Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Electronic Supplementary Information for:

Analysis of the conformational profiles of fenamates shows route towards novel, higher accuracy, force-fields for pharmaceuticals

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1 Preliminary analysis of the barrier to rotation in fenamates

1.1 Sensitivity of intramolecular energy to torsion definition

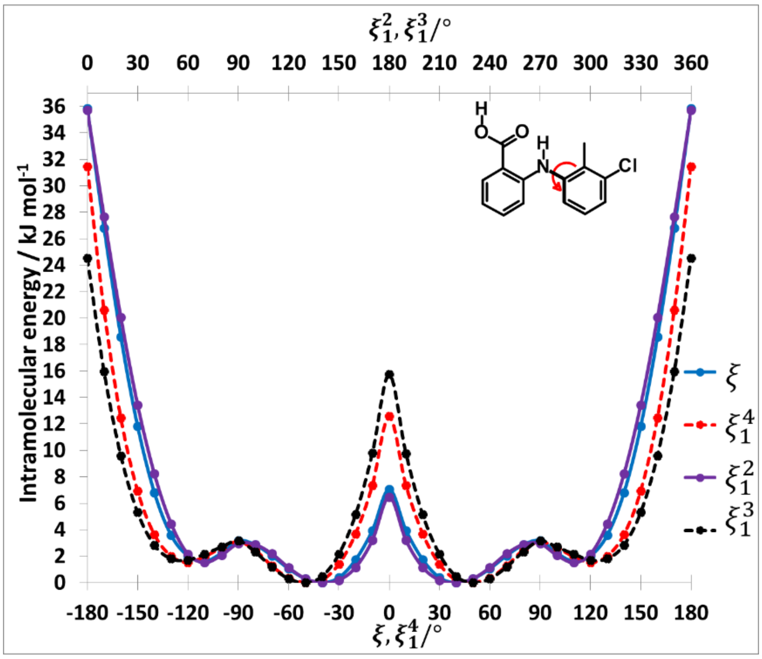


Figure S1: Relaxed scan of TA at PBE0/6-31+G(d) level of theory with the different definitions of torsion between N_1-C_8 bond (ξ=C_7-N_1-C_8-C_9, ξ_1^2 = C_7-N_1-C_8-C_{13}, ξ_1^3 = H_6-N_1-C_8-C_9 and ξ_1^4 = H_6-N_1-C_8-C_{13}) used as the constrained geometric parameter.

1.2 Testing whether the asymmetry of the fenamic acid torsion potential is due to step size.

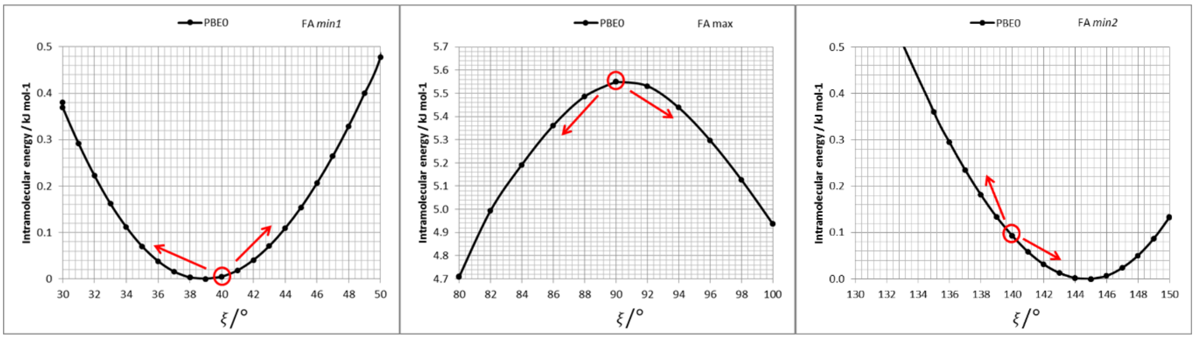


Figure S2: Relaxed scans of FA at PBE0/6-31+G(d) with step sizes 2 and 1° around the maximum and minima respectively. The red circles indicate the starting point of the scans while the arrows indicate the directions of the scans.

This shows that the asymmetry of the *ab initio* curve is not an artefact of the step size.

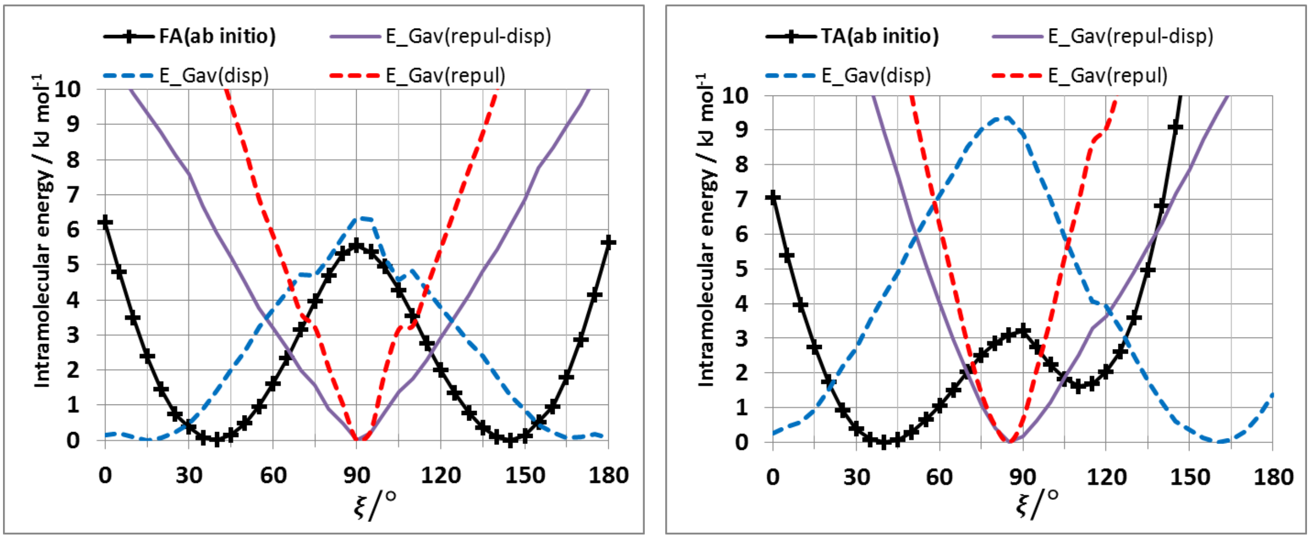
1.3 Gavezzotti’s exp-6 potentials

Table S1: Gavezzotti’s exp-6 atom-atom parameters: $E=A\exp(-BR)-CR^{-6}$ used as starting points in fitting. [1-3] ε is the well depth and R_m is the distance at the minimum. Italics represent the hydrogen-bonded interactions. [a]From the UNI intermolecular potential function in Mercury.

