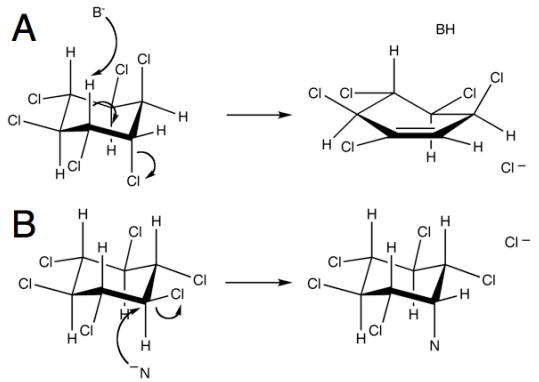
Electronic Supplementary Information

ESI Figure S1: (A) Reaction schemes for the E2 reaction between a base and α-HCH and (B) the S_N2 reaction between a nucleophile and β-HCH.



Experimental Methods and Results

Primer sequences:

LinA2-attB2	[GGGGACAAGTTTGTACAAAAAAGCAGGCTTAATGAGCGATCTGGATCGT]
LinA2-attB2-R2	[GGGGACCACTTTGTACAAGAAAGCTGGGTATCATTACGCGCCGCTCGG]
LinB-attB1	[GGGGACAAGTTTGTACAAAAAAGCAGGCTTAATGAGCCTGGGCGCGAAAC]
LinB-attB1-R2	[CTGCGTCCGGCGTAATGATACCCAGCTTTCTTGTACAAAGTGGTCCCC]

Nucleotide sequences of codon optimized genes:

>linA2 –B90A

atgagcgatctggatcgtctggccagccgtgcggcgattcaggatctgtatagcgataaactgatcgcggtg
gataaacgtcaggaaggccgcctggccagcatttggtgggatgatgcggaatggaccattgaaggcattggc
acctataaaggcccggaaggcgcgctggatctggccaacaacgtgctgtggccgatgtttcatgaatgcatc
cattatggcaccaacctgcgtctggaatttgtgagcgcggataaagtgaacggcattggtgatgtgctgctg
ctgggcaacctggtggaaggcaaccagagcattctgattgcggcggtgtttaccgatgaatatgaacgtcgt
gatggcgtgtggaaatttagcaaacgtaacgcgtgcaccaactattttaccccgctggccggcattcatttt
gcaccgccgggtatccattttgccccgagcggcgcgtaa

>linB-B90A

atgagcctgggcgcgaaaccgtttggcgaaaaaaaattcatcgaaatcaaaggccgtcgtatggcgtatatt
gatgaaggcaccggcgatccgattctgtttcagcatggcaatccgaccagcagctatctgtggcgtaacatt
atgccgcattgcgcgggtctgggccgtctgattgcgtgcgatctgattggcatgggcgatagcgataaactg
gacccgagcggtccggaacgttatacctatgcggaacaccgtgattatctggatgcgctgtgggaagcgctg
gatctgggcgatcgtgtggtgctggttgtgcatgattggggcagcgtgctgggctttgattgggcgcgtcgt
catcgtgaacgtgtgcagggcattgcgtatatggaagcggtgaccatgccgctggaatgggcggattttccg

gaacaggatcgtgacctgtttcaggcgtttcgtagccaggcgggcgaagaactggtgctgcaggataacgtg
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ccgtttctggccgcgggtgaagcgcgtcgtccgaccctgagctggccgcgtcagattccgattgcgggcact
ccggcggatgttgtggcgattgcgcgtgattatgcgggctggctgtctgaaagcccgattccgaaactgttt
attaacgcggaaccgggccatctgaccaccggccgtattcgtgatttttgccgtacctggccgaaccagacc
gaaattaccgtggcgggtgcgcattttattcaggaagatagcccggacgaaattggtgcggcgattgcggcg
tttgtgcgtcgtctgcgtccggcgtaa

Cloning

Codon optimized genes for expression in *E. coli* [BL21 AI] were synthesized by Geneart AG, Regensburg Germany. The synthetic genes was PCR amplified [Taq Platinum, Invitrogen] using the sense primers (LinA2-attB1 or LinB-attB1) and the antisense primers (LinA2-attB2 or LinB-attB1-R2). The amplicons were then cloned into pDONOR201 and transferred to pDEST17 using BP and LR reactions [BP reaction—to create a Gateway® entry clone and LR reaction—to create a Gateway® expression clone] respectively, following the manufacturers' instructions (Invitrogen, CA).

Expression and purification

Constructs of *E. coli* BL21 AI containing pDEST17 with the genes of interest also co-expressed chaperones from pGroEL for expression of LinA2 (Takara Bio Inc, Shiga, Japan). The bacterial clones were cultured in 100 ml of LB supplemented with 100 µg/ml ampicillin (and 34 µg/ml chloramphenicol for LinA2) at 28°C. When the culture reached an OD600 of 0.5 at 550nm, arabinose [Sigma Aldrich] was added to a final concentration of 2 mg/L. Cells were harvested after overnight incubation, washed with 10mM imidazole buffer (pH 7.5) and disrupted by 1 x Bugbuster (Novagen, Darmstadt). The lysate was centrifuged at 16,000g for 20 min and the supernatant was used to purify his-tagged proteins using NTA-Ni2+ agarose (Qiagen, GmbH) using manufacturers' instructions. The purified protein was quantified using Nanodrop (Thermo Scientific, DE). The purified enzyme was stored in storage buffer (pH 7.5) containing 1 mM 2-mercaptoethanol and 10% glycerol at concentration about 1 mg/ml at 4°C.

Enzyme kinetics

Enzyme kinetics was performed within 3 days of purification. In this time period no measurable loss of enzyme activity was observed. LinA and LinB activity was assayed by estimating the depletion of HCH isomers using gas chromatography. The assay reaction was initiated by the addition of enzyme to the reaction mixture (500 µl) containing 1.7 µM HCH isomers in 1x Tris glycine buffer (25mM Tris, 192mM glycine pH 8.3) at room temperature and was stopped by the addition of 0.3% (v/v) formic acid (final concentration) after the respective incubation time. The samples were extracted by equal volume of hexane by vortexing for 5 min and quantitatively analyzed on a GC equipped with a BPX-50 capillary column (30 m by 0.25 mm by 0.32 µm; SGE analytical) and an electron capture detector. The temperature program was isothermal at 100°C for 5 min, followed by an increase to 200°C at 20°C/min, and the carrier gas (He) flow rate was 3.0 ml/min.

Computational Procedures and Results

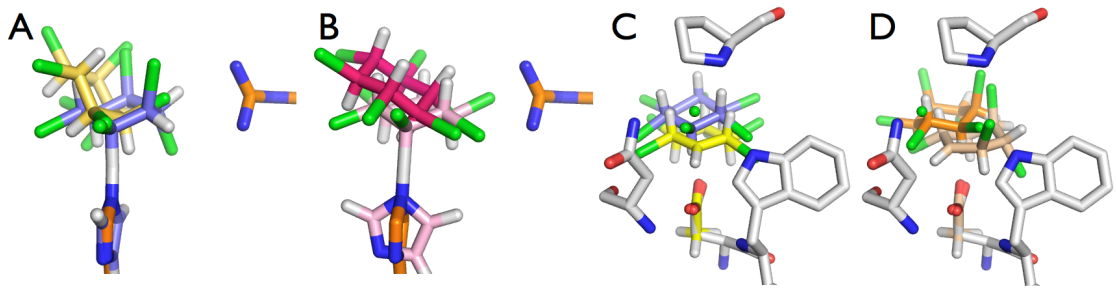
Docking calculations

Docking calculations were performed using AUTODOCK v. 4.2[3] using geometries of HCH isomers as ligands that were calculated through the high-level quantum calculations described above. The receptor molecules (LinA:3A76 and LinB:1MJ5) had all waters removed. Ligands were prepared for calculations by adding gasteiger charges using AUTODOCK. The receptor was prepared by adding hydrogens and Gasteiger chages using AUTODOCK. The grid-box was 30 x 30 x 30 points with spacing of 0.375 Å, which covered the entire substrate binding cavity of LinA and LinB. A genetic algorithm was used for the docking procedure, using the medium number of energy evaluations (2500000). The top ten docked poses were output and clustered into a single essentially identical pose in all cases.

ESI Table S1: Predicted energy and affinity for β-HCH and γ-HCH binding at the active sites of LinA (PDB ID: 3A76)[1] and LinB (PDB ID: 1MJ5)[2] from AUTODOCK.[3]

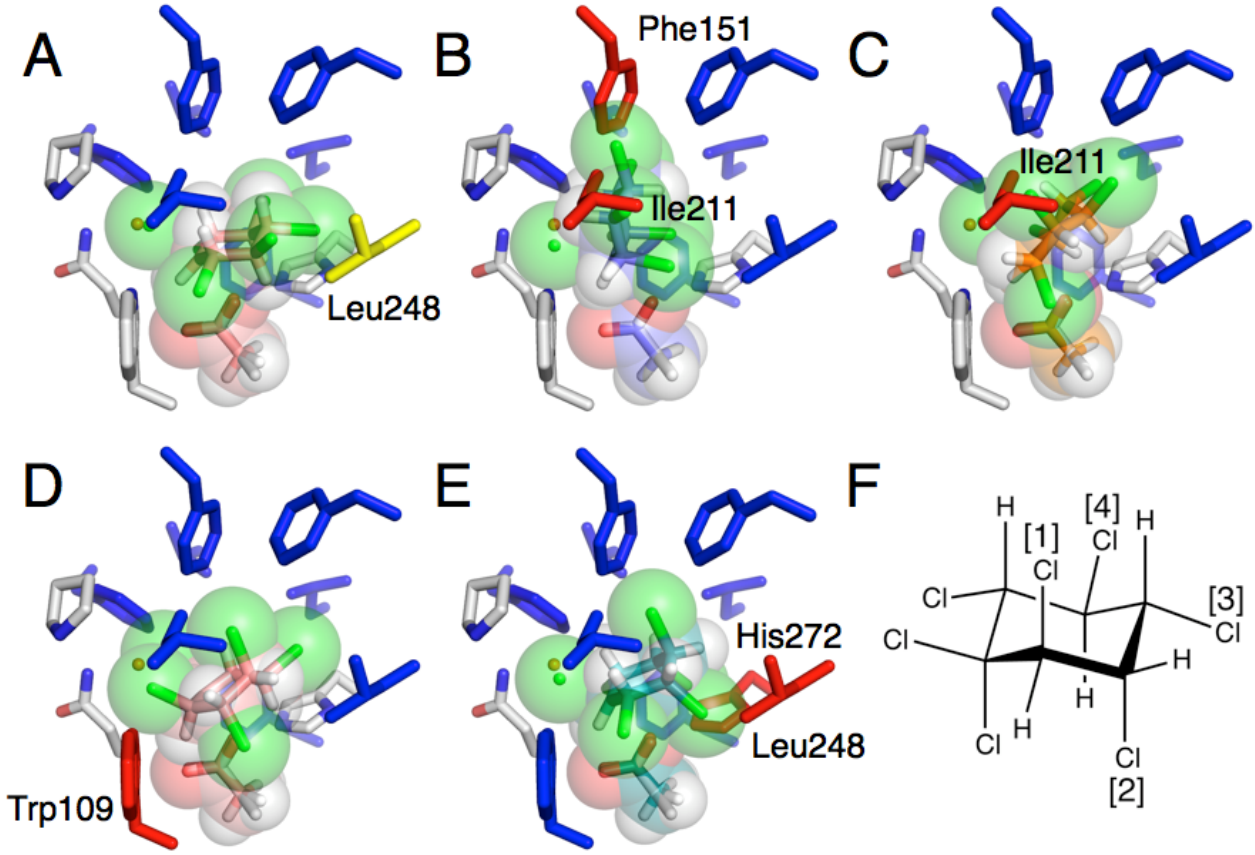
Isomer	Enzyme	Autodock Energy
β-HCH	LinA	-5.96
γ-HCH	LinA	-5.68
β-HCH	LinB	-7.17
γ-HCH	LinB	-3.04

