_i1_exo (IN2-i)	4.9	6.7	10.6
IN2-i_i2_exo	4.9	6.8	10.7
IN2-i_i3_exo	4.8	6.6	10.8
IN2-i_i4_exo	4.8	6.6	10.8

Table S 27: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS3a-i** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5**. Only E-dehydration was considered.

TS3a-i	ΔE	ΔE_0	ΔG	Freq
TS3a-i_i1_E	53.5	50.9	55.8	-1638.7
TS3a-i_i2_E	53.5	50.9	55.6	-1639.5
TS3a-i_i3_E (TS3a-i)	53.5	50.8	55.4	-1639.6
TS3a-i_i4_E	53.6	50.9	55.6	-1640.3

Table S 28: Calculated relative energies (kcal/mol) for all the located conformers for **IN3a-i** regarding the nomenclature displayed for the isophthalaldehyde's conformation displayed in **Scheme S 5**, but being now between the aldehyde and the hydrazone groups.

IN3a-i	ΔE	ΔE_0	ΔG
IN3a-i_i1_E	1.0	0.1	2.9
IN3a-i_i2_E	0.9	0.1	2.9
IN3a-i_i3_E	1.2	0.2	2.9
IN3a-i_i4_E (IN3a-i)	1.0	0.1	2.7

Table S 29: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS4a-i** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5** but being now between the aldehyde and the hydrazone groups.

TS4a-i	ΔE	ΔE_0	ΔG	Freq
TS4a-i_i1	32.3	29.1	30.0	-342.9
TS4a-i_i2	32.3	29.1	29.9	-335.1
TS4a-i_i3	32.5	29.1	29.9	-333.9
TS4a-i_i4 (TS4a-i)	**32.3**	**28.9**	**28.4**	**-335.5**

Table S 30: Calculated relative energies (kcal/mol) for all the located conformers for **IN4a-i** regarding the nomenclature displayed for the isophthalaldehyde's conformation displayed in **Scheme S 5**, but being now between the aldehyde and the hydrazone groups.

IN4a-i	ΔE	ΔE_0	ΔG
IN4a-i_i1	3.9	3.1	6.8
IN4a-i_i2	3.8	3.0	6.8
IN4a-i_i3	3.9	3.1	6.9
IN4a-i_i4 (IN4a-i)	**3.8**	**3.0**	**6.7**

Table S 31: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS5a-i** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5** but being now between the aldehyde and the hydrazone groups. -H2O suffix refer to the assistance of the water molecule generated after the dehydration.

TS5a-i	ΔE	ΔE_0	ΔG	Freq
TS5a-i_i1	39.6	34.4	35.5	-1877.8
TS5a-i_i2 (TS5a-i)	**37.3**	**32.9**	**34.3**	**-1875.9**
TS5a-i_i3	39.8	34.7	35.7	-1877.2
TS5a-i_i4	38.4	34.2	37.3	-1883.0
TS5a-i_i1-H2O	13.2	8.6	13.5	-1431.1
TS5a-i_i2-H2O (TS5a-i-H2O)	**13.1**	**8.4**	**13.3**	**-1431.8**
TS5a-i_i3-H2O	13.3	8.7	13.5	-1432.7
TS5a-i_i4-H2O	13.1	8.5	13.3	-1433.6

Table S 32: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS3b-i** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5**.

TS3b-i	ΔE	ΔE_0	ΔG	Freq

TS3b-i_i1_E (TS3b-i)	**21.5**	**20.1**	**25.3**	**-579.1**
TS3b-i_i2_E	21.3	20.0	25.4	-587.6
TS3b-i_i3_E	21.4	20.1	25.4	-589.8
TS3b-i_i4_E	21.5	20.1	25.5	-585.6
TS3b-i_i1_Z	24.3	23.0	28.2	-642.4
TS3b-i_i2_Z	24.3	22.9	28.1	-637.2
TS3b-i_i3_Z	24.1	22.7	28.0	-649.8
TS3b-i_i4_Z	24.2	22.7	27.9	-647.8

Table S 33: Calculated relative energies (kcal/mol) for all the located conformers for **IN3b-i** regarding the nomenclature displayed for the isophthalaldehyde's conformation displayed in **Scheme S 5**, but being now between the aldehyde and the hydrazone groups.

IN3b-i	ΔE	ΔE_0	ΔG
IN3b-i_i1_E	-0.4	-0.6	3.1
IN3b-i_i2_E (IN3b-i)	**-0.4**	**-0.7**	**3.0**
IN3b-i_i3_E	-0.2	-0.4	3.4
IN3b-i_i4_E	-0.4	-0.7	3.0
IN3b-i_i1_Z	-1.0	-1.2	2.2
IN3b-i_i2_Z	-1.0	-1.1	1.9
IN3b-i_i3_Z	-1.2	-1.3	2.4
IN3b-i_i4_Z	-1.2	-1.3	2.0

Table S 34: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS4b-i** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5** but being now between the aldehyde and the hydrazone groups. -H2O suffix refer to the assistance of the water molecule generated after the dehydration.

TS4b-i	ΔE	ΔE_0	ΔG	Freq
TS4b-i_i1_E	59.9	54.7	56.6	-2042.8
TS4b-i_i2_E	59.8	54.7	56.5	-2042.5
TS4b-i_i3_E	60.0	54.8	56.5	-2043.9
TS4b-i_i4_E (TS4b-i)	**59.9**	**54.7**	**56.4**	**-2043.1**
TS4b-i_i1_Z	62.4	57.6	59.3	-1909.0
TS4b-i_i2_Z	63.1	58.1	60.0	-2047.8
TS4b-i_i3_Z	63.1	58.1	59.9	-2047.1

TS4b-i_i4_Z	62.1	57.4	59.6	-1898.0
TS4b-i_i1 _E-H2O	24.7	20.3	23.8	-1341.9
TS4b-i_i2_E-H2O (TS4b-i-H2O)	24.6	20.2	23.6	-1343.0
TS4b-i_i3 _E-H2O	24.7	20.4	24.5	-1345.7
TS4b-i_i4 _E-H2O	24.7	20.4	24.5	-1342.8
TS4b-i_i1 _Z-H2O	29.0	25.4	30.5	-1037.2
TS4b-i_i2_Z-H2O	29.0	25.4	30.4	-1033.8
TS4b-i_i3_Z-H2O	28.9	25.3	30.3	-1041.9
TS4b-i_i4_Z-H2O	28.8	25.2	30.3	-1026.0

Table S 35: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TSeq-i** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5** but being now between the aldehyde and the hydrazone groups.