Interactions	A/kJmol^{-1}	B/Å^{-1}	C/kJmol^{-1}Å^{-6}	ε/kJmol^{-1}	R_m/Å
H···H	24158.4	4.01	109.2	0.04	3.36
H···C	120792.1	4.10	472.8	0.21	3.29
H···N	228279.0	4.52	502.1	0.39	2.99
H···O	295432.2	4.82	439.3	0.51	2.80
H···Cl	292963.7	4.09	1167.3	0.50	3.30
C···C	226145.2	3.47	2418.4	0.39	3.89
C···N	491494.5	3.86	2790.7	0.84	3.50
C···O	393086.8	3.74	2681.9	0.67	3.61
C···Cl	390660.1	3.52	3861.8	0.67	3.83
N···O	268571.0	3.86	1523.0	0.46	3.50
O···O	195309.1	3.74	1334.7	0.33	3.61
O···Cl	338297.3	3.63	2782.4	0.58	3.72
HB···O (acids)	26416395.3	8.75	857.7	29.29	1.60
HB···N (-NH···OH)	23867340.0[a]	7.78[a]	1577.4[a]	26.61	1.80

Table S2: Other available Gavezzotti exp-6 atom-atom parameters, which are not used for the fenamates

Interactions	A/kJmol^{-1}	B/Å^{-1}	C/kJmol^{-1}Å^{-6}	ε/kJmol^{-1}	R_m/Å
H···S	268571.0	4.03	1167.3	0.46	3.35
C···S	529108.6	3.41	6292.7	0.91	3.96
N···N	365263.2	3.65	2891.1	0.63	3.70
O···S	460909.4	3.63	3790.7	0.79	3.72
S···S	1087672.6	3.52	10757.1	1.86	3.83
Cl···Cl	585969.2	3.52	5794.8	1.00	3.83
HB···O (amides)	15095077.0	7.78	995.8	16.74	1.80
HB···O (alcohols)	18868794.0	7.78	1246.8	20.92	1.80
HB···N (=N-H···N)	30190070.4	7.78	1991.6	33.47	1.80
HB···N (-NH_2···N)	7547601.3	7.37	690.4	8.37	1.90
HB···O (NH_2···NO_2)	5501960.0	7.78	362.8	6.11	1.80
F···F	170916.4	4.22	564.8	0.29	3.20
C···F	196606.2	3.84	1167.3	0.33	3.50
H···F	64257.9	4.11	246.9	0.13	3.30
Si···Si	972667.0	3.21	16539.4	1.67	4.21
Si···C	469001.3	3.34	6326.2	0.79	4.04
Si···H	153289.2	3.61	1343.1	0.29	3.72



(a) (b)

Figure S3: Comparison of the *ab initio* (black) intramolecular energy scans of (a) FA and (b) TA with Gavezzotti's *exp-6* intermolecular energy models summed over all intramolecular atom-atom distances from the third nearest neighbour (1-4) and above. The net effect (purple) is subdivided into the repulsive (red), and dispersion (blue) contributions.

The use of the original *exp-6* potentials to model the intramolecular energies, Figure S3, shows that the repulsion is severely overestimated. The dispersion contribution gives a maximum at ξ ~ 90°, which is of the same order of magnitude as this maximum in the conformational profiles, particularly for FA. This confirms the observation from Figure 3 that electron correlation, the origin of dispersion interactions, makes a significant contribution to this maximum, supplementing the electronic effect (c.f. Figure 6). The difference between TA and FA in Figure S3 is consistent with the large dispersion interaction of the Cl substituent as well as the repulsion from the methyl substituent. Analysis of which particular atom-atom interactions vary most with conformation (Table S3 and Table S4) reveals that intramolecular interactions involving the N-H proton, type HB, as well as certain aromatic and TA methyl protons, type H, vary strongly with conformation (as expected from Figure 5). So the estimate of non-bonded contributions to the torsion potential in Figure S3 is strongly affected by the poorly determined parameters for HB and H.

1.4 Analysis of which atom-atom contributions change most with conformation

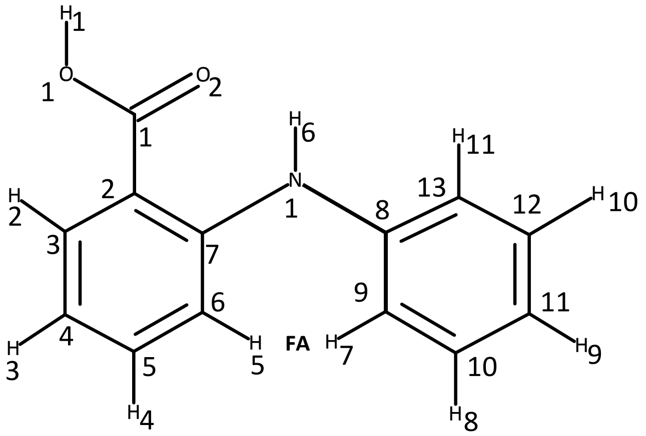


Table S3: Atom-atom interactions of FA that dominate the intramolecular energies. The interaction is listed if the difference between the minimum and maximum total energy ($E_{repul\text{-}dis}$) as ξ is varied is greater or equal to 1 kJ mol^{-1}using Gavezzotti's exp-6 potential. Interactions in blue do not vary by more than 1 kJ mol-1 in TA, or involve H11 which is not present in TA.

$at_i \cdots at_k$	neigh	R_{ik}/kJ mol^{-1}		E_{repul}/kJ mol^{-1}		E_{disp}/kJmol^{-1}		$E_{repul\text{-}disp}$/kJ mol^{-1}	
		min	***max(Δ)***	*min*	***max(Δ)***	*min*	***max(Δ)***	*min*	***max(Δ)***
$C_7 \cdots C_9$	4	3.07	3.71**(0.64)**	0.57	5.33**(4.76)**	-2.89	-0.92**(1.96)**	-0.35	2.45**(2.80)**
$C_7 \cdots C_{13}$	4	3.07	3.71**(0.64)**	0.57	5.32**(4.75)**	-2.88	-0.92**(1.96)**	-0.35	2.44**(2.79)**
$C_6 \cdots C_9$	5	3.10	4.43**(1.33)**	0.05	4.75**(4.70)**	-2.70	-0.32**(2.39)**	-0.39	2.05**(2.43)**
$C_6 \cdots C_{13}$	5	3.11	4.44**(1.33)**	0.05	4.68**(4.63)**	-2.68	-0.32**(2.36)**	-0.39	2.00**(2.38)**
$C_6 \cdots H_7$	6	2.52	4.88**(2.36)**	0.00	3.98**(3.98)**	-1.86	-0.03**(1.82)**	-0.21	2.12**(2.33)**
$C_8 \cdots H_5$	5	2.54	2.88**(0.34)**	0.89	3.57**(2.68)**	-1.75	-0.83**(0.92)**	0.07	1.82**(1.76)**
$C_9 \cdots H_5$	6	2.57	4.16**(1.59)**	0.00	3.17**(3.16)**	-1.63	-0.09**(1.54)**	-0.20	1.54**(1.74)**
$H_5 \cdots H_7$	7	2.08	4.76**(2.68)**	0.00	5.78**(5.78)**	-1.35	-0.01**(1.34)**	-0.04	4.43**(4.47)**
$C_{13} \cdots HB_6$	4	2.51	3.30**(0.78)**	0.16	4.03**(3.87)**	-1.87	-0.37**(1.51)**	-0.21	2.16**(2.36)**
$HB_6 \cdots H_{11}$	5	2.30	3.68**(1.38)**	0.01	2.40**(2.39)**	-0.74	-0.04**(0.70)**	-0.04	1.66**(1.70)**
$C_6 \cdots H_8$	4	2.89	3.10**(0.20)**	4.85	9.85**(5.00)**	-4.12	-2.74 **(1.38)**	2.12	5.73**(3.62)**
$C_6 \cdots H_{11}$	6	2.52	4.88**(2.37)**	0.00	3.96**(3.96)**	-1.85	-0.03**(1.82)**	-0.20	2.11**(2.31)**
$C_{13} \cdots H_5$	6	2.57	4.17**(1.59)**	0.00	3.14**(3.14)**	-1.62	-0.09**(1.53)**	-0.20	1.52**(1.72)**
$H_5 \cdots H_{11}$	7	2.09	4.76**(2.67)**	0.00	5.48**(5.48)**	-1.30	-0.01**(1.29)**	-0.04	4.18**(4.22)**
$C_9 \cdots HB_6$	4	2.51	3.30**(0.79)**	0.16	4.06**(3.90)**	-1.88	-0.36**(1.52)**	-0.21	2.18**(2.38)**
$HB_6 \cdots H_7$	5	2.30	3.69**(1.39)**	0.01	2.38**(2.37)**	-0.74	-0.04**(0.69)**	-0.04	1.64**(1.69)**