ESI Figure S2: Structures of enzyme:substrate complexes obtained by AUTODOCK showing that β-HCH and γ-HCH do not bind productively in LinA and LinB, respectively. For LinA, γ-HCH (A) needs no rotation of the ring, a 50° tilt and 1 Å translation to acquire the TS geometry, whereas β-HCH requires a 70° rotation or the ring, a 15° tilt and a 1.7 Å translation. After this rotation the β-HCH (B) TS is still not well aligned, with the equatorial chlorine in the 3-position clashing with the extended Arg50 side chain, which will prevent leaving group stabilisation. For LinB, β-HCH (C) needs no rotation or tilt and less than a 1 Å translation to acquire the TS geometry, whereas γ-HCH (D) needs 70° rotation, a 10° tilt and a 1 Å translation. After this rotation, the γ-HCH TS is still not well aligned, with the leaving group being 2 Å from the 'anion hole.'



[1] [1] Okai, M., Kubota, K., Fukuda, Y., Nagata, Y., Nagata, K.. Tanokura, M. *J. Mol. Biol.* 2010, **8**. Epub.
[2] A.J. Oakley, M. Kivana, M. Otyepka, Y. Nagata, M.C. Wilce, J. Damorsky. *Biochemistry.* 2004, **43**, 870.
[3] D.S. Goodsell, G.M. Morris, A.J. Olson. *J. Mol. Recog.* 1998, **9**, 1.

ESI Figure S3: TSs of various isomers of β-HCH and γ-HCH superimposed onto the active site of LinB-UT26 (PDB ID: 1MJ5)[4]. Residues coloured yellow indicate a minor steric clash, residues coloured red a major steric clash. As seen in the Figure, the TS of β-HCH is well accommodated, the only minor steric hindrance being with Leu248. This is consistent with experimental data showing a variant containing a Leu248A mutation (LinB-B90A) displays a significant (10-fold) increase in the turnover rate.[5] The various isomers of γ-HCH, with attack at the 1, 2, 3, and 4 positions shown in panels B, C, D, E are all involved in significant steric clashes with residues Phe151, Ile211, Trp109, Leu248 and His272. Additionally the distances of the leaving group to the centre of the anion hole formed by Asn38, Pro208 and Trp207 is 0.5 Å for β-HCH, 0.9, 0.7, 2.1 and 0.6 Å for attack at the 1, 2, 3 and 4 positions.



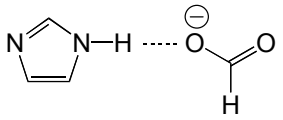
[4] A.J. Oakley, M. Kivana, M. Otyepka, Y. Nagata, M.C. Wilce, J. Damorsky. *Biochemistry*. 2004, **43**, 870.
[5] M. Ito, Z. Prokop, M. Klvaňa, Y. Otsubo, M. Tsuda, J. Damborsky, Y. Nagata. *Arch. Microbiol.* 2007, **188**, 313.

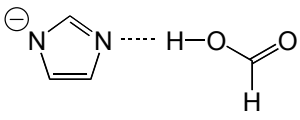
Quantum chemical calculations

All *ab initio* calculations were performed with GAUSSIAN 03[6], except the IRC calculations, which were performed with GAUSSIAN 09[7].

Choice of the model systems

To model the hydrolysis reaction catalysed by LinB, we have used an acetate anion to mimic the active site aspartic acid nucleophile. The choice of the system used to model the elimination/proton abstraction reactions catalysed by LinA was more complicated. LinA utilises an asp-his catalytic dyad, which could be modelled as either of the following species.

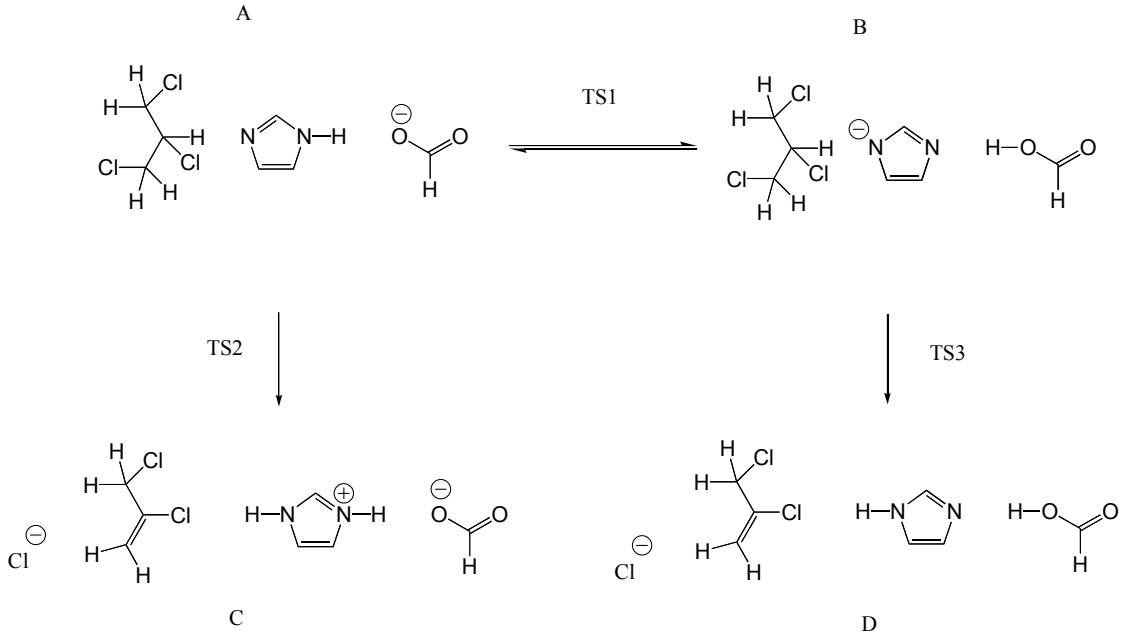




[6] Gaussian 03, Revision E.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Wallingford CT, 2004.

[7] Gaussian 09, Revision A.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

A priori, we did not know which of these species was the active base in the active site, nor which would result in the lowest energy transition state, and hence the fastest rate. To find the lowest energy transition state, we investigated the following reaction scheme in the gas phase, at the HF/6-31+G(d,p) level.



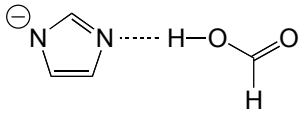
ESI Figure S4: Possible pathways for abstraction of a proton from an organochloride by an imidazole-formate dyad.

Transition states were linked to reactants by IRC calculations to verify the mechanisms. At this level of theory, minimum energy pathway is for sequential proton transfer: A→TS1→B→TS3→D. A high-energy second-order saddle point was found corresponding to concerted proton transfer, only just higher in energy than the process A→TS2. The salient features of the potential energy surface are given below (kJ/mol, relative to A)

ESI Table S2: Energies (kJ/mol) for the reaction described in ESI Figure 4.

	TS1	B	TS2	TS3	Sad. Pt.
HF/6-31+G(d,p)	17.3	5.7	138.9	111.3	139.9

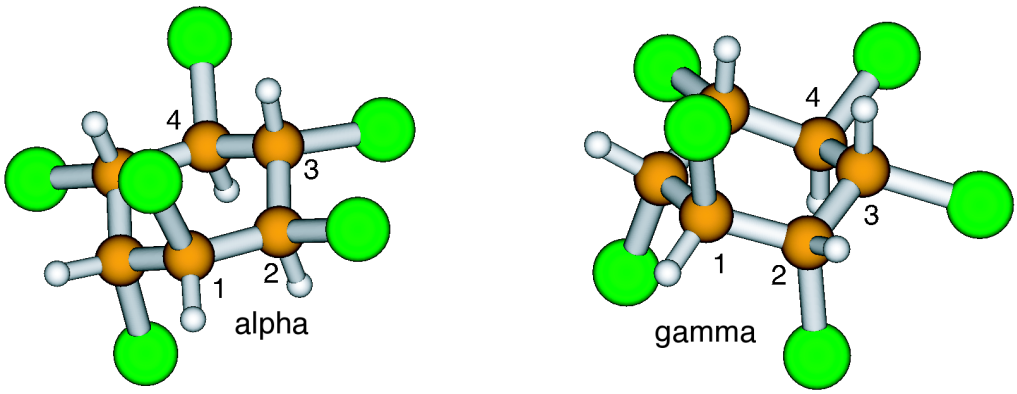
These results suggest that in the lowest energy, resting, state, the histidine will be neutral, but that for the reaction the lowest energy pathway is A→TS1→B→TS3→D and that the rate-determining step for the elimination process is the analog of B→TS3→D, meaning



is the best model for the attacking species in the transition state. We note that although deprotonation by this species at different positions of α-, β- and γ-HCH results in either E2 elimination or a stable carbanion intermediate depending on the substrate and the position of attack, the transition states for the two processes are similar.