TSeq-i	ΔE	ΔE_0	ΔG	Freq
TSeq-i_i1_E (TSeq-i)	8.8	5.5	8.2	-1331.1
TSeq-i_i2_E	8.7	5.4	8.3	-1333.6
TSeq-i_i3_E	8.9	5.6	8.6	-1331.4
TSeq-i_i4_E	8.8	5.5	8.5	-1331.0
TSeq-i_i1_Z	10.8	7.6	11.1	-1288.2
TSeq-i_i2_Z	10.8	7.5	10.9	-1288.9
TSeq-i_i3_Z	10.7	7.5	10.9	-1290.2
TSeq-i_i4_Z	10.6	7.4	10.9	-1289.8

Table S 36: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS3c-i** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5**.

TS3c-i	ΔE	ΔE_0	ΔG	Freq
TS3c_i_i1	34.1	34.5	39.4	-355.4
TS3c_i_i2	34.1	34.5	39.3	-356.4
TS3c_i_i3	34.0	34.4	39.3	-356.2
TS3c_i_i4 (TS3c-i)	34.0	34.4	39.2	-355.3

Table S 37: Calculated relative energies (kcal/mol) for all the located conformers for **IN3c-i** regarding the nomenclature displayed for the isophthalaldehyde's conformation displayed in **Scheme S 5**.

IN3c-i	ΔE	ΔE_0	ΔG
IN3c-i_i1	9.4	10.9	15.4
IN3c-i_i2	9.4	11.0	15.5
IN3c-i_i3 (IN3c-i)	**9.3**	**10.8**	**14.9**
IN3c-i_i4	9.3	10.8	15.4

Table S 38: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS4c-i** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5**.

TS4c-i	ΔE	ΔE_0	ΔG	Freq
TS4c-i_i1	42.1	40.6	44.4	-1864.4
TS4c-i_i2	42.1	40.7	44.6	-1866.0
TS4c-i_i3	42.0	40.6	44.6	-1863.7
TS4c-i_i4 (TS4c-i)	**42.0**	**40.5**	**44.3**	**-1865.4**

Table S 39: Calculated relative energies (kcal/mol) for all the located conformers for **IN4c-i** regarding the nomenclature displayed for the isophthalaldehyde's conformation displayed in **Scheme S 5**.

IN4c-i	ΔE	ΔE_0	ΔG
IN4c-i_i1 (IN4c-i)	**-5.7**	**-3.5**	**1.1**
IN4c-i_i2	-5.7	-3.5	1.2
IN4c-i_i3	-5.8	-3.5	1.4
IN4c-i_i4	-5.8	-3.5	1.4

Table S 40: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS5c** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5**.

TS5c	ΔE	ΔE_0	ΔG	Freq
TS5c_i1 (TS5c-i)	**46.4**	**44.6**	**49.4**	**-1576.8**
TS5c_i2	46.8	45.0	49.8	-1577.7
TS5c_i3	46.6	44.8	49.4	-1576.7
TS5c_i4	46.5	44.8	49.5	-1578.2

Table S 41: Calculated relative energies (kcal/mol) for all the located conformers for **PR-i** regarding the nomenclature displayed for the isophthalaldehyde's conformation displayed in **Scheme S 5**.

PR-i	ΔE	ΔE_0	ΔG
PR-i_i1	-1.9	-3.7	-2.2
PR-i_i2 (PR-i)	-6.2	-7.3	-4.7
PR-i_i3	-5.9	-7.1	-4.3
PR-i_i4	-6.1	-7.3	-4.6

Summary of the results with implicit solvation can be seen in **Figure S 3.**

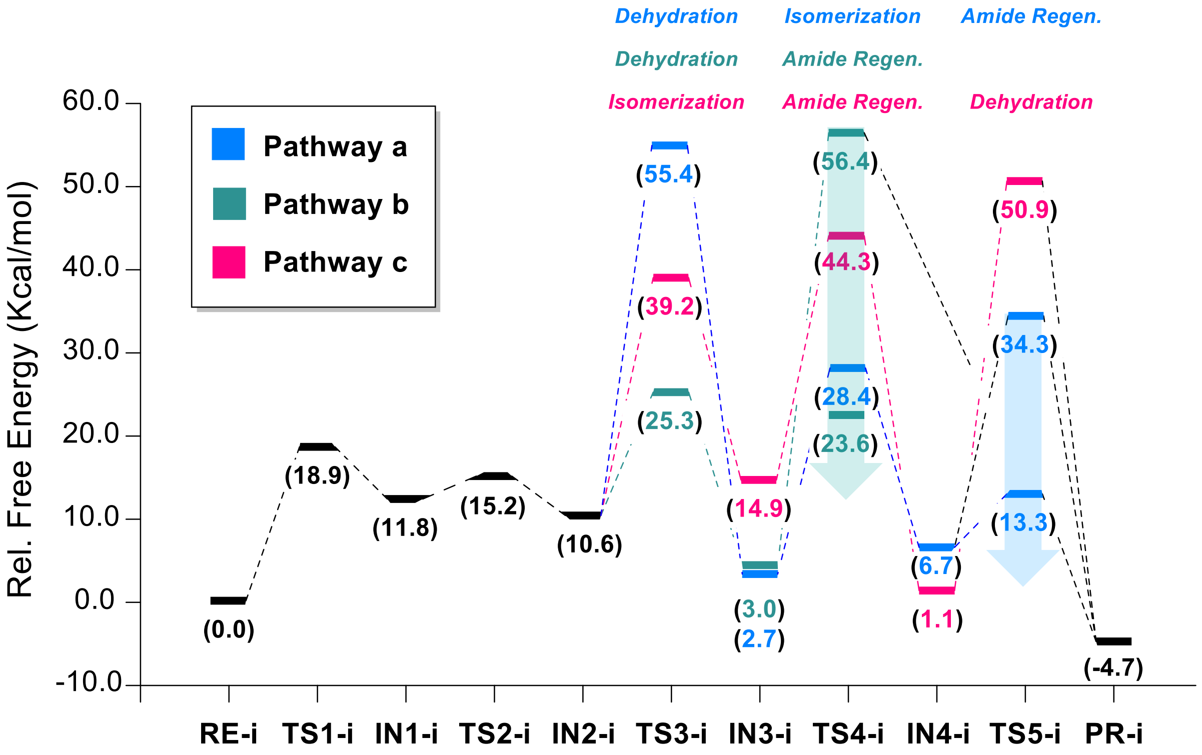


Figure S 3: Energetic profile for the condensation between isophthalaldehyde and isoniazide obtained at the PBE0/6-311+G (d,p) level including water at CPCM level. Arrows represent the stabilization of both **TS4b-i** and **TS5a-i** when assisted with the water molecule formed in the previous step.