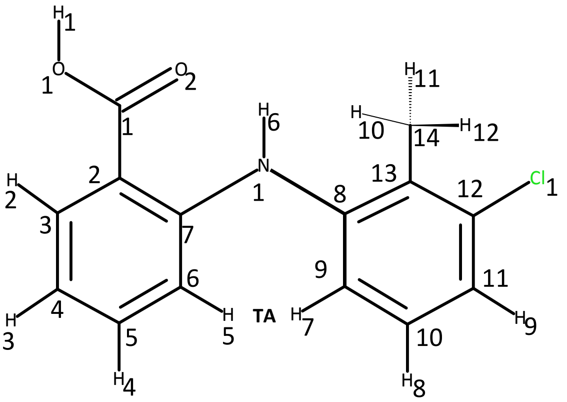


Table S4: Atom-atom interactions of TA that dominate the intramolecular energies. The interaction is listed if the difference between the minimum and maximum total energy ($E_{repul\text{-}dis}$) with ξ is greater or equal 1 kJ mol^{-1}using Gavezzotti's exp-6 potential. Interactions in red do not vary by more than 1 kJ mol-1 in FA or involve atoms that are not in FA, and we highlight interactions between atoms on the same aromatic ring and interactions involving the methyl substituent.

$at_i \cdots at_k$	neigh	R_{ik}/kJ mol^{-1}		E_{repul}/kJ mol^{-1}		E_{disp}/kJ mol^{-1}		$E_{repul\text{-}disp}$/kJ mol^{-1}	
		min	***max(Δ)***	*min*	***max(Δ)***	*min*	***max(Δ)***	*min*	***max(Δ)***
$C_7 \cdots C_9$	4	3.02	3.61**(0.59)**	0.81	6.30**(5.49)**	-3.17	-1.09**(2.09)**	-0.28	3.13**(3.40)**
$C_7 \cdots C_{13}$	4	3.14	3.72**(0.58)**	0.56	4.17**(3.61)**	-2.52	-0.91**(1.61)**	-0.35	1.65**(2.01)**
$C_6 \cdots C_9$	5	3.08	4.12**(1.04)**	0.14	5.13**(4.99)**	-2.82	-0.50**(2.33)**	-0.39	2.31**(2.69)**
$C_6 \cdots C_{13}$	5	3.24	4.44**(1.19)**	0.05	2.92**(2.87)**	-2.07	-0.32**(1.76)**	-0.39	0.85**(1.23)**
$C_6 \cdots H_7$	6	2.48	4.45**(1.97)**	0.00	4.58**(4.58)**	-2.02	-0.06**(1.96)**	-0.20	2.56**(2.76)**
$C_8 \cdots H_5$	5	2.54	2.89**(0.35)**	0.86	3.63**(2.77)**	-1.76	-0.81**(0.95)**	0.05	1.87**(1.82)**
$C_9 \cdots H_5$	6	2.60	3.69**(1.09)**	0.03	2.86**(2.83)**	-1.54	-0.19**(1.35)**	-0.21	1.32**(1.53)**
$H_5 \cdots H_7$	7	2.14	4.18**(2.04)**	0.00	4.51**(4.50)**	-1.13	-0.02**(1.11)**	-0.04	3.37**(3.42)**
$C_{13} \cdots HB_6$	4	2.54	3.22**(0.68)**	0.22	3.64**(3.41)**	-1.76	-0.43**(1.34)**	-0.20	1.87**(2.07)**
$HB_6 \cdots H_{11}$	6	2.19	4.50**(2.31)**	0.00	3.64**(3.64)**	-0.98	-0.01**(0.96)**	-0.04	2.66**(2.71)**
$HB_6 \cdots H_{12}$	6	2.28	3.15**(0.87)**	0.08	2.54**(2.46)**	-0.77	-0.11**(0.66)**	-0.03	1.77**(1.80)**
$C_6 \cdots C_8$	4	2.89	3.10**(0.21)**	4.85	9.95**(5.11)**	-4.14	-2.73**(1.41)**	2.11	5.81**(3.70)**
$C_6 \cdots C_{14}$	6	3.10	5.10**(2.00)**	0.00	4.82**(4.82)**	-2.73	-0.14**(2.59)**	-0.39	2.10**(2.48)**
$C_7 \cdots C_{14}$	5	3.12	4.14**(1.02)**	0.13	4.55**(4.42)**	-2.64	-0.48**(2.16)**	-0.39	1.91**(2.30)**
$C_7 \cdots H_{12}$	6	2.55	3.85**(1.30)**	0.02	3.44**(3.42)**	-1.71	-0.14**(1.56)**	-0.20	1.73**(1.94)**
$N_1 \cdots C_{14}$	4	2.78	2.98**(0.21)**	4.87	10.81**(5.94)**	-6.07	-3.95**(2.12)**	0.93	4.74**(3.82)**
$N_1 \cdots H_{12}$	5	2.43	2.62**(0.19)**	1.62	3.85**(2.22)**	-2.43	-1.54**(0.88)**	0.08	1.42**(1.34)**
$C_{14} \cdots Cl_1$	4	3.04	3.11**(0.07)**	6.88	8.75**(1.87)**	-4.88	-4.27**(0.61)**	2.61	3.87**(1.26)**
$C_{14} \cdots HB_6$	5	2.41	3.71**(1.30)**	0.03	6.18**(6.15)**	-2.41	-0.18**(2.23)**	-0.21	3.77**(3.97)**
$Cl_1 \cdots H_{10}$	5	2.57	3.24**(0.68)**	0.51	8.13**(7.62)**	-4.10	-1.00**(3.09)**	-0.49	4.04**(4.53)**
$Cl_1 \cdots H_{11}$	5	2.69	3.74**(1.05)**	0.07	4.89**(4.83)**	-3.08	-0.42**(2.66)**	-0.50	1.81**(2.31)**

Table S5: Contrasting the atom-atom interactions of FA and TA that dominate the intramolecular energies, formed by combining Table S3 and Table S4. Unique interaction to FA (blue) and TA (red). Interactions between atoms on the same aromatic ring. Interactions involving the TA methyl substituent.