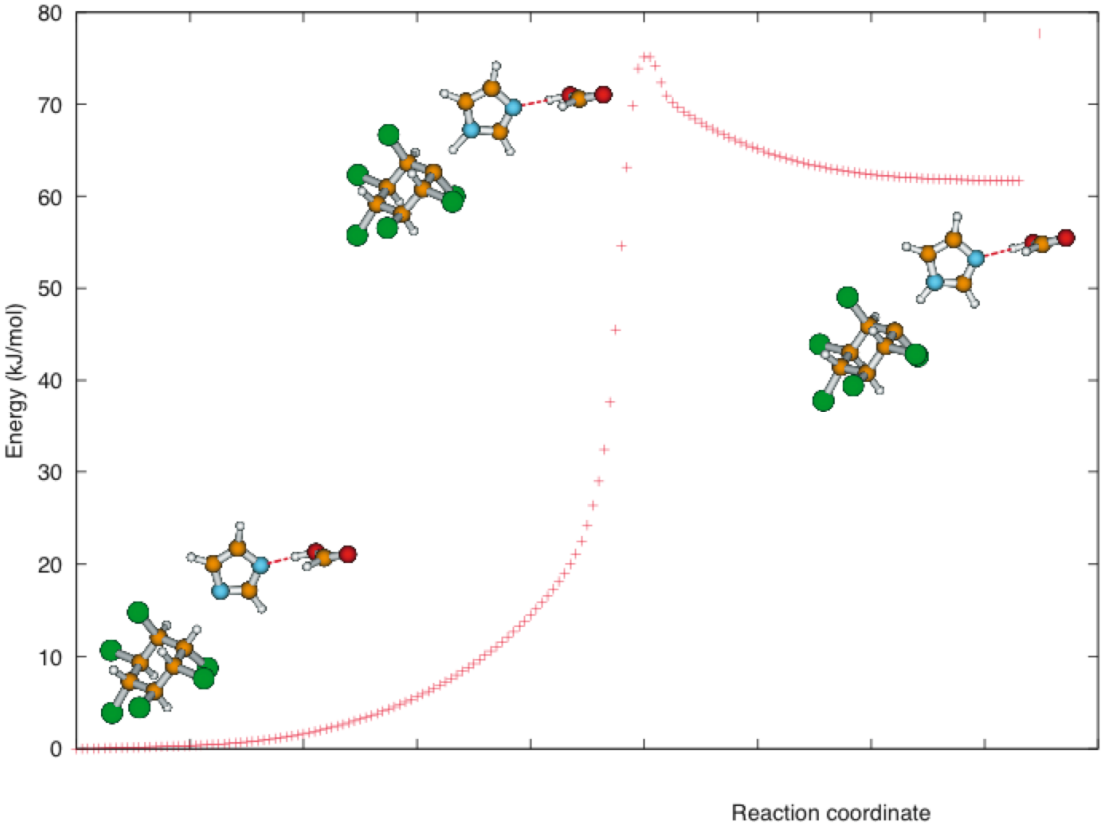
Geometry Optimisations

The geometries of the S_N2 transition states for attack at all unique positions of all isomers (described in ESI Figure 5, below) were screened at the B3LYP/6-31+G(d,p) level of theory. After obtaining a valid transition state at the B3LYP/6-31+G(d,p) level, two additional optimisations were carried out, where the dihedral about the forming bond was shifted by ±120 degrees. The lowest energy conformer was then optimised at the HF/6-31+G(d,p) level, and used for subsequent calculations. For the E2/"E1cb" calculations, transition state geometries for deprotonation at all unique positions of all isomers (described in ESI Figure 4, below) were screened at the HF/6-31+G(d,p) level of theory. For superposition of E2 transition states of α- and γ-HCH onto the active site of LinA, a constraint was placed on the dihedral angle between the imidazole and the HCH ring in order to keep the two species perpendicular as they are in the structure. This had virtually no effect of the energy of the TS (within 1 kJ/mol).

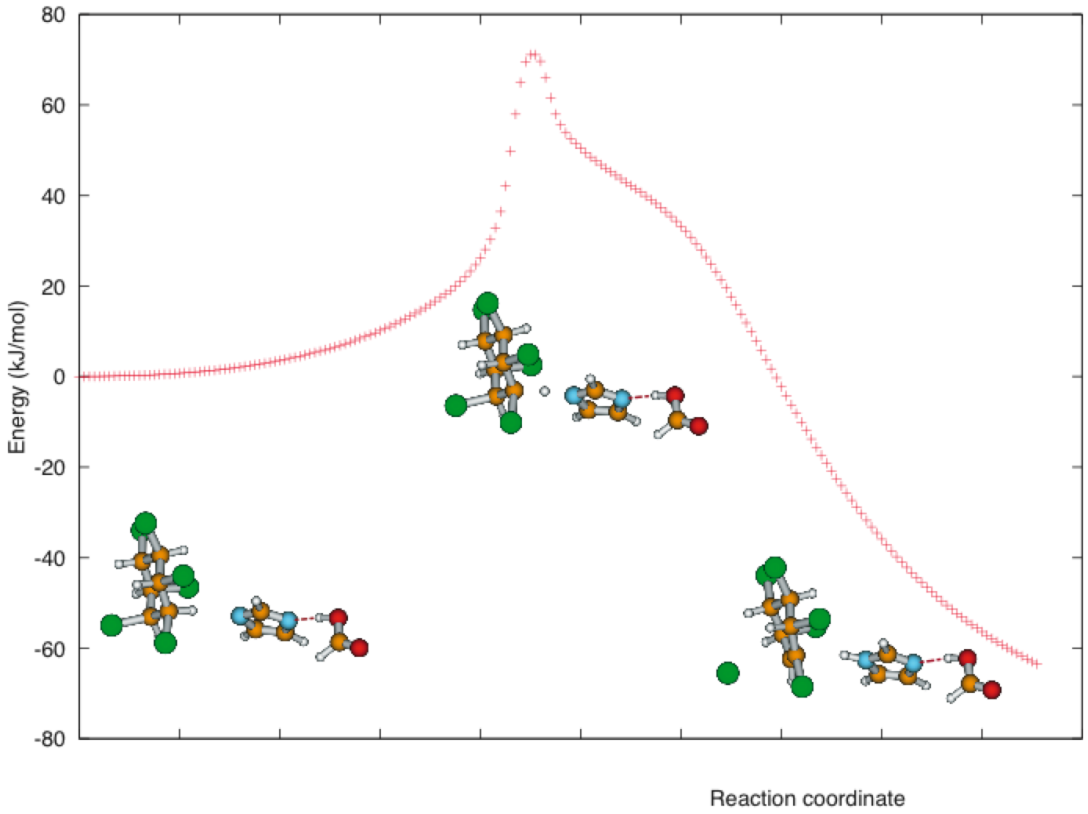


ESI Figure S5: Free energy barriers were calculated for E2/"E1cb" attack and SN2 attack at all positions of α-, β- and γ-HCH. α-HCH has C_2 symmetry with 3 distinguishable positions on the ring, β-HCH has D_{3d} symmetry, and all positions on the ring are equivalent, and γ-HCH has C_s symmetry with four distinguishable positions on the ring. We assumed C1 symmetry in the calculation of the rotational partition function that enters into the entropy because the enzyme active site has C1 symmetry.

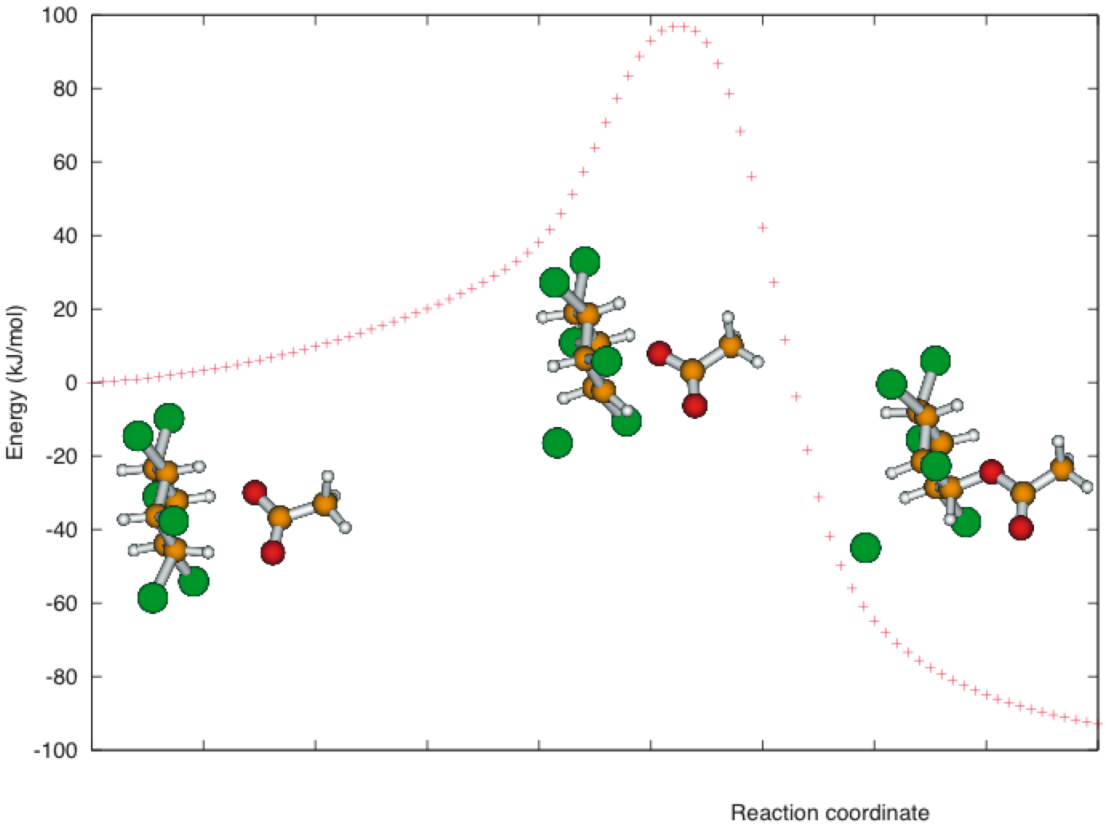
Intrinsic reaction coordinate calculations were performed from all transition states in both directions to ensure that the transition state connected the reactants and products of the reaction path under investigation. Representative examples are shown below.



ESI Figure S6. Reaction coordinate for the attack of a-HCH by [HCOO-…imidazole] at the 1-position. This results in an intermediate carbanion.



ESI Figure S7: Reaction coordinate for attack of a-HCH by [HCOO-…imidazole] at the 2-position. This results in E2 elimination.



ESI Figure S8: Reaction coordinate for S_N2 of β-HCH by acetate.

Energy Calculations

The harmonic oscillator approximation was used to calculate zero-point energies, temperature corrections and entropies, using HF/6-31+G(d,p) frequencies. The frequencies were scaled before calculating these values, using the scaling factors recommended for the HF/6-31+G(d) method, 0.9153 for zero-point energies, 0.8945 for the temperature corrections, and 0.9207 for the entropies[8].

Solvation energies were calculated using the CPCM method together with HF/6-31+G(d) (for which the method was parameterized), and the UAHF radii. These calculations were performed as single points on the gas-phase optimized HF/6-31+G(d,p) geometries, in accordance with the original parameterisation of this method. These solvation energies were then added to the high-level ab initio values of the free energies in the gas-phase, to obtain the corresponding solution-phase free energy:

$$G_{\text{soln}} = G_{\text{gas}} + \Delta G_{\text{solv}} + RT\ln\left(1\ \text{mol L}^{-1}\frac{RT}{P_0}\right)$$

[8] A.P. Scott and L. Radom, *J. Phys. Chem.*, 1996, **100**, 16502.

where the final term converts from the gas-phase standard state (defined by the NIST standard temperature and pressure T = 298.15 K and P_0 = 101325 Pa in our case) to the solution-phase standard state of 1 mol L^{-1}.[9] This final term is equal to 7.9 kJ/mol.

Free energy barriers were calculated from rate constants by rearranging the standard textbook formula[10] (the Eyring equation)

$$k(T) = (k_B T/h)\, c^{(1-m)} \exp(-\Delta G^{\ddagger}/RT)$$

where $-\Delta G^{\ddagger}$ is the Gibbs free energy of activation, R is the universal gas constant, k_B is the Boltzmann constant, h is Planck's constant, *m* is the molecularity of the reaction (1 for a unimolecular reaction, 2 for a bimolecular reaction etc.) and *c* is the standard unit of concentration. In the present work, the standard unit of concentration for both the experimental and calculated *solution-phase* free energies is c = 1 mol L^{-1}. For the pseudo-first-order enzyme catalysed reaction rates, *m* = 1, and $c^{(1-m)}$ =1 (dimensionless).