Implicit + Explicit solvent model relative energies

As it was made for the construction of all **TS1** from the gas phase mechanism, the conformational study for the explicit water solvation considered all conformers depicted in **Scheme S 5**. Previous eclipsed conformations were also considered, increasing to 4 the number of rotamers considered (θ = -60°, 0°, 60°, and 180°), being so 64 possible TS. However, due to the demonstrated higher relative energy of the amide's E-conformers in the TSs, those structures were discarded from the analysis, reducing the conformational explored space to 32 structures. Suffix -w stands for implicit + explicit solvation structures.

Table S 42: Calculated relative energies (kcal/mol) for all the located conformers for **RE-w.**

RE-w	ΔE	ΔE_0	ΔG
RE-w_a1	0.6	0.5	0.1
RE-w_a2	0.9	0.7	0.4
RE-w_a3	0.7	0.5	0.0
RE-w_a4	0.4	0.4	2.2
RE-w_a5	0.8	0.6	0.3
RE-w_a6	0.0	0.0	1.4
RE-w_a7 (RE-w)	**0.8**	**0.6**	**0.0**
RE-w_a8	0.8	0.5	1.9

Since depending on the angle θ displayed in **Scheme S 5** different intermediates are obtained, relative energies concerning structures presenting a θ ≈ 0° can be found in **Table S 43.** For structures presenting other angles (-60 °, 60 °, and 180 °), refer to **Table S 44**.

Table S 43: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS1-w-0** regarding the nomenclature displayed in **Scheme S 5**.

TS1-w-0	ΔE	ΔE_0	ΔG	Freq
TS1-w_i1_Z_endo_0	13.6	12.9	18.2	-962.0
TS1-w_i2_Z_endo_0	13.5	12.9	17.8	-960.7
TS1-w_i3_Z_endo_0	13.6	12.9	18.2	-960.7
TS1-w_i4_Z_endo_0	13.5	12.8	17.8	-963.0
TS1-w_i1_Z_exo_0	13.4	12.7	17.5	-945.6
TS1-w_i2_Z_exo_0	13.4	12.7	17.7	-945.2
TS1-w_i3_Z_exo_0	13.4	12.8	17.8	-946.8
TS1-w_i4_E_exo_0 (TS1-(0)-Z-w)	**13.4**	**12.6**	**17.6**	**-949.4**

Table S 44: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS1-w-(60, 180, -60)** regarding the nomenclature displayed in **Scheme S 5**.

TS1-w-(60, 180, -60)	ΔE	ΔE_0	ΔG	Freq
TS1-w_i1_Z_endo_60	16.2	14.9	20.9	-1072.0
TS1-w_i2_Z_endo_60	16.2	14.9	20.9	-1071.5
TS1-w_i3_Z_endo_60	18.4	17.0	23.4	-1107.4
TS1-w_i4_Z_endo_60	16.1	14.8	21.0	-1072.9

TS1-w_i1_Z_exo_60	18.5	17.2	23.6	-1110.3
TS1-w_i2_Z_exo_60	18.4	17.1	23.4	-1110.4
TS1-w_i3_Z_exo_60	16.1	14.7	20.6	-1071.2
TS1-w_i4_Z_exo_60	17.2	15.6	21.6	-1119.4
TS1-w_i1_Z_endo_180	15.0	13.6	20.0	-1048.9
TS1-w_i2_Z_endo_180	14.9	13.5	19.9	-1050.3
TS1-w_i3_Z_endo_180	15.0	13.7	20.1	-1044.5
TS1-w_i4_Z_endo_180	15.0	13.6	19.8	-1047.0
TS1-w_i1_Z_exo_180	16.6	15.4	21.6	-1060.9
TS1-w_i2_Z_exo_180	16.4	15.3	21.7	-1065.8
TS1-w_i3_Z_exo_180	16.6	15.4	21.8	-1064.8
TS1-w_i4_Z_exo_180	16.5	15.3	21.4	-1058.4
TS1-w_i1_Z_endo_(-60)	17.4	16.2	22.9	-1066.2
TS1-w_i2_Z_endo_(-60)	17.4	16.1	22.6	-1063.9
TS1-w_i3_Z_endo_(-60)	15.1	13.8	19.9	-1027.7
TS1-w_i4_Z_endo_(-60) (TS-(-60)-Z-w)	**15.1**	**13.8**	**19.8**	**-1029.5**
TS1-w_i1_Z_exo_(-60)	15.1	13.9	20.1	-1017.4
TS1-w_i2_Z_exo_(-60)	15.2	14.1	20.7	-1029.9
TS1-w_i3_Z_exo_(-60)	17.3	16.1	22.9	-1067.0
TS1-w_i4_Z_exo_(-60)	17.3	16.0	22.4	-1068.0

Relative energies regarding further steps, including pathways a, b, and c are displayed in **Tables S 45 – 57**.

Table S 45: Calculated relative energies (kcal/mol) for all the located conformers for **IN1-w** regarding the nomenclature displayed in **Scheme S 5**.

IN1-w	ΔE	ΔE_0	ΔG
IN1-w_i1_Z_endo	3.5	6.0	11.1
IN1-w_i2_Z_endo	3.4	6.0	11.3
IN1-w_i3_Z_endo	3.5	6.0	11.1
IN1-w_i4_Z_endo	3.4	6.0	11.0
IN1-w_i1_Z_exo	3.2	5.8	11.3
IN1-w_i2_Z_exo	3.1	5.7	11.1

IN1-w_i3_Z_exo	3.1	5.8	11.1
IN1-w_i4_Z_exo (IN1-w)	3.2	5.7	10.7

Table S 46: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS2-w** regarding the nomenclature displayed in **Scheme S 5**.