		FA		TA		FA		TA	
$at_i \cdots at_k$	neigh	R_{ik}/kJ mol^{-1}		R_{ik}/kJ mol^{-1}		$E_{repul\text{-}disp}$/kJ mol^{-1}		$E_{repul\text{-}disp}$/kJ mol^{-1}	
		min	*max(**Δ**)*	*min*	*max(**Δ**)*	*min*	*max(**Δ**)*	*min*	*max(**Δ**)*
C···C									
$C_7 \cdots C_9$	4	3.07	3.71**(0.64)**	3.02	3.61**(0.59)**	-0.35	2.45**(2.80)**	-0.28	3.13**(3.40)**
$C_7 \cdots C_{13}$	4	3.07	3.71**(0.64)**	3.14	3.72**(0.58)**	-0.35	2.44**(2.79)**	-0.35	1.65**(2.01)**
$C_6 \cdots C_9$	5	3.10	4.43**(1.33)**	3.08	4.12**(1.04)**	-0.39	2.05**(2.43)**	-0.39	2.31**(2.69)**
$C_6 \cdots C_8$	4			2.89	3.10**(0.21)**			2.11	5.81**(3.70)**
$C_6 \cdots C_{13}$	5	3.11	4.44**(1.33)**	3.24	4.44**(1.19)**	-0.39	2.00**(2.38)**	-0.39	0.85**(1.23)**
$C_6 \cdots C_{14}$	6			3.10	5.10**(2.00)**			-0.39	2.10**(2.48)**
$C_7 \cdots C_{14}$	5			3.12	4.14**(1.02)**			-0.39	1.91**(2.30)**
C···H									
$C_7 \cdots H_{12}$	6			2.55	3.85**(1.30)**			-0.20	1.73**(1.94)**
$C_6 \cdots H_7$	6	2.52	4.88**(2.36)**	2.48	4.45**(1.97)**	-0.21	2.12**(2.33)**	-0.20	2.56**(2.76)**
$C_6 \cdots H_8$	4	2.89	3.10**(0.20)**			2.12	5.73**(3.62)**		
$C_6 \cdots H_{11}$	6	2.52	4.88**(2.37)**			-0.20	2.11**(2.31)**		
$C_8 \cdots H_5$	5	2.54	2.88**(0.34)**	2.54	2.89**(0.35)**	0.07	1.82**(1.76)**	0.05	1.87**(1.82)**
$C_9 \cdots H_5$	6	2.57	4.16**(1.59)**	2.60	3.69**(1.09)**	-0.20	1.54**(1.74)**	-0.21	1.32**(1.53)**
$C_{13} \cdots H_5$	6	2.57	4.17**(1.59)**			-0.20	1.52**(1.72)**		
H···H									
$H_5 \cdots H_7$	7	2.08	4.76**(2.68)**	2.14	4.18**(2.04)**	-0.04	4.43**(4.47)**	-0.04	3.37**(3.42)**
$H_5 \cdots H_{11}$	7	2.09	4.76**(2.67)**			-0.04	4.18**(4.22)**		
C···HB									
$C_{13} \cdots HB_6$	4	2.51	3.30**(0.78)**	2.54	3.22**(0.68)**	-0.21	2.16**(2.36)**	-0.20	1.87**(2.07)**
$C_9 \cdots HB_6$	4	2.51	3.30**(0.79)**			-0.21	2.18**(2.38)**		
$C_{14} \cdots HB_6$	5			2.41	3.71**(1.30)**			-0.21	3.77**(3.97)**
HB···H									
$HB_6 \cdots H_{11}$	5	2.30	3.68**(1.38)**			-0.04	1.66**(1.70)**		
$HB_6 \cdots H_7$	5	2.30	3.69**(1.39)**			-0.04	1.64**(1.69)**		
$HB_6 \cdots H_{11}$	6			2.19	4.50**(2.31)**			-0.04	2.66**(2.71)**
$HB_6 \cdots H_{12}$	6			2.28	3.15**(0.87)**			-0.03	1.77**(1.80)**
N···C									
$N_1 \cdots C_{14}$	4			2.78	2.98**(0.21)**			0.93	4.74**(3.82)**
N···H									
$N_1 \cdots H_{12}$	5			2.43	2.62**(0.19)**			0.08	1.42**(1.34)**
C···Cl									
$C_{14} \cdots Cl_1$	4			3.04	3.11**(0.07)**			2.61	3.87**(1.26)**
Cl···H									
$Cl_1 \cdots H_{10}$	5			2.57	3.24**(0.68)**			-0.49	4.04**(4.53)**
$Cl_1 \cdots H_{11}$	5			2.69	3.74**(1.05)**			-0.50	1.81**(2.31)**

2 The fitting algorithm and methodology

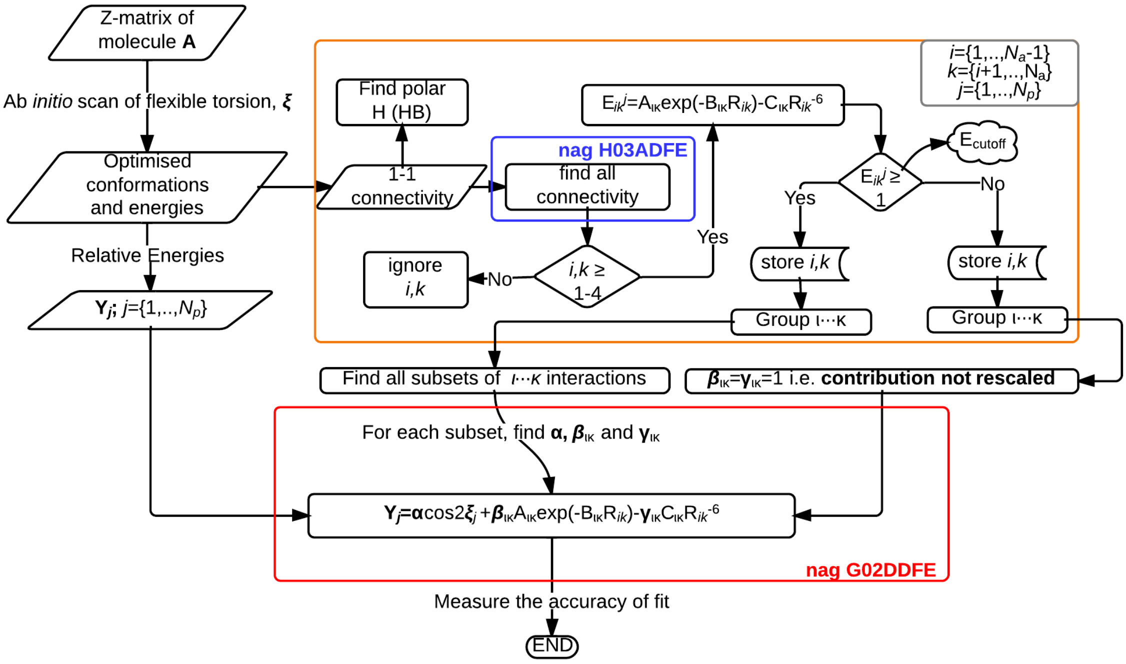


Figure S4: An algorithm showing the overview of modelling *ab initio* intramolecular energy by an atom-atom potential.

As shown in Figure S4, the fitting procedure extracts the geometries in *mol*2 format and the corresponding *ab initio* energies from the *ab initio* relaxed scan results from the GAUSSIAN03 output. The other input is starting values of the atom-atom exp-6 potential parameters (equation 2 and Table S1). The covalent 1-1 connectivity is used in atom typing, in this case to distinguish the polar hydrogen, HB, from non-polar hydrogen, H, atoms. All atom-atom connectivity (i.e. nearest neighbor) within the molecule is determined with the H03ADF NAG[4] subroutine.

