Counterintuitive Torsional Barriers Controlled By Hydrogen Bonding

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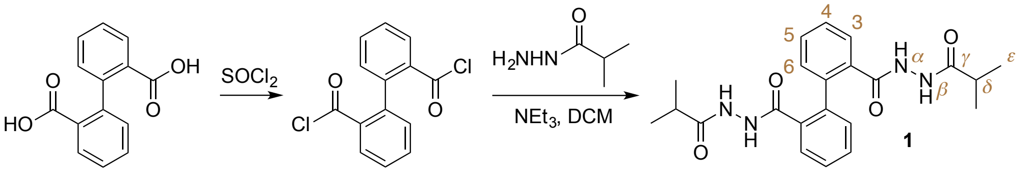
Supporting Information

1. General methods

All reagents were purchased from chemical suppliers and used without further purification. Solvents were of analytical grade and either used as purchased or dried according to procedures described elsewhere.[1] Characterization by Nuclear Magnetic Resonance spectroscopy (NMR) was carried out using a Bruker Ascend 500 MHz spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) and are referenced to TMS using the residual signal of the solvent as an internal reference. Coupling constants (*J*) are reported in hertz (Hz). Standard abbreviations used to indicate multiplicity are: s = singlet, d = doublet, t = triplet, hept = heptuplet, m = multiplet. Products were also characterized by High Resolution Mass Spectrometry (HRMS), performed at the COSMIC facility of the Old Dominion University (Norfolk, VA) using a Bruker Daltonics 12 Tesla APEX-Qe FTICR mass spectrometer with an Apollo II Ion Funnel and positive-ion mode electrospray ionization. The X-ray diffraction data were collected at 173 K on a Bruker SMART CCD diffractometer with MoKα radiation (λ = 0.71073 Å). The diffraction data were corrected for absorption using the SADABS program.[1] The structures were solved using SHELXS97[2] and refined by full matrix least-squares on F2 using SHELXL-2014 in the anisotropic approximation for all non-hydrogen atoms. The hydrogen atoms were introduced at calculated positions and not refined (riding model).[2–4]

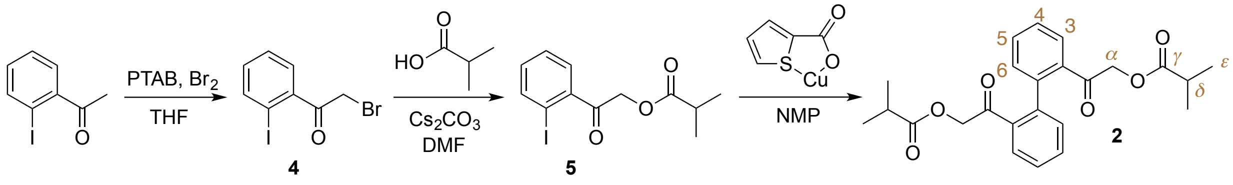
2. Preparation of biphenyls 1 and 2 and *N'*-acylhydrazide 3

Preparation of biphenyl **1**



Diphenic acid (0.12 g, 0.50 mmol) was dissolved in SOCl$_2$ (1.5 mL) under inert atmosphere and the resulting solution was stirred at 70 ºC for 6 h. The solvent was then evaporated under reduced pressure to afford an oily residue to which isobutyric acid hydrazide (0.15 g, 1.5 mmol), NEt$_3$ (0.69 ml, 5.0 mmol) and dry dichloromethane (10 mL) were immediately added. The mixture was degassed and stirred overnight at room temperature. After evaporation, the residue was purified by column chromatography (silica gel; eluent CHCl$_3$/MeOH/NH$_3$ 90:9:1); white solid (0.13 g, 65%). ^{1}H-NMR (500 MHz, CDCl$_3$): δ 10.50 (s, 2H, H$^\alpha$), 7.90 (s, 2H, H$^\beta$), 7.49 (d, *J* = 7.4 Hz, 2H, H^3), 7.44 (t, *J* = 7.0 Hz, 2H, H^4 or H^5), 7.38 (t, *J* = 7.2 Hz, 2H, H^4 or H^5), 7.33 (d, *J* = 7.4 Hz, 2H, H^6), 2.34 (hept, *J* = 6.9 Hz, 2H, H$^\varepsilon$), 1.10 (d, *J* = 6.9 Hz, 6H, H$^\delta$), 1.06 (d, *J* = 6.9 Hz, 6H, H$^{\delta'}$). ^{13}C-NMR (126 MHz, CDCl$_3$): δ 176.26, 168.04, 138.05, 134.36, 130.81, 129.75, 127.91, 126.95, 33.70, 19.49, 19.15. HRMS (ESI-FTICR): m/z = 433.184550 [M+Na]$^+$ (calcd. 433.184626 for $C_{22}H_{26}N_4O_4Na$).