TS2-w	ΔE	ΔE_0	ΔG	Freq
TS2-w_i1_endo	12.3	10.5	16.7	-1308.8
TS2-w_i2_endo	12.2	10.5	16.9	-1308.2
TS2-w_i3_endo	12.2	10.6	17.1	-1307.9
TS2-w_i4_endo	12.2	10.5	16.5	-1306.6
TS2-w_i1_exo	11.4	9.9	16.1	-1278.9
TS2-w_i2_exo (TS2-w)	11.3	9.8	15.9	-1282.6
TS2-w_i3_exo	11.3	9.8	16.3	-1281.8
TS2-w_i4_exo	11.3	9.8	16.2	-1277.8

Table S 47: Calculated relative energies (kcal/mol) for all the located conformers for **IN2-w** regarding the nomenclature displayed in **Scheme S 5**.

IN2-w	ΔE	ΔE_0	ΔG
IN2-w_i1_endo	3.8	5.4	10.7
IN2-w_i2_endo	2.7	4.2	9.3
IN2-w_i3_endo	3.7	5.4	10.9
IN2-w_i4_endo	3.7	5.3	10.6
IN2-w_i1_exo	2.7	4.3	9.6
IN2-w_i2_exo	2.7	4.2	9.6
IN2-w_i3_exo (IN2-w)	2.1	3.2	7.8
IN2-w_i4_exo	2.6	4.2	9.5

Table S 48: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS3a-w** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5**.

TS3a-w	ΔE	ΔE_0	ΔG	Freq
TS3a-w_i1_E	36.2	33.4	39.9	-1215.5
TS3a-w_i2_E	36.1	33.3	39.8	-1208.9
TS3a-w_i3_E	36.1	33.3	39.8	-1209.0

TS3a-w_i4_E (TS3a-w)	**36.0**	**33.2**	**39.8**	**-1207.2**
TS3a-w_i1_Z	39.0	36.1	42.6	-1245.1
TS3a-w_i2_Z	38.5	36.2	43.0	-1052.9
TS3a-w_i3_Z	38.9	36.1	42.6	-1226.3
TS3a-w_i4_Z	38.9	36.0	42.2	-1256.1

Table S 49: Calculated relative energies (kcal/mol) for all the located conformers for **IN3a-w** regarding the nomenclature displayed for the isophthalaldehyde's conformation displayed in **Scheme S 5**, but being now between the aldehyde and the hydrazone groups.

IN3a-w	ΔE	ΔE_0	ΔG
IN3a-w_i1_E	1.1	0.1	2.8
IN3a-w_i2_E (IN3a-w)	**-0.3**	**-1.6**	**0.9**
IN3a-w_i3_E	-1.3	-1.6	3.0
IN3a-w_i4_E	0.8	-0.1	3.3
IN3a-w_i1_Z	3.2	2.2	4.1
IN3a-w_i2_Z	4.5	3.6	5.9
IN3a-w_i3_Z	3.2	2.3	4.6
IN3a-w_i4_Z	3.0	2.1	4.8

Table S 50: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS4a-i**wregarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5** but being now between the aldehyde and the hydrazone groups.

TS4a-w	ΔE	ΔE_0	ΔG	Freq
TS4a-w_i1_E (TS4a-w)	**16.6**	**13.6**	**19.5**	**-342.3**
TS4a-w_i2_E	16.5	13.6	19.6	-339.1
TS4a-w_i3_E	16.7	13.8	19.6	-334.9
TS4a-w_i4_E	16.5	13.6	19.6	-335.8
TS4a-w_i1_Z	20.8	18.3	24.1	-305.0
TS4a-w_i2_Z	20.8	18.3	24.3	-321.9
TS4a-w_i3_Z	20.6	18.3	24.6	-315.6
TS4a-w_i4_Z	20.6	18.1	24.3	-313.5

Table S 51: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS3b-w** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5**.

TS3b-w	ΔE	ΔE_0	ΔG	Freq
TS3b-w_i1_E (TS3b-w)	**21.0**	**18.7**	**22.8**	**-741.3**
TS3b-w_i2_E	20.9	18.7	23.2	-739.8
TS3b-w_i3_E	21.0	18.7	23.3	-734.9
TS3b-w_i4_E	21.0	18.8	23.6	-744.2
TS3b-w_i1_Z	23.8	21.8	26.7	-626.0
TS3b-w_i2_Z	23.8	21.8	26.9	-618.3
TS3b-w_i3_Z	24.0	21.9	27.0	-636.3
TS3b-w_i4_Z	24.0	22.0	27.2	-621.4

Table S 52: Calculated relative energies (kcal/mol) for all the located conformers for **IN3b-w** regarding the nomenclature displayed for the isophthalaldehyde's conformation displayed in **Scheme S 5**, but being now between the aldehyde and the hydrazone groups.

IN3b-w	ΔE	ΔE_0	ΔG
IN3b-w_i1_E (IN3b-w)	**-1.2**	**-1.9**	**-0.3**
IN3b-w_i2_E	-1.2	-1.9	0.1
IN3b-w_i3_E	-2.8	-2.6	1.9
IN3b-w_i4_E	-1.4	-1.7	1.9
IN3b-w_i1_Z	-4.6	-4.6	-0.8
IN3b-w_i2_Z	-4.5	-4.5	-0.9
IN3b-w_i3_Z	-4.5	-4.7	-1.2
IN3b-w_i4_Z	-4.7	-4.8	-1.0

Table S 53: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS4b-w** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5** but being now between the aldehyde and the hydrazone groups. -H2O suffix refer to the assistance of the second water molecule generated after the dehydration.

TS4b-w	ΔE	ΔE_0	ΔG	Freq
TS4b-i_i1_E	24.2	19.3	22.8	-1436.0
TS4b-i_i2_E	24.1	19.3	22.7	-1435.5
TS4b-i_i3_E	24.2	19.4	23.2	-1430.2
TS4b-i_i4_E	24.2	19.3	22.8	-1435.3

TS4b-i_i1_Z	28.8	23.9	27.8	-1370.9
TS4b-i_i2_Z	28.8	24.3	29.0	-1319.0
TS4b-i_i3_Z	28.8	24.4	29.2	-1290.1
TS4b-i_i4_Z	28.8	24.3	28.7	-1258.8
TS4b-i_i1 _E-H2O	13.3	8.8	14.9	-917.7
TS4b-i_i2_E-H2O	13.2	8.8	14.9	-925.3
TS4b-i_i3 _E-H2O	13.4	8.8	14.8	-942.2
TS4b-i_i4 _E-H2O (TS4b-w)	**13.2**	**8.7**	**14.7**	**-930.3**
TS4b-i_i1 _Z-H2O	17.2	12.2	18.6	-1041.2
TS4b-i_i2_Z-H2O	17.1	12.3	18.7	-1034.8
TS4b-i_i3_Z-H2O	17.1	12.2	18.5	-1046.7
TS4b-i_i4_Z-H2O	17.1	12.2	18.7	-1042.4

Table S 54: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TSeq-w** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5** but being now between the aldehyde and the hydrazone groups.