The algorithm determines which atom-atom types affect the conformational profile significantly, i.e. an atom-atom interaction involving those types of atoms changes sufficiently to be meaningfully fitted. This was done by calculating each atom-atom distance where the atoms were separated by three or more bonds (bond-paths ≥ 1-4), evaluating the corresponding energy contributions with the model discussed in section 2.3, and determining whether the change with conformation (ξ) was greater than or equal to E_{cutoff}, which was set at a generous 1 kJ mol^{-1}. These atom-atom interactions are grouped into unique atom-atom types ($\iota\cdots\kappa$). If no atom-atom interaction of a given type ($\iota\cdots\kappa$) varied more than E_{cutoff}, for example Cl···O and O···HB, then these parameters were not considered for fitting. The atom-atom contacts that contribute significantly enough to the variation in conformational energy to be considered for fitting are given in Table S3 for FA and Table S4 for TA and contrasted in Table S5. These are mainly the contacts that would be expected from the molecular geometry (C_6, C_7, N_1, C_8, C_9 and bonded hydrogen atoms), but also include the Cl and methyl substituents in TA. We systematically tried fitting all subsets of combinations of the atom-atom rescaling parameters.

The fitting systematically compared the ability of various selections of the linear parameters (α, $\beta_{\iota\kappa}$, $\gamma_{\iota\kappa}$, c) to represent the *ab initio* data. The models were defined to be linear so that a general linear regression model could be used. Within the routine, a matrix decomposition process establishes whether a unique solution has been obtained, or whether the parameters being fitted are linearly dependent. Unless otherwise noted, all fits had a unique solution. Finally, we calculate the standard error, ΔE_{intra}, in the model's intramolecular energy after adjustment so that both the *ab initio* energies, E_{ab}, and the analytical fitted model energies, E_{model}, are defined relative to zero for the lowest energy. The fitted constant *c* differs from (E_{base}, by a fraction of a kJ mol^{-1} as *c* is fitted to the overall conformational curves whereas E_{base} is defined by the minimum energy of the analytical model. Hence, our measure of the quality of the fit is:

$$\sigma_{intra} = \sqrt{\frac{\sum (E_{ab} - E_{model})^2}{(N_p - N_k)}} \qquad \text{S1}$$

where Np and Nk are the number of data points and fitted coefficients respectively. There are only N_k -1 physical parameters, as one (c ~ E_{base}) is only adjusting the baseline.

3 Representation of torsional potential by various analytical models

3.1 Cosine series model

There is a slow convergence in the quality of the fit as the number of terms in the cosine series increases.

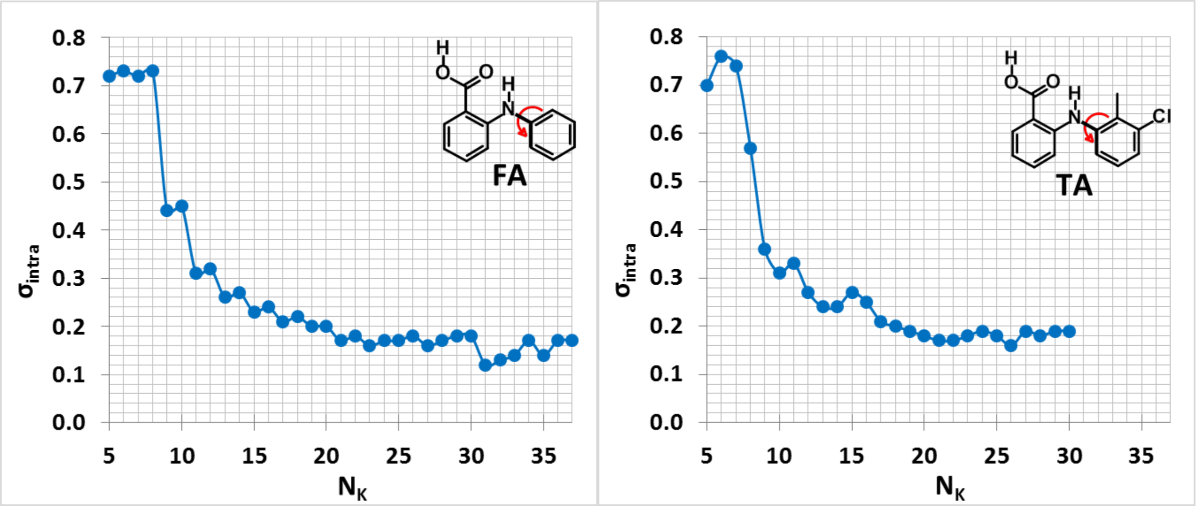


Figure S5: Plot of the standard error of the intramolecular energies against the number of cosine terms i.e. the number of fitted parameters, N_K. The fit is ill-determined, i.e. no unique solution, for TA after N_k=21.

3.2 Rescaling the Repulsion Model

An alternative model is to rescale just the repulsion terms (i.e. fit selected $\beta_{\iota\kappa}$ in equation S2) as the intermolecular atom-atom model is clearly badly overestimating the intramolecular steric effects (Figure S3).

$$E(\xi) = \sum_{i,k} \beta_{\iota\kappa} A_{\iota\kappa} \exp(-B_{\iota\kappa} R_{ik}) - C_{\iota\kappa} R_{ik}^{-6} \qquad \text{S2}$$

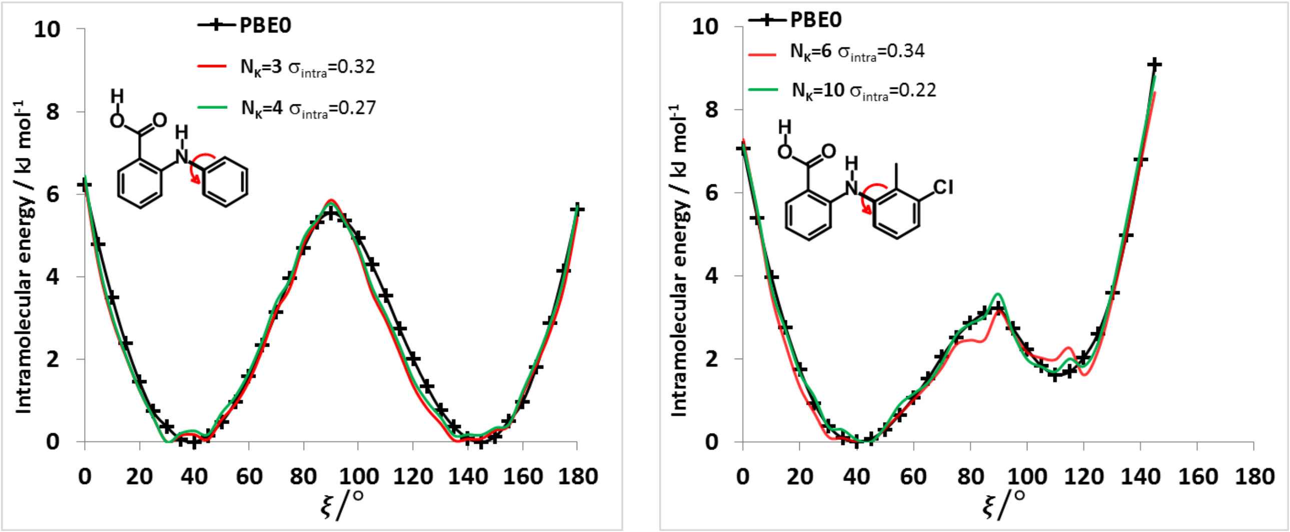
Rescaling just a few of Gavezzotti's repulsion parameters, for example just those involving the poorly parameterized H···H interactions, results in a qualitatively good fit (Figure S6), as shown by the results for fitting all combinations of repulsion parameters for FA (Table S6) and the summary in Table S7 of the 511 such fits for TA. Rescaling just two repulsion contributions for FA (C···H and H···H) and five for TA (C···H, C···HB, C···N, H···H and H···HB) produces a model that reproduces the torsional profile well (Figure S6). The rescaling of the C···N interaction seemed particularly critical for TA (Table S7), which can be attributed to the importance of the C(methyl)···N interaction in describing the steric clash involving the methyl group (Figure 5). However, many of the fitted rescaling parameters were negative ($\beta_{\iota\kappa} < 0$), which implies that the exponential steric repulsion had become attractive. Thus, again, this appears to be a fitting exercise, so that exponential terms are reducing the over-estimate of the barrier at 90° by the intermolecular dispersion parameters (Figure S3).