ESI Table S3: Energies of individual species

	RMP2/ gtmp2large (a.u.)	scaled zpe (a.u.)	MP2 free energy (a.u.)	$\Delta G_{solv.}$ (a.u.)
Reactants				
α-HCH	-2989.992332	0.113421	-2989.919775	-0.009036
β-HCH	-2989.986992	0.112993	-2989.915340	-0.015888
γ-HCH	-2989.986688	0.113394	-2989.914101	-0.009912
$acetate^-$	-228.125641	0.047288	-228.106340	-0.120444
$HCOO^-$-imidazole	-414.708774	0.091941	-414.653659	-0.098214
S_N2 transition states				
α1	-3218.116443	0.160936	-3218.005516	-0.067091
α2	-3218.109402	0.160989	-3217.998979	-0.064764
α3	-3218.115762	0.161344	-3218.003750	-0.067473
β	-3218.127947	0.161253	-3218.016349	-0.064381
γ1	-3218.098212	0.160810	-3217.987259	-0.070198
γ2	-3218.106054	0.161079	-3217.995650	-0.066421
γ3	-3218.104093	0.161434	-3217.992636	-0.064796
γ4	-3218.098624	0.161365	-3217.986994	-0.072365
E2 transition states				
α2	-3404.708406	0.201354	-3404.566435	-0.052860
γ3	-3404.701931	0.201387	-3404.559930	-0.052828
"E1cb" transition states				
α1	-3404.705223	0.201190	-3404.564120	-0.048987

[9] C.J. Cramer amd D.G. Truhlar in "Free Energy Calculation in Rational Drug Design", M.R. Reddy and M.D. Erion (eds.), Kluwer/Plenum: New York, 2001, p163.
[10] See for example D.R. Stull, E.F. Westrum, Jr. and G.C. Sinke, *The Thermodynamics of Organic Compounds*, John Wiley and Sons: New York, 1969; P.J. Robinson, *J. Chem. Educ.*, 1978, **55**, 509; J.I. Steinfeld, J.S. Francisco and W.L. Hase, *Chemical Kinetics and Dynamics*, Prentice-Hall: Englewood Cliffs, New Jersey, 1989.

α3	-3404.701208	0.201373	-3404.559020	-0.053832
β	-3404.702098	0.201016	-3404.560908	-0.052398
γ1	-3404.700997	0.201209	-3404.559501	-0.049975
γ2	-3404.697512	0.201101	-3404.556255	-0.052270
γ4	-3404.692864	0.201317	-3404.550790	-0.056174

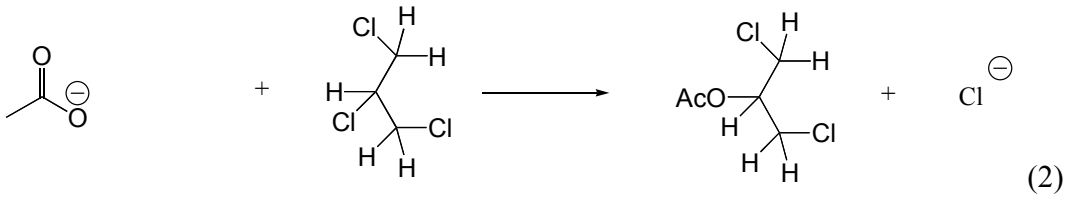
Free energy calculation by the ONIOM-core procedure

The free energy barriers for the various reactions described in this work were calculated *via* an ONIOM-type procedure[11]. We describe the electronic energy calculation first.

Using the S_N2 reaction as an example, we approximate the reaction

$$AcO^- + HCH \rightarrow AcO\text{-}HCH + Cl^- \qquad (1)$$

by the "core" reaction

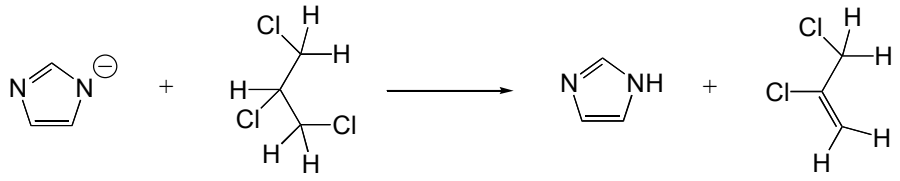


(2)

We calculate the barrier for the model reaction (1) at the G3(MP2)RAD level[12] (denoted E_{G3}(core)) and then add a correction for the neglected substituent effects at the computationally cheaper MP2/G3MP2LARGE level. Specifically, the term E_{MP2}(full)-E_{MP2}(core) is used, where E_{MP2}(full) denotes the barrier of the model reaction (1) calculated at the MP2/G3MP2LARGE level and E_{MP2}(core) denotes the barrier of the full reaction (2) calculated at the MP2/G3MP2LARGE level. This is effective because the energy difference E_{MP2}(full)-E_{MP2}(core) is intrinsically easier to model than either barrier on its own, due to error cancellation. For more details, see references in footnote 10.

All of the S_N2 reactions were modelled using the same core reaction (2), while all of the elimination reactions used reaction (3) for the core:

[11] E.I. Izgorodina and M.L Coote, *J. Phys. Chem. A*, 2006, **110**, 2486; E.I. Izgorodina, D.R.B. Brittain, J.L. Hodgson, E.H. Krenske, C.Y. Lin, M. Namazian, and M.L. Coote, *J. Phys. Chem. A*, 2007, **111**, 10754; C.Y. Lin, J.L. Hodgson, M. Namazian, and M.L. Coote, *J. Phys. Chem. A*, 2009, **113**, 3690.
[12] D.J. Henry, M.B. Sullivan and L. Radom , *J. Chem. Phys.*, 2003, **118**, 4849.



(3)

Since the model systems are the same for a given reaction type, E_{G3}(core)- E_{MP2}(core) is constant for a given reaction type.
Results from these ONIOM-core calculations are given in ESI Tables 4 and 5

ESI Table S4: ONIOM core calculations

	scaled zpe (a.u.)	CCSD(T)/ 6-31G(d) (a.u.)	RMP2/ 6-31G(d) (a.u.)	RMP2/ gtmp2large (a.u.)	Combined (a.u.)	G3(MP2)-RAD (a.u.)
$CH_2ClCHClCH_2Cl$	0.076259	-1495.830983	-1495.742065	-1496.171115	-1496.260033	-1496.438880
TS (acetate)	0.124252	-1723.715337	-1723.584065	-1724.295163	-1724.426435	-1724.718238
TS (imidazolide)	0.128714	-1720.828112	-1720.695268	-1721.383322	-1721.516166	-1721.817382
imidazolide	0.056892	-224.984276	-224.938208	-225.199104	-225.245172	-225.367541

ESI Table S5: ONIOM Reaction energies
The ONIOM correction E_{G3}(core)- E_{MP2}(core) is -13.6 kJ/mol for the SN2 reactions and +5.6 kJ/mol for the E2/"E1cb" reactions. This table is a more detailed version of Table 2 in the manuscript.

	Mechanism	$\Delta G^{\ddagger}_{gas}$ (kJ/mol)	$\Delta G^{\ddagger}_{solv}$ (kJ/mol)
SN2 transition states			
α1	SN2	40.5	196.4
α2	SN2	57.6	219.7
α3	SN2	45.1	200
β	SN2	0.4	181.4
γ1	SN2	73.5	223.6
γ2	SN2	51.5	211.5
γ3	SN2	59.4	223.6
γ4	SN2	74.2	218.6
E2 transition states			
a2	E2	24.0	158.9
g3	E2	26.2	163.4
"E1cb" transition states			
α1	carbanion	30.1	175.1
α3	carbanion	43.4	175.8
β	carbanion	26.8	180.9
γ1	carbanion	27.3	172.1
γ2	carbanion	35.8	174.6
γ4	carbanion	50.2	178.7

All transition states were linked with reactants and products using IRC calculations to verify the mechanisms given in the table above. These calculations were performed with

GAUSSIAN 09[7] instead of GAUSSIAN 03[6] to take advantage of improvements in the algorithms[13,14,15]. IRC calculations were performed with a stepsize of 0.1 atomic units, for upt to 100 steps. We include three representative examples below.

Appendix A

Geometries

Reactants

alpha

```
0 1
C -0.0045008683 0.023115074 0.010964691
C 0.0009261925 0.026587404 1.541741085
C 1.4314505533 0.0268862241 2.0842979694
C 2.2745095774 1.1839153046 1.5364686368
C 2.2353282852 1.2443759201 -0.0051704189
C 0.8003030572 1.2008646793 -0.54217808
H -0.5159738217 -0.8443496762 1.9093886897
Cl 1.4174623685 0.0007542443 3.8676556499
H 1.9341594287 2.1201620913 1.9506838337
Cl 3.0260534555 2.7554139221 -0.5447923642
Cl 0.7575854139 1.197194787 -2.3252673844
Cl 0.6036951175 -1.5713198297 -0.5546459243
Cl 3.9719156088 0.9841200055 2.0642674805
H -1.0178311227 0.0876040536 -0.3494311453
H 1.8809953323 -0.9083850981 1.7889444794
H 2.8121604442 0.432754757 -0.4205115688
H 0.2851108942 2.1015283186 -0.2464810798
Cl -0.9663499165 1.4317778186 2.1090654504
```

beta

```
0 1
Cl 0.0496655492 -0.0860756423 -0.1376512731
C -0.0066320135 0.0114257661 1.6471375401
C 1.4243737309 0.0764568972 2.1928612991
H -0.5333875057 0.9237143977 1.8871890183
C 1.461951721 0.0113971468 3.7239591514
```

[13] H. P. Hratchian and H. B. Schlegel, *J. Chem. Phys.*, 2004, **120**, 9918.

[14] H. P. Hratchian and H. B. Schlegel, in "Theory and Applications of Computational Chemistry: The First 40 Years", C. E. Dykstra, G. Frenking, K. S. Kim, and G. Scuseria (eds.), Elsevier: Amsterdam, 2005, 195-249.