TSeq-w	**ΔE**	**ΔE_0**	**ΔG**	**Freq**
TSeq-w_i1_E	7.3	3.0	7.1	-957.5
TSeq-w_i2_E (TSeq-w)	**7.2**	**2.9**	**7.0**	**-959.9**
TSeq-w_i3_E	5.3	1.8	7.8	-1071.7
TSeq-w_i4_E	7.2	3.0	7.7	-945.8
TSeq-w_i1_Z	8.3	3.9	7.4	-1018.1
TSeq-w_i2_Z	8.3	4.1	7.8	-1021.8
TSeq-w_i3_Z	8.2	3.9	7.7	-1019.0
TSeq-w_i4_Z	8.1	3.9	7.9	-1022.3

Table S 55: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **IN3c-w-(60, 180, -60)** regarding the nomenclature displayed in **Scheme S 5**.

IN3c-w-(60, 180, -60)	**ΔE**	**ΔE_0**	**ΔG**	**Freq**
IN3c-w_i1_endo_60	-5.1	-2.8	2.2	17.7
IN3c-w_i2_endo_60	-5.0	-2.8	2.0	14.6
IN3c-w_i3_endo_60	-5.3	-2.8	2.5	17.5
IN3c-w_i4_endo_60	-5.2	-2.8	2.4	16.9

IN3c-w_i1_exo_60	-7.0	-4.5	1.1	12.9
IN3c-w_i2_exo_60	-7.2	-4.7	1.1	15.1
IN3c-w_i3_exo_60	-7.1	-4.6	1.2	14.6
IN3c-w_i4_exo_60	-7.1	-4.6	0.9	11.5
IN3c-w_i1_endo_180	-5.1	-2.8	2.7	18.6
IN3c-w_i2_endo_180	-5.3	-3.0	2.5	18.5
IN3c-w_i3_endo_180	-5.1	-2.7	2.8	19.5
IN3c-w_i4_endo_180	-5.2	-2.9	2.4	15.9
IN3c-w_i1_exo_180	-7.0	-4.7	0.6	12.8
IN3c-w_i2_exo_180	-7.1	-4.7	0.8	15.3
IN3c-w_i3_exo_180	-7.0	-4.6	0.7	11.5
IN3c-w_i4_exo_180	-7.0	-4.6	0.9	18.2
IN3c-w_i1_endo_(-60)	-5.4	-3.1	2.3	17.7
IN3c-w_i2_endo_(-60)	-5.4	-3.1	1.9	16.1
IN3c-w_i3_endo_(-60)	-5.5	-3.1	2.2	18.0
IN3c-w_i4_endo_(-60)	-5.5	-3.2	2.1	17.1
IN3c-w_i1_exo_(-60)	-7.7	-5.1	0.9	17.2
IN3c-w_i2_exo_(-60)	-7.7	-5.2	0.5	13.5
IN3c-w_i3_exo_(-60) (IN3c-w)	**-7.8**	**-5.4**	**0.3**	**15.4**
IN3c-w_i4_exo_(-60)	-7.8	-5.3	0.4	18.5

Table S 56: Calculated relative energies (kcal/mol) and first vibrational frequencies for all the located conformers for **TS4c-w** regarding the nomenclature for the isophthalaldehyde's conformation displayed in **Scheme S 5**.

TS4c-w	ΔE	ΔE_0	ΔG	Freq
TS4c-w_i1_E (TS4c-w)	**27.2**	**25.1**	**32.3**	**-1187.8**
TS4c-w_i2_E	27.2	25.2	32.4	-1188.6
TS4c-w_i3_E	27.4	25.4	32.8	-1186.5
TS4c-w_i4 _E	27.3	25.3	32.5	-1179.8
TS4c-w_i1_Z	28.2	26.3	33.9	-1070.8
TS4c-w_i2_Z	28.1	26.3	33.8	-1074.1
TS4c-w_i3_Z	28.1	26.3	33.9	-1064.8
TS4c-w_i4 _Z	28.1	26.3	34.0	-1071.4

Table S 57: Calculated relative energies (kcal/mol) for all the located conformers for **PR-w** regarding the nomenclature displayed for the isophthalaldehyde's conformation displayed in **Scheme S 5** but being now between the aldehyde and the hydrazone groups.

PR-w	ΔE	ΔE_0	ΔG
PR-i_i1_E	-7.9	-8.9	-6.5
PR-i_i2 _E	-3.8	-4.1	-0.4
PR-i_i3_E	**-6.8**	**-8.0**	**-6.7**
PR-i_i4_E	-8.1	-9.0	-6.1
PR-i_i1_Z	-3.0	-3.8	-2.3
PR-i_i2 _Z	-2.5	-3.4	-1.2
PR-i_i3_Z	-3.1	-3.9	-2.1
PR-i_i4_Z	-3.0	-3.8	-2.1

Energy comparison between gas, implicit, and implicit + explicit solvent models is depicted in **Figure S 4**. No assistance for the previously generated water molecule was considered. Otherwise, alternative mechanism with water assistance can be seen in **Figure S 5.**