Table S6: Complete set of the rescaling repulsion contribution of the exp-6 potential for all possible combinations of interaction atom types C···C, C···H, C···HB, H···H, and H···HB for FA. N_k are the number of fitted rescale repulsion parameters, $\beta_{\iota\kappa}$, and the intercept, *c*.

	$\beta_{\iota\kappa}$					***c***	σ_{intra}
N_k	C -C	C -H	C -HB	H -H	H -HB	kJ mol^{-1}	
2	-	-2.26	-	-	-	-3.20	1.68
2	-	-	-1.48	-	-	-9.11	2.84
2	-	-	-	-0.88	-	-21.02	2.87
2	-	-	-	-	-4.23	-34.64	2.99
2	-3.32	-	-	-	-	397.60	4.51
3	-	-4.53	-	2.69	-	5.23	0.32
3	-	-4.28	-	-	5.39	15.00	0.32
3	-2.10	-2.17	-	-	-	310.14	0.36
3	-	-5.23	3.65	-	-	-2.84	0.4
3	-5.23	-	-1.73	-	-	626.37	0.45
3	-6.21	-	-	-1.24	-	713.45	0.65
3	-6.66	-	-	-	-5.49	743.23	0.66
3	-	-	-9.91	-	20.82	75.67	1.27
3	-	-	-9.09	7.22	-	23.02	1.74
3	-	-	-	-7.38	19.72	25.42	2.47
4	-	-4.46	-	2.10	2.57	8.80	0.27
4	-	-4.67	1.44	2.43	-	4.00	0.3
4	0.79	-4.38	-	2.58	-	25.72	0.32
4	0.41	-3.90	-	-	4.59	70.91	0.32
4	-	-4.32	1.09	-	5.25	14.44	0.33
4	-1.73	-2.54	1.33	-	-	272.53	0.37
4	-4.58	-	-2.96	-	3.94	572.27	0.4
4	-5.07	-	-2.18	1.37	-	611.48	0.45
4	-6.39	-	-	-0.35	-1.57	725.75	0.64
4	-	-	-9.58	0.06	22.75	79.11	1.25
5	1.30	-4.67	-	2.18	2.78	-20.63	0.28
5	-	-4.48	1.04	2.10	2.51	8.55	0.28
5	2.36	-5.91	2.18	2.70	-	-132.20	0.29
5	-0.16	-3.27	0.37	-	4.81	129.56	0.31
5	-4.56	-	-2.84	0.61	4.79	572.13	0.39
6	2.08	-5.50	1.70	2.37	2.25	-100.62	0.28

Table S7: Summary table of the best fit to the TA *ab initio* conformational scans by rescaling N_k repulsion parameters. The rescale parameters, $\beta_{\iota\kappa}$, and the baseline energy, $-E_{base}$, are given alongside the quality of the fit. The parameters used in Figure S6 are in bold.

	$\beta_{\iota\kappa}$									E_{base}	σ_{intra}
N_k	C-C	C-Cl	C-H	C-HB	CL-H	C-N	H-H	H-HB	H-N	/ kJ mol^{-1}	
2	-	9.09	-	-	-	-	-	-	-	112.81	1.30
3	-0.08	-	-	-	-	-2.99	-	-	-	-135.47	0.93
4	-	-	-	-	7.51	-2.69	-	-	14.54	117.47	0.87
5	-	-	-2.79	6.22	-	-4.64	-	-5.49	-	-54.29	0.51
6	**-**	**-**	**-3.06**	**4.72**	**-**	**-4.47**	**4.26**	**-5.29**	**-**	**-52.79**	**0.34**
7	-	-	-3.92	4.72	-	-4.87	5.32	-6.11	-0.54	-76.90	0.25
8	-	5.03	-3.59	3.87	2.65	-3.40	5.81	-5.70	-	3.00	0.22
9	-	5.31	-3.43	3.55	3.18	-3.27	5.96	-5.39	1.90	17.48	0.21
10	**0.84**	**5.41**	**-3.19**	**3.30**	**3.47**	**-3.31**	**6.11**	**-5.27**	**2.19**	**6.81**	**0.22**



(a) (b)

Figure S6: Comparison of the relative energies from *ab initio* calculations (solid black lines) of (a) FA and (b) TA with selected best fit *exp-6* rescaled repulsion models. For FA, the selected N_k=3 σ_{intra}=0.32 kJ mol^{-1} model has β_{C-H}=-4.53, β_{H-H}=2.70, and c=5.23, while the N_k=4 σ_{intra}=0.27 kJ mol^{-1} model has β_{C-H}=-4.46, β_{H-H}=2.10, β_{H-HB}=2.57, and c=8.80. For TA, the selected N_k=6 (σ_{intra}=0.34 kJ mol^{-1}) and 10 (σ_{intra}=0.22 kJ mol^{-1}) parameters are given in bold in Table S7.

3.3 Physical model

If we assume a model that describes both the electronic effects and allows rescaling of the atom-atom interactions:

$$E(\xi) = \alpha\cos(2\xi) + \sum_{i,k} \beta_{\iota\kappa} A_{\iota\kappa} \exp(-B_{\iota\kappa} R_{ik}) - \gamma_{\iota\kappa} C_{\iota\kappa} R_{ik}^{-6} \qquad \text{S3}$$

then there are a huge number of ways of finding a satisfactory fitting of the data (Table S8 and Table S9).

Table S8: The rescale parameters for the repulsion, $\beta_{\iota\kappa}$, dispersion, $\gamma_{\iota\kappa}$, and electronic, α, contributions of the physical *exp*-6 and cos2ξ model for all possible combinations of atom type interactions C···C, C···H, C···HB, H···H and H···HB for FA. N_K are the number of fitted rescale parameters, $\beta_{\iota\kappa}$ and $\gamma_{\iota\kappa}$, and the intercept, *c*. The intercept is approximately the baseline energy, E_{base}. All fits obtained for FA with the physically correct sign for the repulsion, βικ, and dispersion, γικ, and electronic α parameters are highlighted. This includes the parameter sets used in Figure 8.