Preparation of biphenyl **2**

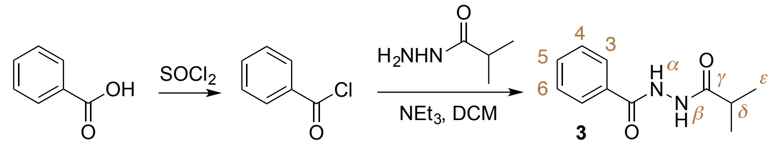


2-Bromo-1-(2-iodophenyl)ethan-1-one (**4**). Trimethylphenyl ammonium bromide (0.65 g, 3.0 mmol) was dissolved in dry THF (4.0 mL) under argon. Bromine (0.15 mL, 3.0 mmol) and 1-(2-iodophenyl)ethan-1-one (0.28 mL, 2.0 mmol) were then added. The red color of the mixture turned yellow within 5 min. After being stirred for 30 min in an ice bath under inert atmosphere, the mixture was filtered and the solvent was evaporated. Purification by silica gel column chromatography (hexane/EtOAc 20:1) afforded a pale yellow oil (0.45 g, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, J = 7.9 Hz, 1H, H^6), 7.44 (d, J = 4.3 Hz, 2H, H^3 + H^4 or H^5), 7.17 (dt, J = 7.9, 4.6 Hz, 1H, H^4 or H^5), 4.44 (s, 2H, H^α).[5]

Ester 5. Isobutyric acid (87 µL, 0.96 mmol) was dissolved in ethanol (3.5 mL). Cesium carbonate (0.31 g, 0.96 mmol) was then added, and the mixture was sonicated for 5 min and stirred at room temperature for 30 min until the salt was completely dissolved. The solvent was then evaporated. In a separate flask, α-bromoketone **4** (0.26 g, 0.80 mmol) was dissolved in dry DMF (2.0 mL) under inert atmosphere and added to the residue described above. The mixture was stirred at room temperature overnight under argon. Partition between water (15 mL) and ethyl acetate (15 mL), followed by washing of the organic layer with water (3 × 15 mL), drying with sodium sulfate and evaporation afforded an oily residue, which was used without further purification (0.25 g, 93%). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.92 (dt, J = 7.6, 0.8 Hz, 1H, H^3), 7.48 – 7.38 (m, 2H, H^4 + H^5), 7.16 (ddd, J = 7.9, 6.1, 2.9 Hz, 1H, H^6), 5.09 (s, 2H, H^α), 2.67 (hept, J = 7.0 Hz, 1H, H^ε), 1.18 (d, J = 7.0 Hz, 6H, H^δ). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 197.95, 176.47, 141.59, 140.56, 132.28, 128.51, 128.07, 91.16, 66.74, 33.71, 18.84. HRMS (ESI-FTICR): m/z = 354.980015 $[M+Na]^+$ (calcd. 354.980158 for $C_{12}H_{13}IO_3Na$).

Biphenyl 2. Ester **5** (0.17 g, 0.50 mmol) and copper(I)-thiophene-2-carboxylate (0.29 g, 1.5 mmol) were mixed with *N*-methyl-2-pyrrolidone (2.0 mL). The mixture was thoroughly degassed and stirred overnight at room temperature. The resulting slurry was diluted with ethyl acetate (10 mL) and filtered. The organic solution was washed with aqueous ammonia (15% v/v, 3 × 10 mL) and dried with sodium sulfate. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (hexane/EtOAc 90:10) to afford a pale yellow solid (0.10 g, 59%). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.74 (dd, J = 7.8, 1.5 Hz, 2H, H^3), 7.54 (td, J = 7.6, 1.4 Hz, 2H, H^4 or H^5), 7.48 (td, J = 7.6, 1.3 Hz, 2H, H^4 or H^5), 7.23 (dd, J = 7.6, 1.3 Hz, 2H, H^6), 4.90 (d, J = 16.9, 2H, H^α), 4.76 (AB system, J = 16.9, 2H, $H^{\alpha'}$), 2.60 (hept, J = 7.0 Hz, 2H, H^ε), 1.14 (d, J = 7.0 Hz, 12H, H^δ). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 196.51, 176.39, 140.02, 135.73, 131.69, 131.18, 128.28, 127.96, 67.09, 33.61, 18.87. HRMS (ESI-FTICR): m/z = 433.161937 $[M+Na]^+$ (calcd. 433.162160 for $C_{24}H_{26}O_6Na$).