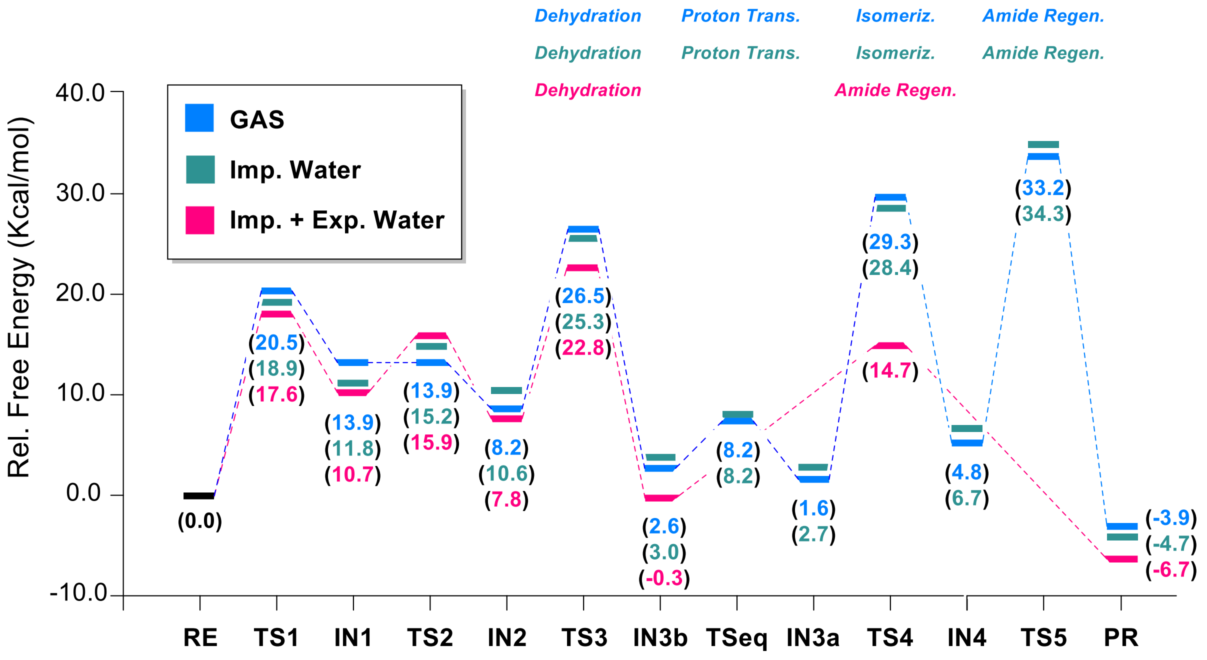


Figure S 4: Comparison of the energy profile in the unassisted water molecule mechanism in both gas phase, implicit solvation, and implicit + explicit water solvation models. Fast equilibration between **IN3a** and **IN3b** has been included in contrast to the main text in which was omitted for clarity.

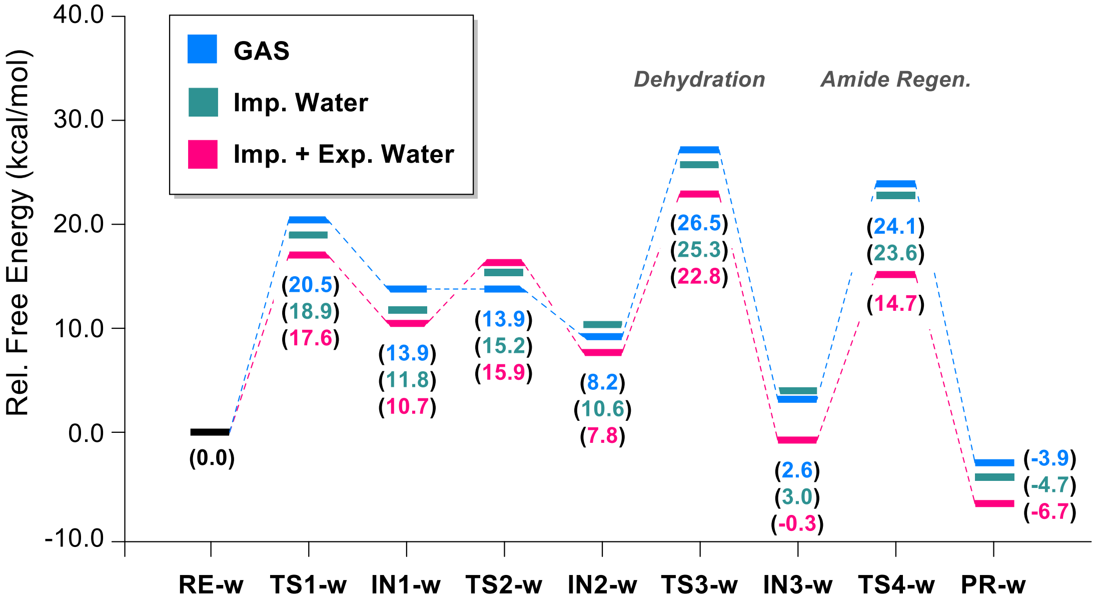


Figure S 5: Comparison of the energy profile in the assisted water molecule mechanism in both gas phase, implicit solvation, and implicit + explicit water solvation models.

Optimized Structures

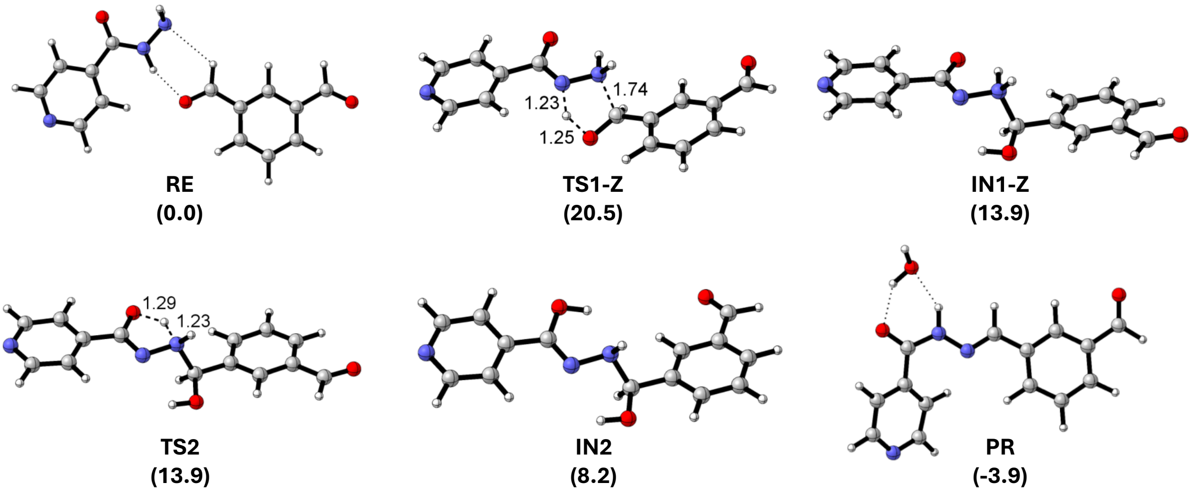


Figure S 6: Optimized structures for the common pathway in the gas phase.