	$\beta_{\iota\kappa}$					$\gamma_{\iota\kappa}$					α	*c*	σ_{intra}
N_k	C-C	C-H	C-HB	H-H	H-HB	C-C	C-H	C-HB	H-H	H-HB	kJ mol^{-1}		
4	-	-	-	11.08	-	-	-	-	50.03	-	-3.91	59.10	0.33
4	-	6.19	-	-	-	-	20.82	-	-	-	-1.57	180.54	0.36
4	-7.97	-	-	-	-	-15.08	-	-	-	-	-2.72	105.07	0.45
4	-	-	-	-	34.67	-	-	-	-	136.98	-5.30	12.27	0.57
4	-	-	36.30	-	-	-	-	110.38	-	-	-9.45	334.27	0.76
6	-3.66	4.61	-	-	-	-10.53	14.77	-	-	-	-0.80	37.67	0.10
6	-4.36	-	-	6.10	-	-7.64	-	-	29.66	-	-1.14	158.31	0.12
6	-8.52	-	-1.88	-	-	-12.27	-	-2.29	-	-	0.55	306.24	0.17
6	-6.00	-	-	-	11.35	-8.62	-	-	-	54.15	-1.43	235.14	0.18
6	-	-1.03	14.76	-	-	-	5.74	40.73	-	-	-2.20	173.92	0.23
6	-	-	-	12.08	-1.82	-	-	-	65.37	-29.18	-2.08	95.66	0.24
6	-	-2.55	-	6.19	-	-	0.13	-	20.48	-	-2.16	15.16	0.25
6	-	-	8.01	10.74	-	-	-	16.54	58.00	-	-3.39	123.69	0.26
6	-	0.28	-	-	11.09	-	7.83	-	-	34.79	-1.17	75.59	0.28
6	-	-	-13.26	-	65.19	-	-	-69.60	-	328.79	-5.39	-244.32	0.36
8	-2.75	3.51	-	-	2.71	-9.35	13.44	-	-	4.12	-0.75	-5.33	0.08
8	-2.36	4.14	-	-1.57	-	-10.78	18.76	-	-17.19	-	-0.76	-93.72	0.09
8	-3.73	-	-	6.26	3.34	-6.81	-	-	34.75	2.22	-0.66	152.08	0.09
8	-4.93	5.51	-1.89	-	-	-12.18	15.30	-6.42	-	-	-0.47	64.98	0.10
8	-5.30	-	-7.37	7.25	-	-10.54	-	-24.17	32.67	-	-0.44	33.44	0.10
8	-6.98	-	-16.55	-	30.47	-12.63	-	-60.95	-	147.74	0.12	-58.34	0.13
8	-	-4.19	5.20	11.95	-	-	-8.46	6.91	60.39	-	-2.46	9.91	0.19
8	-	-	18.43	11.85	-16.77	-	-	58.81	72.51	-111.25	-1.96	303.42	0.19
8	-	-0.89	26.97	-	-31.96	-	9.52	96.22	-	-180.54	-0.82	404.42	0.21
8	-	-4.45	-	15.41	-10.16	-	-9.70	-	77.19	-63.85	-1.66	7.66	0.21
10	-4.45	6.86	-5.55	-5.41	-	-15.77	26.64	-14.89	-41.79	-	0.17	-137.51	0.05
10	-5.24	4.69	-7.40	-	9.53	-12.47	12.57	-24.81	-	38.80	-0.22	0.77	0.07
10	-3.20	4.65	-	-0.26	5.93	-9.77	15.32	-	-3.49	17.63	-0.64	34.05	0.08
10	-5.98	-	-14.29	4.55	18.04	-11.88	-	-51.12	18.25	86.95	-0.25	-69.83	0.09
10	-	1.66	27.17	6.71	-29.44	-	7.88	93.84	43.50	-178.54	-1.13	447.67	0.14
12	-3.83	7.09	-1.55	-5.70	-4.47	-14.98	28.35	-0.35	-42.60	-29.03	0.18	-97.07	0.06

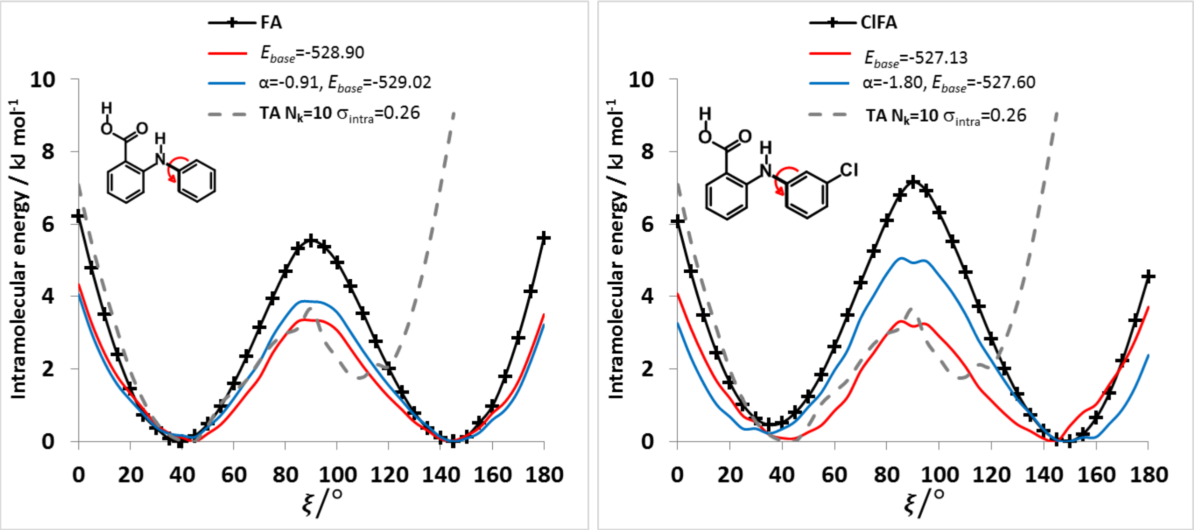
Table S9: The rescale parameters for the repulsion, $\beta_{\iota\kappa}$, dispersion, $\gamma_{\iota\kappa}$, and electronic, α, contributions of the physical exp-6 and $\cos2\xi$ model for all possible combinations of atom type interactions C···C, C···Cl, C···H, C···HB, Cl···H, C···N, H···H, H···HB and H···N for TA. N_K are the number of fitted rescale parameters, $\beta_{\iota\kappa}$ and $\gamma_{\iota\kappa}$, and the intercept, ***c***. The intercept is approximately the baseline energy, E_{base}. The parameters used in Figure 8b, and for testing transferability in Figure 9b and Figure S7 are highlighted.