[15] H. P. Hratchian and H. B. Schlegel, *J. Chem. Theory and Comput.,* 2005, **1**, 61.

```
H 2.0135748013 -0.7276575165 1.7762009322
Cl 2.1904807227 1.5988443695 1.651079119
C 0.6901904536 -1.1954313004 4.269662676
Cl 3.1633985045 -0.086153529 4.2657758599
H 1.0600311551 0.9236784028 4.1405833822
C -0.7408318164 -1.2605006374 3.7239283326
H 1.2169694007 -2.1077167535 4.0296399604
Cl 0.6339464037 -1.0978550024 6.0544535714
C -0.7783956243 -1.1953974299 2.1928315089
Cl -1.5069373878 -2.7828945716 4.2656222199
H -1.3300300115 -0.4563805634 4.140583797
H -0.3765113517 -2.1076754176 1.7761616331
Cl -2.4798567317 -1.0977786161 1.6509812716
```

gamma

```
0 1
C -0.0559842431 0.0203387998 0.0435232444
C 0.0360974154 -0.024312412 1.5739179403
C 1.480632112 -0.0903440791 2.0934349272
C 2.2369319129 1.1382464798 1.5647211653
C 2.2419199444 1.2342308343 0.0339255465
C 0.8236639374 1.1324392558 -0.5475437692
Cl -0.9928274506 -1.3314935282 2.2141225668
Cl 1.4738021236 -0.0633303184 3.8805955725
H 1.7386143352 2.0241909476 1.9312973634
H 2.657396073 2.1891002678 -0.2419266318
H 0.8761325349 1.0246580458 -1.6171757215
Cl 0.3300714747 -1.5474512887 -0.7327197541
Cl 3.9008232216 1.2534198469 2.1935878947
H -1.0806830246 0.2144079926 -0.2263290478
H 1.9641560196 -1.0080592604 1.7965164999
Cl 3.3142761436 0.0290118908 -0.7452095671
Cl -0.0106516011 2.7139667292 -0.2729826134
H -0.4123709289 0.8879797964 1.9402443841
```

acetate

```
-1 1
C -0.0106815432 0.0140149359 -0.0000402733
C -0.0066326503 0.007694129 1.5465365129
O 1.1024568372 -0.1330806952 2.0783363724
O -1.1161475648 0.1153347702 2.0851533208
H -0.8441736478 0.5930226486 -0.3862949787
H 0.9278129802 0.3947428348 -0.3917379891
H -0.1265250665 -1.0117379906 -0.3483396305
```

HCOO-…imidazole

```
-1 1
O 0.359810188 0.0120987835 -0.1434017361
C 0.0538822915 0.0133260225 1.0399593881
```

```
O 0.791414818 0.0068110078 2.0477777701
H -1.0359406238 0.021167596 1.2624054547
H 0.3811634769 -0.0126573121 3.6883652151
N 0.1621711077 -0.0306955917 4.6937126006
C -0.0635381766 -1.1320856365 5.4617138515
H -0.0234780668 -2.1222264719 5.0601281391
H 0.1686844312 2.0292732283 5.1508701854
C 0.0378219476 1.0267949296 5.5043403553
N -0.2493309463 0.6975070024 6.731667954
C -0.3166784092 -0.6689893975 6.7151916472
H -0.5400646546 -1.2321031663 7.5987578392
```

SN2 transition states

alpha 1

```
-1 1
C 0.0940862417 0.2402037193 0.0044455448
C 0.0875732619 0.1687572861 1.5431772292
C 1.4752043158 -0.2161201597 2.0638353037
C 2.0768301632 -1.4544769487 1.4601672477
C 1.9833869818 -1.4784425802 -0.0751231945
C 0.599246164 -1.0656330379 -0.6177544305
Cl -1.1681381475 -1.0067137536 2.0686587131
Cl 2.7525145968 1.501239812 0.912006783
Cl 3.754639035 -1.7073685242 1.995866033
Cl 2.3354367112 -3.156189905 -0.6393977362
Cl 0.7212777672 -0.8807557199 -2.4025101801
Cl -1.5370883941 0.6739430456 -0.613063024
H 1.9070993915 0.3191847283 2.865071469
H 2.7474325504 -0.850021183 -0.4951182747
H -0.1867817403 1.117086449 1.9692923507
H 1.5082300706 -2.2706543816 1.8751970695
H -0.1142769822 -1.8559655087 -0.4523002767
H 0.7243896459 1.0553171022 -0.2892620944
O 1.0581793489 -1.3620541792 3.8838048735
C 0.72009396 -0.6285371773 4.8503663364
O 0.5054683686 0.5764101918 4.783635331
C 0.5710298686 -1.3414752132 6.1886943043
H 1.4805916297 -1.8885346967 6.4151271142
H 0.3541917332 -0.6347116593 6.9798284743
H -0.234616542 -2.0664877058 6.1163550339
```

alpha 2

```
-1 1
C -0.1142584991 -0.1836184594 -0.2632072229
C -0.260662621 0.4161754913 -1.6780292172
C 1.0911830443 0.5011480334 -2.4348057179
C 2.2875480214 0.559050753 -1.4743789609
C 2.0096528493 1.1692434029 -0.1178868731
C 0.6753969944 0.8517391643 0.555497138
```

```
Cl -1.5377349931 -0.3571560145 -2.6655917653
Cl 1.3987773465 -0.8931071768 -3.5407933093
Cl 3.7145327028 1.2781953421 -2.258474757
Cl 0.8311242831 0.4502521587 2.2840075541
Cl -1.7173639732 -0.4375553829 0.4956245704
O 3.033886653 -0.5684514072 0.7090375003
C 4.0037682635 -0.311304859 1.4796058573
C 4.6871115527 -1.5324756741 2.081539085
O 4.403029428 0.8056528682 1.7683236704
Cl 1.3368694818 3.3378728691 -0.9210461422
H 2.5809606345 -0.4471206265 -1.2461934016
H 0.1123786486 1.7645738848 0.5604376709
H 1.0651044557 1.3697228111 -3.067281301
H 2.7747163009 1.6794158922 0.422622855
H 0.3733692661 -1.1462822987 -0.2703055336
H -0.5955250602 1.4339558598 -1.565965319
H 4.9832618173 -2.2162877984 1.2922855545
H 3.9782638434 -2.0559788669 2.7166113589
H 5.551609559 -1.2406599666 2.6643667063
```

alpha 3

```
-1 1
C -0.0013798682 -0.0314809429 0.0043045296
C 0.0041674571 -0.0220986768 1.5370625282
C 1.4191283669 0.0931391051 2.103285683
C 2.1240423375 1.3829015825 1.662099462
C 2.0420740809 1.5772814086 0.1342178126
C 0.7459326328 1.1742401189 -0.5577927848
Cl -0.7871854884 -1.4909635812 2.2089794221
Cl 2.4707607863 -1.3073180815 1.6466849299
Cl 1.5947655001 2.7250449175 2.7257659586
Cl 2.6065518098 3.1836639933 -0.372523422
Cl -1.6533111174 -0.1104972364 -0.6586318471
O -0.4956140154 2.5244510152 0.6234313576
C -1.0884109741 3.4140923388 -0.0519921963
C -2.0014442132 4.3259609155 0.7595885994
O -0.9896751076 3.5827855006 -1.2566469536
Cl 1.728308366 0.0778263709 -2.3717376765
H 3.171230873 1.2878381589 1.8946170542
H 0.302841875 1.8042148991 -1.2916826216
H 1.3737716595 0.0627327345 3.1778503677
H 2.7834818554 0.898332614 -0.2470210351
H 0.4890387048 -0.9209939574 -0.3446923383
H -0.5650247979 0.8169378987 1.8947032495
H -2.4330922912 5.0952985735 0.1316376346
H -2.7939843211 3.7327029577 1.2068022961
H -1.4369741107 4.7789073729 1.5686899899
```

beta

```
-1 1
```

```
C 0.0083044803 -0.1195207419 0.1531846004
C 0.0187161579 -0.0793414096 1.6696645948
C 1.4280886316 -0.20328295 2.2621923659
C 2.2155974674 -1.3591109999 1.6303477518
C 2.2526400887 -1.3155798225 0.0967007745
C 0.8474878685 -1.1972566312 -0.5069000364
Cl -0.7858851083 1.3962783834 2.2619049679
Cl 1.267275298 -0.5262734393 4.0329858612
Cl 3.9017851741 -1.329722456 2.2572938247
Cl 2.9923933419 -2.8535211838 -0.4977770963
Cl 0.9383854942 -0.9295201533 -2.2663389357
Cl -2.0618092486 -1.2672986469 -0.0457079575
H -0.5817267844 -0.8998942096 2.0194295668
H 1.9619103966 0.7207326664 2.1619143901
H 1.7986818837 -2.3008432249 1.9553183673
H 2.8789825702 -0.5163444622 -0.2464316109
H 0.3318708974 -2.1322399723 -0.3799576885
H -0.4677483191 0.6411110002 -0.4186600794
O 1.6129034168 1.3081798182 0.0307642962
C 1.3372061259 2.366194633 -0.6182110377
O 0.2728337781 2.6149076206 -1.1512265889
C 2.4780094813 3.3717519204 -0.7009624769
H 2.1769730233 4.2448251495 -1.265494383
H 2.7758553103 3.6659685483 0.3008967911
H 3.3382685741 2.9068005634 -1.1729302614
```

gamma 1

```
-1 1
C 0.2645777451 0.0109852856 -0.1383074611
C -0.0260434571 0.0690047441 1.3754433893
C 1.2549627578 0.0323388867 2.2256121837
C 2.1476718607 1.2242220013 1.8427811264
C 2.5257806754 1.2492417678 0.3432581688
C 1.2809033163 1.0791366217 -0.5223193656
Cl 0.8268767855 -1.6287934686 -0.5963388529
Cl -1.1824835555 -1.2243489542 1.8338851308
Cl 0.8224455418 0.1518640472 3.9659424378
Cl 3.6252168368 1.3206165074 2.8580111409
Cl 3.7723349123 0.0166543111 -0.0209522735
Cl 0.0866844698 3.0894921406 0.3286129574
H -0.631207135 0.1891669637 -0.7057944888
H -0.5502868183 0.986683418 1.5677235506
H 1.7762293538 -0.9041559589 2.1082164649
H 1.6173281387 2.1344324822 2.0498560607
H 2.9696314431 2.2016995596 0.1139517838
H 1.1016039496 1.6858926573 -1.3638953205
O 2.2011207925 0.3121965354 -2.4525518904
C 1.3374881047 0.2935862355 -3.3654868104
O 0.1443927241 0.5512934139 -3.2271333295
C 1.853209289 -0.0997226015 -4.7461069209
H 1.0842671836 0.0316050349 -5.4973620291
H 2.7282151403 0.4912742334 -4.9965226023
```

```
H 2.1610799451 -1.1413658642 -4.7215230501
```

gamma 2

```
-1 1
C 0.1723494889 -0.5410263671 -0.2457592726
C 0.1023501699 -0.8317052055 1.2510032841
C 1.2376853984 -0.1189416974 2.0053405115
C 1.0941773542 1.3781114356 1.6638257094
C 1.3992104297 1.6921441565 0.1777960662
C 1.1632810186 0.4895551462 -0.7534487915
Cl 1.6191199616 -2.3691423661 -1.0309868696
Cl -0.0860100315 -2.5498719799 1.6628505203
Cl 1.0458063696 -0.3907033384 3.7661496686
Cl 1.9842400034 2.4664100296 2.7733807251
Cl 3.0979173373 2.2323752894 -0.1232952417
Cl 0.7444266329 1.0411430342 -2.3980344735
H -0.5461941194 -0.98981157 -0.8919475527
H -0.8248267672 -0.3898646834 1.5622383563
H 2.2071700746 -0.5140458978 1.7411142118
H 0.0606253482 1.6433114049 1.8022465867
H 0.7807059172 2.5193871669 -0.1137027008
H 2.093952365 -0.0266151287 -0.8704584274
O -1.2588907812 1.0272071891 -0.0274306241
C -2.3820235983 0.813194384 -0.5843831458
O -2.7455405526 -0.2509631218 -1.0483790514
C -3.3012280548 2.0242112538 -0.6494536874
H -3.4182400423 2.4545427222 0.3401159505
H -2.8454090048 2.7799739446 -1.2822219538
H -4.2676549175 1.749124199 -1.0515597983
```