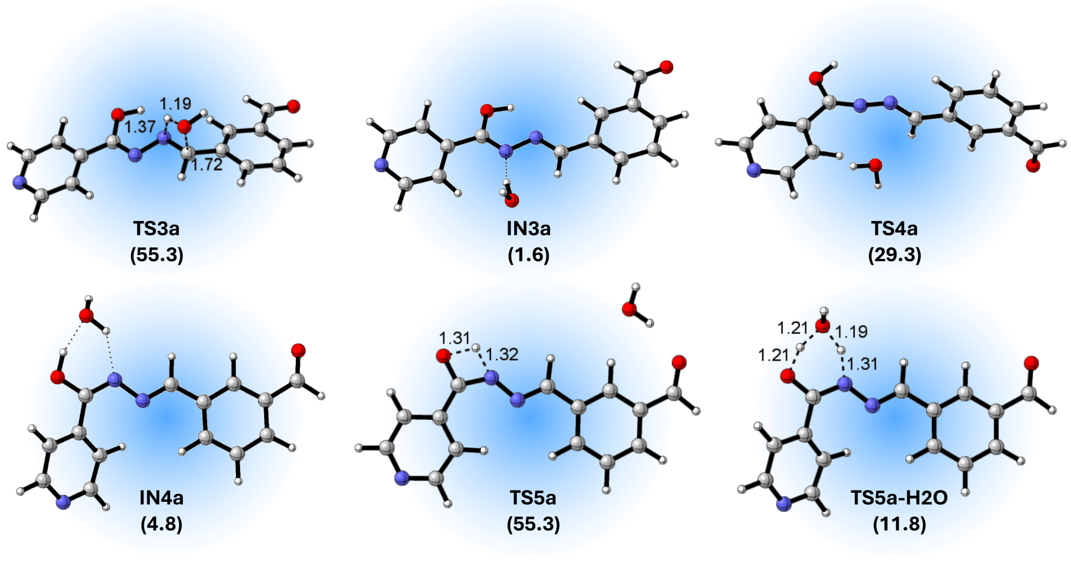


Figure S 7: Optimized structures for the pathway a in the gas phase.

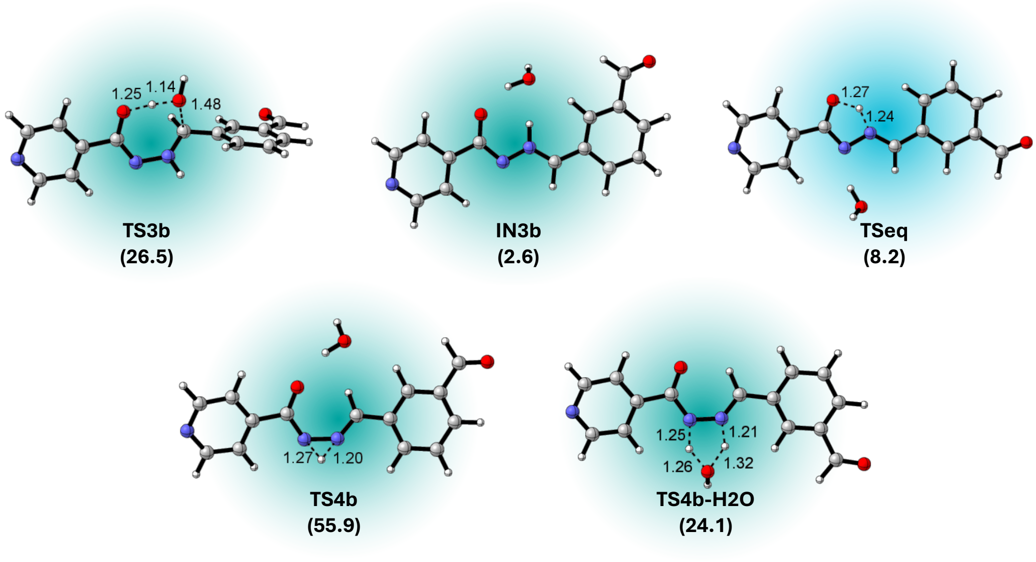


Figure S 8: Optimized structures for the pathway b in the gas phase.

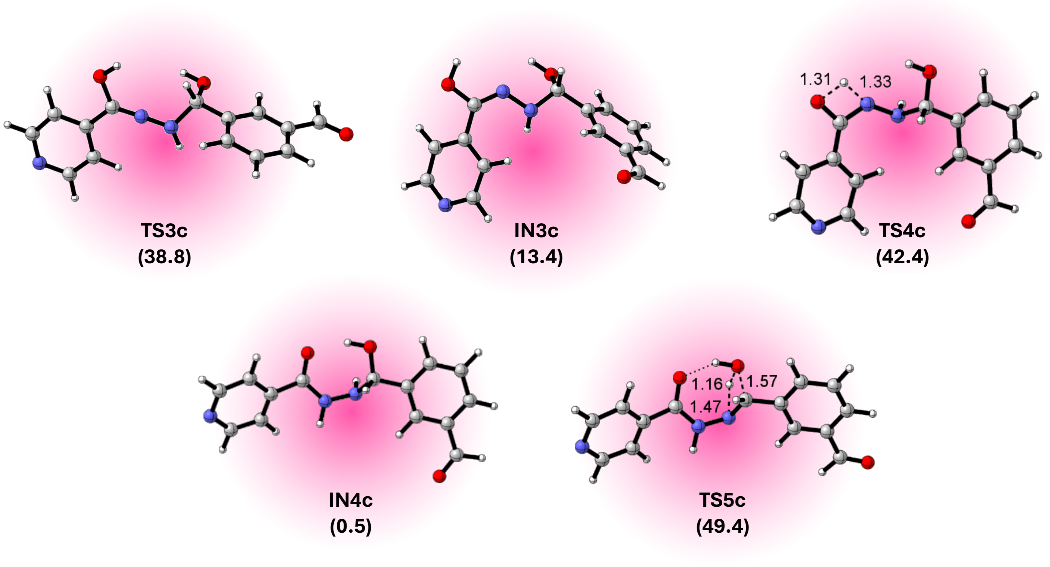


Figure S 9: Optimized structures for the pathway c in the gas phase.