	$\beta_{\iota\kappa}$									$\gamma_{\iota\kappa}$									α	***c***	σ_{intra}
N_k	C-C	C-Cl	C-H	C-HB	Cl-H	C-N	H-H	H-HB	H-N	C-C	C-Cl	C-H	C-HB	Cl-H	C-N	H-H	H-HB	H-N	kJ mol^{-1}		
4	-	10.19	-	-	-	-	-	-	-	-	5.93	-	-	-	-	-	-	-	-1.35	-87.14	1.08
4	-	-	-	-	-	9.30	-	-	-	-	-	-	-	-	29.01	-	-	-	-5.30	248.70	1.11
4	-	-	-	-	-	-	-	-	18.39	-	-	-	-	-	-	-	-	51.01	-2.93	141.71	1.49
4	-	-	-	-	-	-	-	8.61	-	-	-	-	-	-	-	-	38.84	-	-2.54	-20.26	1.65
4	-	-	-	3.03	-	-	-	-	-	-	-	-	11.02	-	-	-	-	-	-1.67	11.69	1.68
4	1.81	-	-	-	-	-	-	-	-	0.95	-	-	-	-	-	-	-	-	-7.61	-131.77	1.93
6	-	-	-	-	-	22.37	1.73	-	-	-	-	-	-	-	65.17	18.10	-	-	-1.35	635.66	0.49
6	-	4.84	-	-	-	19.74	-	-	-	-	41.73	-	-	-	71.86	-	-	-	-8.48	994.13	0.67
6	-	-	15.60	-	-	-	18.56	-	-	-	-	8.17	-	-	-	119.67	-	-	-13.11	86.71	0.77
6	-	-	-	-	9.67	21.71	-	-	-	-	-	-	-	44.31	69.77	-	-	-	-1.67	891.21	0.78
6	6.59	-	-	-	-	44.09	-	-	-	9.55	-	-	-	-	123.97	-	-	-	-16.02	992.70	1.02
6	-	-	-	-	-	-	6.04	-	22.88	-	-	-	-	-	-	20.12	-	75.06	-6.74	275.80	1.20
8	-	19.33	-	5.67	-	21.65	-	-	-	-	72.89	-	22.07	-	69.76	-	-	-	-1.02	1141.79	0.15
8	-	-	-	-	19.57	30.68	-	4.98	-	-	-	-	-	81.30	96.34	-	26.47	-	-0.96	1337.73	0.16
8	-	16.18	-	-	-	28.74	-	6.76	-	-	62.63	-	-	-	89.52	-	37.54	-	-3.61	1196.25	0.23
8	-	0.38	-	-	-	24.51	1.33	-	-	-	11.39	-	-	-	75.74	15.28	-	-	-3.20	836.68	0.28
8	-	-	10.15	8.01	-	-	5.05	-	-	-	-	0.83	4.37	-	-	111.23	-	-	-9.62	41.60	0.37
8	-	-	-	-	6.34	26.50	0.27	-	-	-	-	-	-	20.75	79.27	11.06	-	-	-3.13	861.83	0.41
8	-	-	-	-	-	22.11	1.27	3.67	-	-	-	-	-	-	63.26	18.98	12.48	-	-0.09	623.15	0.47
8	-	-	1.56	-	-	23.56	1.05	-	-	-	-	1.89	-	-	68.73	15.61	-	-	-1.78	675.21	0.51
8	-	-	14.22	-	-	-	11.94	12.25	-	-	-	11.18	-	-	-	86.25	53.31	-	-6.21	142.90	0.63
8	-	-	7.68	-	-	-	14.97	-	13.53	-	-	2.21	-	-	-	81.54	-	27.30	-4.36	92.57	0.71
10	-	10.49	-	-	26.00	27.31	-	6.79	-	-	3.66	-	-	91.02	81.40	-	38.89	-	-4.26	1122.44	0.08
10	-	-	1.35	-	8.53	21.73	-	4.26	-	-	-	4.04	-	27.24	68.67	-	24.76	-	-1.93	837.13	0.09
10	-	8.53	-	-	-	23.86	2.27	5.83	-	-	37.42	-	-	-	74.31	12.38	29.41	-	-2.22	946.98	0.10
10	-	-	-	-	14.65	27.85	0.89	5.42	-	-	-	-	-	57.88	85.69	7.20	25.68	-	-1.07	1121.09	0.11
10	-	11.43	1.94	4.57	-	20.86	-	-	-	-	48.33	3.41	18.29	-	67.62	-	-	-	-0.96	1026.45	0.16
10	0.50	-	-	-	17.63	26.92	-	4.96	-	0.85	-	-	-	70.84	86.15	-	27.44	-	-0.32	1234.33	0.18
10	**-**	**-**	**1.80**	**-**	**-**	**20.79**	**-**	**6.04**	**0.89**	**-**	**-**	**6.27**	**-**	**-**	**61.76**	**-**	**35.44**	**8.83**	**-0.51**	**719.55**	**0.26**
10	-	-	4.13	5.06	-	13.34	0.18	-	-	-	-	4.73	11.46	-	40.10	25.32	-	-	-0.67	482.88	0.31
10	3.14	-	9.45	11.22	-	-	5.35	-	-	5.31	-	1.10	18.33	-	-	100.29	-	-	-9.66	95.31	0.32
10	-	11.60	7.43	9.25	-	-	3.65	-	-	-	27.57	0.57	15.32	-	-	80.17	-	-	-4.87	171.14	0.36
12	-	-	-	0.93	13.21	28.31	3.14	-	15.19	-	-	-	5.69	41.86	82.38	9.41	-	38.12	-4.14	1109.68	0.07
12	-	7.09	-	2.53	17.21	26.53	-	-	9.03	-	11.98	-	10.91	55.30	79.56	-	-	17.92	-3.50	1111.02	0.08
12	-	-	2.37	1.37	10.32	23.50	-	-	7.00	-	-	4.32	7.02	27.19	72.55	-	-	10.37	-3.51	885.71	0.08
12	-	-	4.25	-	8.43	22.74	0.65	6.56	-	-	-	5.88	-	24.15	69.38	13.56	31.01	-	-4.40	840.16	0.08
12	-	-	0.46	-	-	20.81	5.36	2.74	13.91	-	-	3.44	-	-	57.22	13.60	23.19	50.07	-2.45	780.76	0.27
14	-	-	3.84	2.14	8.86	20.10	1.90	-	8.05	-	-	4.56	6.90	20.56	61.36	16.35	-	14.62	-5.32	764.76	0.08
14	-	-	2.49	0.12	9.54	24.42	-	3.16	4.10	-	-	4.57	2.14	24.39	75.63	-	12.79	2.09	-3.60	861.86	0.09

The quality of selected fits is shown in Figure 8. We noted that the relaxed scans are sensitive to a large number of atom-atom distances, so that the 5° change in ξ does not necessarily give a smooth curve between the analytical values. This is because of the differences in the molecular relaxation and resulting atom-atom distances. The differences in atom-atom distances with relaxation are not an artefact of the step size; Figure S2 in ESI shows that a smooth but still asymmetric ab initio energy curve is produced by a smaller step size. All the fits with the physically correct parameters were unique solutions. However, there were some variations in the parameters for a given atom-atom interaction depending which other atomic types were being fitted. It is noticeable that for TA (Table S9), the C···N parameters consistently need to be drastically rescaled, reflecting the importance of the methyl carbon in the conformational profile of TA. Indeed, TA differs from FA in having many more intramolecular atom-atom distances that change significantly within the range ξ= 0-145° including some within the same aromatic ring, such as the methyl–chloro interactions (Table S5).

4 An Additional Transferability Test

A more stringent test of transferability than that shown in Figure 9 is to apply the parameters fitted to TA parameters to FA and ClFA. This gives a qualitatively correct result around the minima (Figure S7) and the steric barriers at 0 and 180°. However, the barrier height around 90° remains similar to that in TA, and this underestimation is only partially corrected by refitting the $\alpha\cos(2\xi)$ term. Nonetheless, this error of less than 2 kJ mol^{-1} compares favourably with the errors in transferrable force field. The qualitative accuracy in the transferability of the atom-atom coefficients terms (Figure S7) is promising, given the limitations in the parameter optimization. In particular, the poorer transferability may be because the same parameters are used for both aromatic and methyl C and H interactions in TA, and the methyl···N interaction was critical in fitting the parameters to the TA profile.



(a) (b)

Figure S7: Comparison of the relative energies from *ab initio* calculations (solid black lines) of (a) FA and (b) ClFA with models using $\beta_{\iota\kappa}$ and $\gamma_{\iota\kappa}$ parameters transferred from TA (whose contrasting profile is shown in grey dashes). The red curve has only had the baseline adjusted, whereas the blue curve has α parameter refitted to FA or ClFA respectively. The transferred TA parameters are those of N_k=10 σ_{fit}=0.26 kJ mol^{-1} highlighted in Table S8 of the ESI.

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