gamma 3

```
-1 1
C -0.0706994304 0.3999135918 0.0409192657
C 0.1768083829 0.1642930959 1.5449055574
C 1.5586476491 0.3040575603 2.1767074451
C 2.410449697 1.3328475487 1.4342178952
C 2.4808478104 1.0059084544 -0.0544268711
C 1.1080626493 1.0416880147 -0.7346256111
Cl -0.6575145626 -1.0098135883 -0.8971250989
Cl 0.1429831414 -2.2435320389 1.9386117044
Cl 1.4157958398 0.6650190064 3.9186107089
Cl 4.0750617841 1.4245400275 2.1076733579
Cl 3.2233485842 -0.6064929781 -0.3765999211
Cl 0.7394731556 2.7558042498 -1.1848063094
H -0.9090651149 1.0656652895 0.0316638667
H -0.6866292453 0.0710796416 2.15392278
H 2.0401983631 -0.652842647 2.1291229761
H 1.9909634591 2.3157235914 1.5469059471
H 3.1301507069 1.7120383309 -0.5420606507
H 1.1992484186 0.5527676457 -1.6854317764
```

```
O -0.1317475662 2.2400139657 1.8504096676
C -1.3309650835 2.6200511319 1.9970604686
O -2.3171325809 1.9573866474 1.7174295541
C -1.4918551683 4.0230288632 2.56160295
H -2.5391489225 4.280235459 2.6553229954
H -1.0084805663 4.077067381 3.5318900554
H -0.9938014007 4.7335517553 1.9090990433
```

gamma 4

```
-1 1
C -0.1622901442 0.2843118288 -0.161761709
C 0.0006803632 -0.1184740874 1.3184137259
C 1.3920833367 -0.0307239164 1.9326387655
C 2.2686031922 1.1135102803 1.4392631064
C 2.1411411839 1.5355898461 -0.0390188638
C 0.681478596 1.5177800203 -0.5177583044
Cl 0.0320811839 -0.9705355657 -1.4210993191
Cl -0.8062316243 -1.6582271648 1.687103477
Cl 0.7862295853 0.8896992097 3.9193242105
Cl 3.9636658226 0.9328644332 1.9412749919
Cl 3.1897914944 0.7448105268 -1.252835252
Cl -0.1523330555 2.9849625777 0.1728941599
H -1.196337224 0.5660815055 -0.2685420343
H -0.584733475 0.6179047171 1.8390191401
H 1.8019801937 -0.8398912726 2.4893087139
H 1.9261330364 1.9818566886 1.9728186569
H 2.4733788909 2.5595594354 -0.0729895827
H 0.6532608644 1.6740176284 -1.580946735
O 2.2517494383 -1.4708768731 0.4818414986
C 2.768243551 -2.4760061196 1.0327899064
O 2.8211944019 -2.6919704172 2.2385641479
C 3.3732969058 -3.49494751 0.0711376812
H 3.7969694165 -4.333244411 0.6108355108
H 2.6048494266 -3.845038525 -0.611702809
H 4.1421146393 -3.0130128353 -0.5255730836
```

E2 transition states

alpha 2

```
-1 1
C -0.088558862 -0.0546767319 0.1050620593
C 0.0006305248 0.0770453302 1.6209206932
C 1.423915182 0.0932819383 2.1018089464
C 2.2689748656 1.1751926202 1.4242173112
C 2.1688209515 1.0563240042 -0.0964044797
C 0.7234015975 1.0505060751 -0.5974625869
Cl -0.8526643303 -1.32384964 2.3982378092
Cl 2.3871610485 -1.4889140105 1.8313451605
Cl 1.7839577984 2.7910373766 2.035559887
Cl 3.168986081 2.3173771077 -0.8886316304
```

```
Cl 0.7245873529 0.7653337094 -2.3760904422
Cl -1.8078160083 0.0750040232 -0.4371544513
N -1.5457249045 1.9846102854 2.7590261501
C -1.3052783371 2.6876569567 3.9043258825
C -2.4491992359 3.3473483643 4.2291495508
N -3.4079281851 3.0601243088 3.2973843328
C -2.8122857162 2.2441262773 2.454199286
H 1.4632972571 0.2011166298 3.1717318771
H 0.2349474565 -1.0225609396 -0.2533240771
H 3.300622588 1.0654593263 1.7115797018
H -0.7656326574 1.1614794998 2.1778549602
H 0.2590516552 2.0114621322 -0.4452800641
H 2.6352966441 0.12321291 -0.368398313
H -0.3538544649 2.6746207814 4.3940443903
H -2.6395755268 4.0026752431 5.0555929074
H -3.294577097 1.8192335746 1.5974123361
H -5.0220791531 3.7083355172 3.2685485502
O -5.954355209 4.0080645279 3.3392580136
C -6.6649408753 3.1696818947 4.0362262877
O -7.8236850997 3.3084241823 4.280735652
H -6.1034074447 2.3045540864 4.3912261126
```

gamma 3

```
-1 1
C 0.0192393838 -0.0445700665 -0.0353451059
C -0.0174804687 -0.0898207923 1.4924156324
C 1.3598651235 0.0020267142 2.0968704106
C 2.3451139208 -1.0310622347 1.5288244347
C 2.2674950188 -1.2472272014 0.0099924308
C 0.821531412 -1.2695333993 -0.4920594327
Cl -1.0241714907 1.2656072348 2.1532746655
Cl 2.2000126158 1.6533694092 1.9489827048
Cl 2.0731214015 -2.6303443346 2.3299099441
Cl 3.2867751326 -0.0243246672 -0.8340299419
Cl 0.811134286 -1.5402062037 -2.2680315135
Cl -1.6507923979 -0.144402757 -0.7121968258
N -1.5104783966 -2.1200958444 2.5008393705
C -2.7252727657 -2.5209054089 2.0242785454
C -3.2201845985 -3.4422980946 2.8933924151
N -2.3273532726 -3.6170823398 3.9156400211
C -1.3356269974 -2.804814874 3.6263648299
H 0.3559338849 -2.1504038389 -0.0763639408
H 2.7312781866 -2.1879103681 -0.2326410406
H 3.3506407029 -0.7644997159 1.7997893618
H 1.2999096438 -0.1161860785 3.1647982492
H 0.4288232232 0.8670550293 -0.4484352035
H -0.763162437 -1.2362322353 2.0159669476
H -3.1388803498 -2.1227670074 1.1221139672
H -4.1443770676 -3.9829075371 2.8499169837
H -0.4596617813 -2.7013915263 4.2351912769
H -2.4717758953 -4.7226867197 5.2553163322
O -2.6162445432 -5.2737848992 6.0541770645
C -3.2924275073 -4.6238492502 6.9569280205
```

```
O -3.6045397585 -5.0711627511 8.016903637
H -3.5601460725 -3.6085896278 6.6612003719
```

"E1cb" transition states

alpha 1

```
-1 1
C 0.0277911422 -0.0573716102 -0.0038666963
N 0.0175186032 -0.037052139 1.3609802538
C 1.2957343071 -0.0156834379 1.7235432783
N 2.1321026584 -0.020455086 0.7097302051
C 1.3291517823 -0.047513497 -0.3980913953
C -2.0956919765 -0.1048665146 3.0400375517
C -3.1606454955 -1.0974243895 2.58860916
C -4.3078353794 -1.2523565288 3.5894338178
C -4.9600285176 0.0850661174 3.9448949462
C -3.9179257585 1.1331549283 4.3822857054
C -2.7494391603 1.222477868 3.3908041685
Cl -5.5247355723 -2.4490600408 3.0210413704
Cl -3.7798845382 -0.5732806938 0.9592962733
Cl -1.3335358353 -0.8672022019 4.5531968324
Cl -1.5298783702 2.4049222323 3.9821722913
Cl -4.7504980747 2.7289598101 4.5217502604
Cl -6.1431135123 -0.1564331197 5.2821458139
H -0.9566928277 -0.0317769494 2.1016424936
H -3.5517405135 0.9023885498 5.3690890967
H -2.7160259922 -2.0629641459 2.4130500601
H -3.1123203571 1.6435965034 2.4652556903
H -5.5315614735 0.4555702249 3.1093119037
H -3.8851923174 -1.69033572 4.4782121024
H -0.8746295824 -0.0788542746 -0.5786439349
H 1.7337915262 -0.061458458 -1.3902081619
H 1.5994786692 0.0022833693 2.7512270576
H 3.8816962226 -0.055131854 0.7092987252
O 4.8575457642 0.029869172 0.6750622974
C 5.2182816873 1.2796501427 0.6176131624
O 6.3488027767 1.6521554387 0.5565164782
H 4.3826908207 1.9806698653 0.6293665637
```

alpha 3

```
-1 1
C 0.0190972608 -0.1343560206 0.0168651834
N 0.0538703589 -0.0404489172 1.3414253832
C 1.3623072348 0.1936294246 1.6512616717
C 2.0576283166 0.224277833 0.4829775568
N 1.1929132643 0.0146266352 -0.5570591985
C -2.0531315374 -0.1192488167 3.0507072616
C -1.7912363321 -0.7701009847 4.4184528412
C -1.817174643 -2.2958930067 4.3034181799
C -3.1410534275 -2.8132660269 3.7427805926
C -3.4531537017 -2.16365036 2.3943487604
C -3.3773652034 -0.6379848954 2.4932965789
```

```
Cl -0.1728061349 -0.2596538298 5.0434667431
Cl -2.3167067373 1.6671647774 3.3921663623
Cl -3.7726160396 0.070307158 0.880211457
Cl -2.3437197217 -2.8837204665 1.1747519317
Cl -4.5385366577 -2.5246383679 4.8520182978
Cl -1.4590278991 -3.134497746 5.8518234238
H -4.4409650553 -2.4513984011 2.0748206935
H -0.9114766194 -0.1240207526 2.1202592746
H -3.093403816 -3.883527665 3.6344667461
H -4.2186007739 -0.3395292026 3.1054493194
H -2.4840643604 -0.4478154781 5.1833101553
H -1.0393469978 -2.6120424552 3.6262842648
H 1.6917579766 0.3209667841 2.6605707389
H 3.1062442119 0.3796422549 0.3252941633
H -0.8889456876 -0.3160791447 -0.5219730875
H 1.6121984103 -0.0813646266 -2.2365885528
O 1.8590298635 -0.0298310028 -3.1865004326
C 1.7837858066 1.1928045038 -3.6249957114
O 2.0407763281 1.5263729431 -4.740779546
H 1.4585632076 1.9119967874 -2.8721214004
```