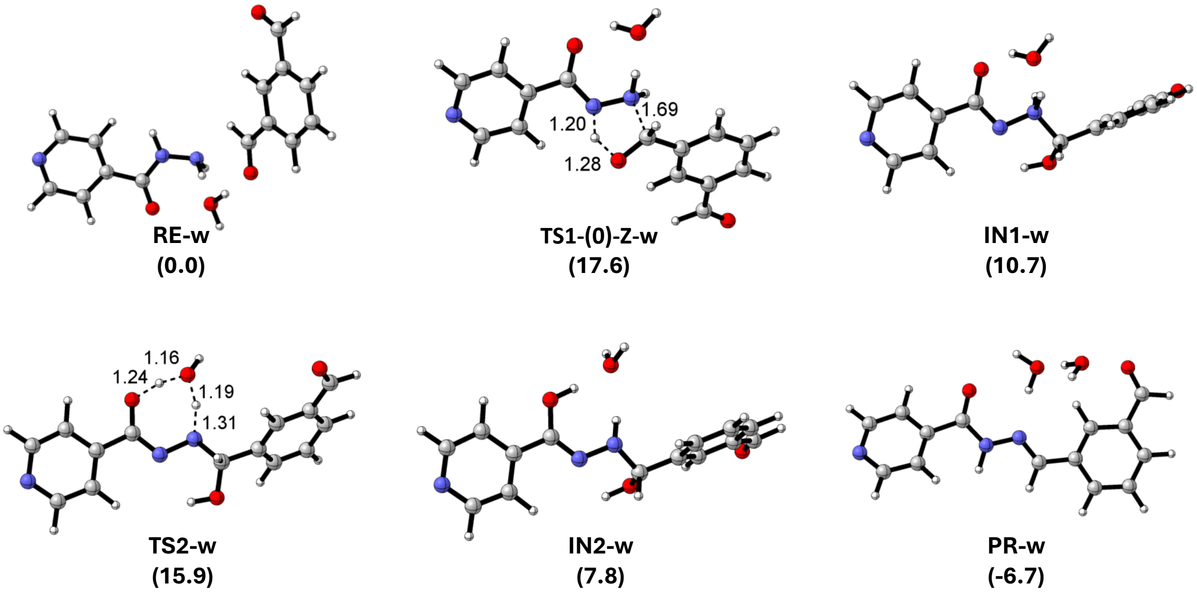


Figure S 10: Optimized structures for the common pathway in the implicit + explicit solvation model.

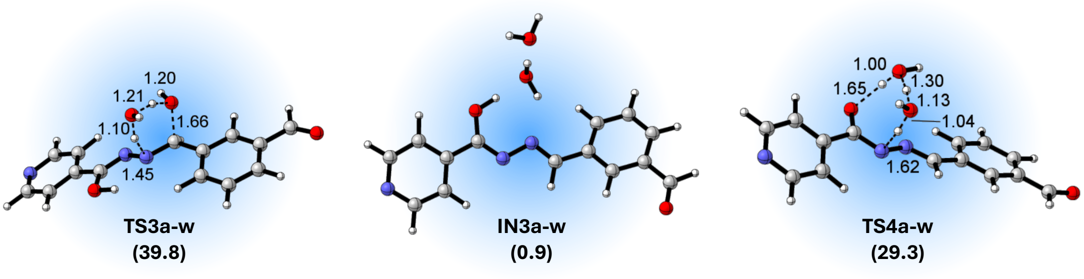
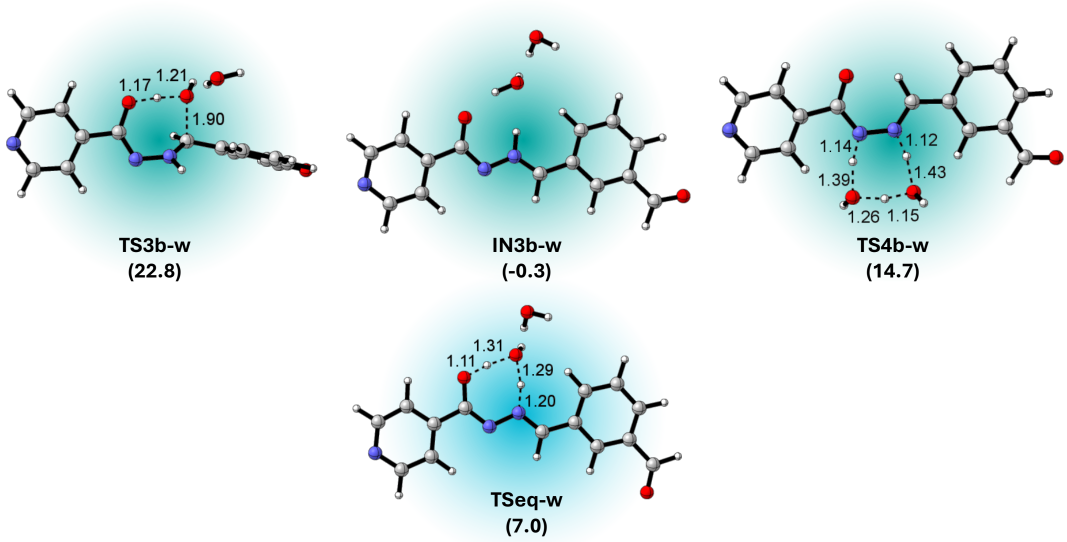


Figure S 11: Optimized structures for the pathway a in the implicit + explicit solvation model.



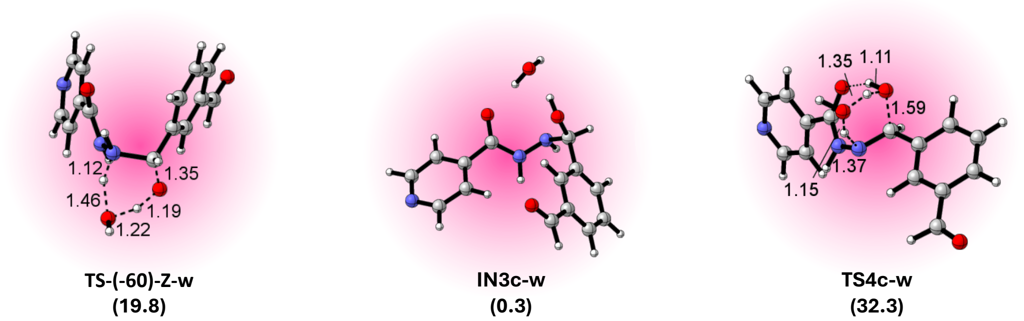
TS3b-w
(22.8)

IN3b-w
(-0.3)

TS4b-w
(14.7)

TSeq-w
(7.0)

Figure S 12: Optimized structures for the pathway b in the implicit + explicit solvation model.



TS-(-60)-Z-w
(19.8)

IN3c-w
(0.3)

TS4c-w
(32.3)

Figure S 13: Optimized structures for the pathway c in the implicit + explicit solvation model.