beta

```
-1 1
C -0.0278534963 0.0122731459 0.0182485891
C 0.030835385 0.0910466086 1.5410831112
C 1.4893522186 0.0315527915 1.9857312053
C 2.2838146201 1.2029583745 1.4008810558
C 2.1758563596 1.2525160779 -0.1251723947
C 0.7272408652 1.1846635347 -0.6146346279
Cl -0.7626897114 -1.4358067729 2.1680233059
Cl 1.5964371914 0.1265076733 3.7884699816
Cl 4.0264375517 1.0535702113 1.8364025973
Cl 2.9418668972 2.7624583852 -0.7303765898
Cl 0.7473511467 1.0180740787 -2.4096782342
Cl -1.7447234283 0.0798754006 -0.5457193281
N -1.321284419 2.2148132522 2.5692052209
C -2.3320463222 2.9136002265 1.9731266281
C -2.6913894813 3.9102186011 2.8252394925
N -1.9164010996 3.8387493233 3.95046945
C -1.1231356916 2.8124562829 3.7407545053
H 1.9788997393 -0.9031978384 1.736472959
H 1.9432713675 2.130859902 1.8323342363
H 2.7418143152 0.4398970635 -0.5550403715
H 0.2151869543 2.1100392411 -0.4034121344
H 0.3488436992 -0.9231085131 -0.3802299133
H -0.7180888676 1.2487855958 2.1134620321
H -2.7175546636 2.6458151153 1.0118402445
H -3.4452963703 4.6619218277 2.7038665238
H -0.3836307857 2.4756324702 4.4390669645
H -1.9861098137 4.9338190229 5.3195357996
O -2.1199631075 5.4937874744 6.1118660746
C -3.0082344646 4.9738897722 6.9098811311
O -3.3599731646 5.4654239547 7.9369402996
```

```
H -3.4182387753 4.0270468971 6.5561692884
```

gamma 1

```
-1 1
C 0.0411289402 -0.0104268956 0.0520257751
N 0.0282603038 0.0054097798 1.4159963992
C 1.3070300265 0.0223303374 1.7808465541
N 2.1449516477 0.0179108316 0.7686365109
C 1.3428614013 -0.0023560036 -0.340700462
C -2.0792265618 0.006016601 3.0950612992
C -2.9171872761 1.2818878219 3.0973482305
C -4.1092583576 1.2424455192 4.0627748869
C -4.9828328632 -0.0070802511 3.8862908967
C -4.0913825249 -1.2401236494 4.0875102042
C -2.8985006323 -1.2816425106 3.1231465057
Cl -1.1560731833 0.0288945035 4.7261910114
Cl -3.4462692718 1.6761894737 1.4094982978
Cl -5.0606192021 2.7655800936 3.996640389
Cl -6.2992520525 -0.0043827401 5.113657365
Cl -5.0206137757 -2.7778750754 4.0518332556
Cl -3.4208175523 -1.7182385646 1.4435556055
H -3.677538082 -1.1997087172 5.0832914379
H -2.2593047021 -2.0968194691 3.4170366749
H -0.962156635 0.0050832261 2.1442757973
H -2.2898793971 2.1121371781 3.3741853203
H -5.4663497281 -0.0201423179 2.9226696201
H -3.6949255863 1.2278785098 5.0590651991
H -0.8618002859 -0.0248959756 -0.5218960709
H 1.7487883458 -0.0060255202 -1.3323432877
H 1.6105737494 0.0398427963 2.8086694285
H 3.8902964668 0.0848573023 0.7886782127
O 4.8684176832 0.0147189916 0.7771891287
C 5.2486839567 -1.2290484257 0.7208528111
O 6.3856719686 -1.5855801445 0.6895069865
H 4.4231541821 -1.9418566866 0.7035819996
```

gamma 2

```
-1 1
C 0.0125804036 -0.011982448 0.0016375089
C 0.0266412361 0.0145997544 1.524842038
C 1.4546410878 -0.0059008488 2.0500007919
C 2.481115151 -0.9273625968 1.3620094405
C 2.3350589789 -0.8758984487 -0.1614558415
C 0.8958795113 -1.0935629417 -0.6473662744
Cl -0.8200664404 -1.4715889452 2.2089674965
Cl 2.1535561764 1.6909368531 1.8966576062
Cl 2.3655903171 -2.5964653128 2.0248113111
Cl 3.5218785123 -1.9769995986 -0.9366928664
Cl 0.8595858292 -0.9475500759 -2.4441139387
Cl -1.6709767619 -0.0903180976 -0.6218847429
N -1.4887930603 1.9678148998 2.6244452442
C -2.8185386583 1.8430675186 2.9029666268
```

```
C -3.2243025097 3.0107755808 3.4689502172
N -2.1575225712 3.8654386167 3.545578644
C -1.1559716727 3.1895998235 3.029097331
H 0.376085946 0.9516635044 -0.3296633194
H -0.7763922683 1.1228200811 2.1067324546
H 1.4570516649 -0.194769624 3.1092238955
H 3.4797821277 -0.6138211879 1.6154705334
H 0.5413439018 -2.0845860288 -0.4147155288
H 2.6463849873 0.1120625208 -0.4666286801
H -3.3603426638 0.9479782924 2.6801414833
H -4.1969953592 3.2867013044 3.8237499345
H -0.1598719343 3.5742691837 2.9395329203
H -2.1506969074 5.4657413573 4.2407233785
O -2.1916020296 6.399036389 4.5400229347
C -2.5543739403 7.1874546818 3.5697109581
O -2.6853291919 8.3677080061 3.6733589043
H -2.7352526589 6.6707633038 2.6261971806
```

gamma 4

```
-1 1
C 0.0563462986 0.0064470327 0.0457398178
N 0.0370915717 0.0226825332 1.4088596488
C 1.3115787828 0.0330585691 1.7782609601
N 2.1569466716 0.0270442488 0.7696500909
C 1.3599808784 0.0106273711 -0.3429557945
C -2.1403358133 -0.1574950218 3.0050997607
C -3.4794952224 0.380743045 2.49466362
C -3.6105303507 1.906955704 2.5591193041
C -3.2989861592 2.4414008036 3.9635976807
C -2.0718557676 1.8236335949 4.6475797543
C -2.02718213 0.3021282746 4.4611016699
Cl -4.750433434 2.1409897678 5.0205683235
Cl -2.6099862869 2.782985981 1.3547255941
Cl -3.8720174536 -0.1674875736 0.8221742839
Cl -2.3444449132 -1.9860012732 3.0824964054
Cl -0.564566315 -0.3443589631 5.2934381459
Cl -0.5934619493 2.6782637674 4.0966458453
H -2.842731089 -0.0901928145 5.0580794836
H -2.124791059 2.0369581882 5.7021898607
H -3.206077197 3.5128106883 3.9379638884
H -4.6237294011 2.1740819696 2.3089165166
H -0.9659220903 0.0053513904 2.1496849853
H -4.3046519179 -0.0095336466 3.0795984689
H -0.8433751184 -0.0054210275 -0.5334665194
H 1.7698787574 0.0059845517 -1.3332578308
H 1.6110298208 0.0470137274 2.8073307194
H 3.8829769222 0.0751185194 0.7869048856
O 4.863784357 -0.0032290419 0.7692266253
C 5.2337614658 -1.2498839409 0.7531280356
O 6.3682658409 -1.6173413591 0.7202827908
H 4.4030632618 -1.9565905195 0.7718865953
```

ONIOM core

CH2ClCHClCH2Cl.log

```
0 1
C 0.0184382693 -0.0330648481 0.045204779
Cl 0.2641093977 -0.0039671422 1.8109970218
H 1.003684115 -0.0416575101 -0.397905905
H -0.4918238539 -0.9535013183 -0.1942297159
C -0.7570107001 1.177268522 -0.461429508
C -0.6990260674 1.2096198357 -1.9840908119
Cl -2.4556610333 1.1171250521 0.1023038736
H -0.3352932965 2.0839254923 -0.0553173887
Cl -1.3183027889 2.7368511635 -2.6647405293
H 0.3284160292 1.1279411233 -2.3078524755
H -1.277081122 0.4066041671 -2.4152726728
```

TS_acetate_CH2ClCHClCH2Cl.log

```
-1 1
C 0.0497046074 -0.0000646209 0.0338226372
C -0.0084919075 0.0003285789 1.5589723061
O 1.1208807113 -0.0002568066 2.1289884241
O -1.0938203619 0.0011307789 2.1150255593
C 1.1774301385 0.0004052831 4.2749860195
C 1.986585636 -1.2688252792 4.2513059365
C 1.9880175643 1.2687079903 4.250464827
Cl 0.7873487002 0.0014313983 6.6498499491
H -0.9471290072 0.0004253571 -0.3892762021
H 0.1170986649 0.0009586916 4.1739309153
H 0.5949366839 0.874979475 -0.3076492152
H 0.5939085673 -0.8759062603 -0.3072431772
Cl 0.9978832064 2.7472163752 4.1654532212
H 2.5863731797 1.3394772608 5.1412254863
Cl 0.99477647 -2.7462701524 4.1672948066
H 2.5848703355 -1.3396822484 5.1421063397
H 2.6006983192 -1.2576172529 3.367590722
H 2.6021289332 1.2562211721 3.3667687019
```

TS_imidazolide_CH2ClCHClCH2Cl.log

```
-1 1
H -0.1600479303 0.7913553703 0.2209023035
C -0.0828459825 0.4061689216 1.2191346591
C 1.0174634609 0.3459980553 2.0256316428
N 0.6275491602 -0.2292775875 3.1965584062
C -0.6748258758 -0.483470669 3.0341068287
N -1.1584723452 -0.1245758289 1.8698791063
H -1.2623888151 -0.9499825938 3.8021722378
H 1.3094266853 -0.408178426 4.2373007483
H 2.0293411968 0.6517840658 1.8527512203
C 2.011561522 -0.5437873014 5.5013282043
```

```
Cl 2.0677964644 -2.3331751397 5.8995967246
C 3.4093475597 0.0129752451 5.5119319641
Cl 4.3813960728 -0.4290809623 4.0400954487
C 1.1264508756 0.1592175651 6.4695890335
Cl 1.7309794271 0.3301049147 8.234447782
H 0.1764213482 -0.3339380155 6.5795565176
H 4.0109615953 -0.3116331532 6.3477095232
H 3.3642877773 1.0929415051 5.5027321312
H 0.9794841248 1.1839381305 6.1635840501
```

imidazolide

```
-1 1
N 0.040526416 0. 0.0473533001
C -0.0135519168 0. 1.4035657172
C 1.2710323782 0. 1.9028314602
N 2.1470330987 0. 0.8660826114
C 1.3473782032 0. -0.1957647673
H -0.9476383548 0. 1.9370400818
H 1.5996610416 0. 2.9270940078
H 1.7375424983 0. -1.1996050011
```

Model

A

```
-1 1
C -0.1567165488 -0.6143268226 0.2162373679
N -0.0595431435 -0.2320532383 1.4905090631
C 1.2659975568 -0.0440066427 1.7375629644
C 1.9107224107 -0.3287448098 0.5760044238
N 1.0011418048 -0.6889977008 -0.3843637861
O -2.0970965527 0.1076266866 3.1941779861
C -2.6893860073 1.1632750303 3.5116476074
O -3.6188693371 1.3222715852 4.2860714355
C 1.8003510128 0.0065225755 -3.6338669392
C 3.2659668412 -0.3754250463 -3.5251439946
Cl 4.3069476044 1.0020674442 -3.0495433447
C 0.8917701696 -1.2084074131 -3.7204614959
Cl 1.2813987997 -2.3247713474 -5.0800428825
Cl 1.5195108842 1.1217391471 -5.0218315036
H 1.6264255433 0.2689055654 2.6941582485
H -1.1023081699 -0.8318460909 -0.2378645613
H 1.4960274679 0.542845549 -2.7489082904
H 2.9619610056 -0.2918093998 0.3740725657
H -0.1312528167 -0.9019487332 -3.8609653699
H 3.6505672588 -0.753324763 -4.4572845249
H 3.3731275853 -1.1208544104 -2.7516617775
H 0.9800382562 -1.7704489714 -2.8053419894
H -0.8443444442 -0.0866567544 2.1520033501
H -2.3056333791 2.0784947482 3.0110660519
```

B

```
-1 1
C -0.0869070046 -0.7636933737 0.2433572806
N -0.0814855526 -0.4095310769 1.5245632376
C 1.2305592193 -0.1493159322 1.7797257797
C 1.9445915834 -0.3608277753 0.631658116
N 1.0925586131 -0.7557271116 -0.3566161265
O -2.1303661187 -0.0384340061 3.1840986125
C -2.465083238 1.2120179339 3.105444215
O -3.3496075954 1.7211287266 3.727608105
C 1.6864886587 0.0917237854 -3.5234625205
C 3.1519494987 -0.2815176722 -3.3997296721
Cl 4.1985999711 1.1197916612 -3.0071833508
C 0.7875320424 -1.130395327 -3.5958500798
Cl 1.1690918131 -2.2492926919 -4.9607125667
Cl 1.4005949135 1.1866932393 -4.9314337887
H 1.5715289952 0.1644321841 2.7477108991
H -0.9939182742 -1.0403064208 -0.2644236556
H 1.3761877873 0.636283601 -2.6459506908
H 2.9991258112 -0.2491210623 0.4651115142
H -0.2393746613 -0.8335396061 -3.7278181013
H 3.5347816076 -0.7108595324 -4.3101606889
H 3.2540892617 -0.9778526345 -2.581603143
H 0.8959698441 -1.6848759876 -2.678465693
H -1.3671943629 -0.2438771941 2.5786650199
H -1.8584306139 1.7872224606 2.4042400904
```

TS1

```
-1 1
C 1.962438 -0.333445 -0.758983
N 3.095850 0.363856 -0.721269
C 2.718043 1.652174 -0.947931
C 1.363667 1.659839 -1.110710
N 0.884826 0.385775 -0.987471
O 5.360316 -0.484412 -0.270435
C 5.698653 -0.484674 0.956972
O 6.749657 -0.851600 1.423156
C -2.154948 -0.159986 0.372225
C -2.989242 0.843722 -0.403052
Cl -3.083225 2.441029 0.403502
C -1.829133 -1.395413 -0.449264
Cl -3.278175 -2.254773 -1.096223
Cl -2.956311 -0.610149 1.924587
H 3.426580 2.455179 -0.977404
H 1.948546 -1.397393 -0.614999
H -1.204226 0.276192 0.635333
H 0.717030 2.493500 -1.303151
H -1.291867 -2.112020 0.148550
H -4.001266 0.502024 -0.539890
H -2.522381 1.013641 -1.361491
H -1.223700 -1.100236 -1.289900
H 4.267194 -0.075028 -0.493255
```

```
H 4.923786 -0.102313 1.638355
```

TS2

```
-1 1
C 1.603999 -0.279284 -0.169928
N 2.738799 0.303355 -0.493243
C 2.434666 1.551462 -0.964816
C 1.090464 1.683185 -0.908358
N 0.583377 0.514730 -0.405424
O 5.061235 -0.726093 -0.411028
C 5.905890 -0.626746 0.518694
O 7.039044 -1.059053 0.558321
C -2.049163 -0.179501 0.017420
C -3.060997 0.924856 -0.078743
Cl -2.406724 2.558218 0.422771
C -2.378802 -1.323043 -0.865628
Cl -4.114586 -2.046176 -0.746871
Cl -1.942681 -0.753908 1.763771
H 3.193115 2.227974 -1.293785
H 1.526957 -1.266527 0.234089
H -0.525527 0.253530 -0.253588
H 0.457721 2.504143 -1.166327
H -1.751952 -2.179126 -0.685657
H -3.939992 0.789443 0.532998
H -3.359790 1.057417 -1.108468
H -2.322781 -1.028892 -1.902900
H 3.726709 -0.129214 -0.417311
H 5.549563 -0.068023 1.407025
```

TS3

```
-1 1
N 0.569439 0.477049 -0.419026
C 1.607978 -0.326334 -0.219024
N 2.752748 0.181163 -0.618448
C 2.425770 1.413409 -1.115963
C 1.083913 1.600823 -0.994642
O 5.260350 -0.880508 -0.524028
C 5.810401 -0.483719 0.587544
O 6.922037 -0.753441 0.922291
C -2.025316 -0.158564 0.077207
Cl -2.058920 -0.632889 1.851354
C -3.044338 0.919557 -0.167678
Cl -2.499031 2.572223 0.370417
C -2.268407 -1.358008 -0.766846
Cl -3.990869 -2.097927 -0.751374
H 3.165618 2.074329 -1.520939
H 1.508515 -1.294357 0.231627
H -0.600570 0.230003 -0.187082
H 0.467935 2.435854 -1.255884
H -1.642446 -2.186984 -0.485450
H -3.988096 0.765578 0.333531
H -3.217295 1.017604 -1.230040
```

H -2.120976 -1.118066 -1.809196
H 4.345070 -0.539474 -0.607785
H 5.157761 0.132709 1.207095

Saddle point (order 2)

-1 1
N 0.604293 0.498614 -0.399800
C 1.626074 -0.306648 -0.192228
N 2.766222 0.256432 -0.529970
C 2.461148 1.510621 -0.984548
C 1.118397 1.662367 -0.902741
O 5.011976 -0.764773 -0.469702
C 5.772231 -0.594098 0.530562
O 6.900096 -1.001643 0.681289
C -2.018183 -0.171341 0.035625
Cl -1.966876 -0.706526 1.795082
C -3.029602 0.928271 -0.117549
Cl -2.405699 2.567836 0.393094
C -2.320614 -1.335705 -0.832728
Cl -4.055882 -2.056000 -0.752331
H 3.217626 2.185204 -1.324244
H 1.540037 -1.296348 0.205648
H -0.523420 0.242650 -0.228545
H 0.493492 2.494876 -1.143999
H -1.697463 -2.185431 -0.613645
H -3.934011 0.793374 0.456179
H -3.283627 1.046141 -1.161137
H -2.229417 -1.063823 -1.873667
H 3.827669 -0.223740 -0.475038
H 5.325982 0.002039 1.346417

Frozen E2 TS geometries (dihedral 3 2 13 14 fixed at 60 degrees)

alpha 2

-1 1
C -0.0997555001 0.0244533919 0.1233286492
C 0.0860794383 0.0611802986 1.6355933005
C 1.5328430174 -0.0123593081 2.0323119391
C 2.3869886934 1.0722778836 1.3725545362
C 2.1904318515 1.0599947513 -0.1434946951
C 0.7195604091 1.1382462153 -0.5574772722
Cl -0.7798728825 -1.355169799 2.3805474227
Cl 2.4050123901 -1.6132082752 1.6085168162
Cl 2.0237327369 2.6610400781 2.1238987852
Cl 3.1917688093 2.3340990285 -0.9137944465
Cl 0.6094014625 0.9653684153 -2.3473257849
Cl -1.837813012 0.2589019141 -0.3003140624
N -1.3648862593 1.9393230564 2.9341524418
C -1.4118332619 3.3028353765 2.8742166682
C -2.3931738253 3.7179763113 3.718880037

N -2.9631779531 2.6247992374 4.3108468698
C -2.3135076801 1.6002318917 3.8022248081
H 1.6364515483 0.0287023918 3.1025375234
H 0.1631884764 -0.9308927901 -0.3106706991
H 3.4275071293 0.8972688607 1.5858476601
H -0.6159045304 1.1326252407 2.2891566433
H 0.3039071843 2.1048693359 -0.3230872955
H 2.6027955815 0.1306374665 -0.5022182201
H -0.7584603261 3.871250764 2.2464991915
H -2.7222441212 4.7152604778 3.9328765743
H -2.5232573946 0.579888898 4.0513995187
H -4.2777176273 2.6474885615 5.4503885731
O -4.9397254668 2.6980282286 6.1739168319
C -4.3583438422 2.8148095416 7.332009902
O -4.9357779804 2.9051306296 8.3713846591
H -3.268854103 2.8248255715 7.2788691945

gamma 3

-1 1
C -0.0166186773 -0.0266601389 -0.0177712305
C -0.0507711178 -0.0795804471 1.5090283841
C 1.3230639629 -0.0198875914 2.1237423013
C 2.291460778 -1.0641908336 1.548856412
C 2.2193692993 -1.2604196241 0.0270336945
C 0.7765912444 -1.2534004081 -0.4849011875
Cl -1.0297167567 1.3014303289 2.1714256746
Cl 2.1965578817 1.6156431758 2.002081161
Cl 1.9838738201 -2.6659447729 2.3333578334
Cl 3.2634545515 -0.0442218692 -0.7951574138
Cl 0.77334511 -1.4993958175 -2.2642900987
Cl -1.6885347971 -0.1185053938 -0.6850030303
N -1.6262658608 -2.0306672127 2.5372297058
C -1.6023223043 -3.3937372703 2.4513866902
C -2.7034979067 -3.8638817214 3.0950272537
N -3.4196983476 -2.8062088507 3.583667945
C -2.7323430091 -1.7463105413 3.2186765279
H 0.2952568702 -2.1335083371 -0.0869563469
H 2.6696408715 -2.2054352653 -0.2244657377
H 3.3003352016 -0.8208463542 1.82904456
H 1.251041269 -0.1528434753 3.1891663675
H 0.3996005674 0.8841107701 -0.4264773963
H -0.8323135177 -1.1941446368 2.0362079176
H -0.8168751058 -3.9234035769 1.9545255387
H -3.0190289253 -4.87778454 3.2397043282
H -3.0243873414 -0.7399681825 3.4399877126

H -4.8753848755 -2.9191513127 4.5380920021
O -5.7434200678 -3.0139195744 4.985188711
C -6.7197727212 -2.9970062371 4.1243294763
O -7.8717740239 -3.1082744429 4.4101019144
H -6.3944603844 -2.8702658443 3.0909569427

Appendix B

Normal modes

Frequency calculations at the HF/6-31+G(d,p) level were performed for all of the optimised species in this study; all had the correct number of imaginary frequencies (0 for minima, one for transition states, 2 for the second-order saddle point). The magnitudes of the imaginary frequencies are given below.

	Imaginary frequency (cm^{-1})
SN2 transition states	
α1	450.7291
α2	471.2723
α3	484.0998
β	-487.657
γ1	390.3305
γ2	481.5617
γ3	489.5813
γ4	470.0583
E2 transition states	
α2	-1715.4097
γ3	-1665.3678
"E1cb" transition states	
α1	-1471.9049
α3	-1597.6255
β	-1524.906
γ1	-1501.9192
γ2	-1467.7453
γ4	-1600.096
Model system	
TS1	-1298.4001
TS2	-730.5534
TS3	-1490.3366
2^{nd}-order saddle point	-1126.8034 -651.0317
Frozen E2 TS geometries	
α2	-1725.5640
γ3	-1679.8901