Preparation of N'-isobutyrylbenzohydrazide (**3**)



Benzoic acid (0.24 g, 2.0 mmol) was dissolved in thionyl chloride (5.0 mL) under inert atmosphere and the resulting solution was stirred at 70 ºC for 20 h. Evaporation under reduced pressure afforded an oily residue to which isobutyric acid hydrazide (0.31 g, 3.0 mmol), NEt_3 (0.69 mL, 5.0 mmol) and dry dichloromethane (30 mL) were immediately added. The mixture was degassed, stirred for 24 h at room temperature, concentrated, and the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH/NH_3 95:5:1) to afford a white solid (0.39 g, 95%). ^{1}H-

NMR (500 MHz, $CDCl_3$): δ 9.60 (s, 1H, H^{α} or H^{β}), 9.26 (s, 1H, H^{α} or H^{β}), 7.84 (d, *J* = 7.2 Hz, 2H, H^2), 7.54 (t, *J* = 7.4 Hz, 1H, H^4), 7.43 (t, *J* = 7.7 Hz, 2H, H^3), 2.62 (hept, *J* = 6.9 Hz, 1H, H^{ε}), 1.24 (d, *J* = 6.9 Hz, 6H, H^{δ}). ^{13}C-NMR (126 MHz, $CDCl_3$): δ 174.06, 164.19, 132.31, 131.43, 128.69, 127.26, 33.54, 19.33. HRMS (ESI-FTICR): m/z = 435.200310 $[M_2+Na]^+$ (calcd. 435.200276 for $C_{22}H_{28}N_4O_4Na$).

3. Characterization of scaffolds 1 – 3 and their precursors

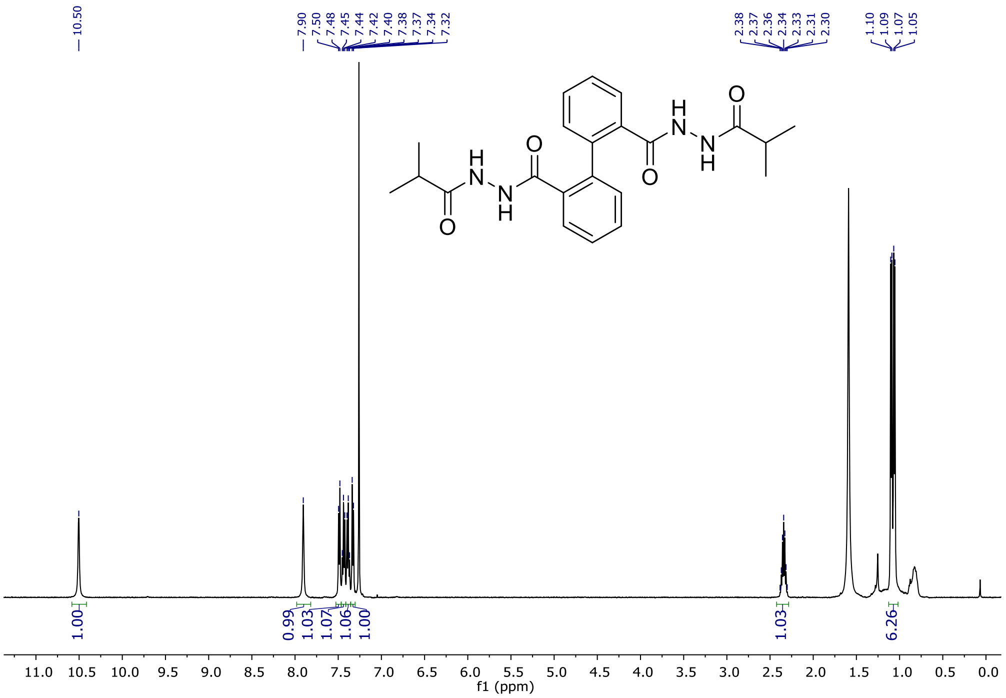


Figure S1. ^{1}H-NMR spectrum (CDCl$_3$) of biphenyl **1**.

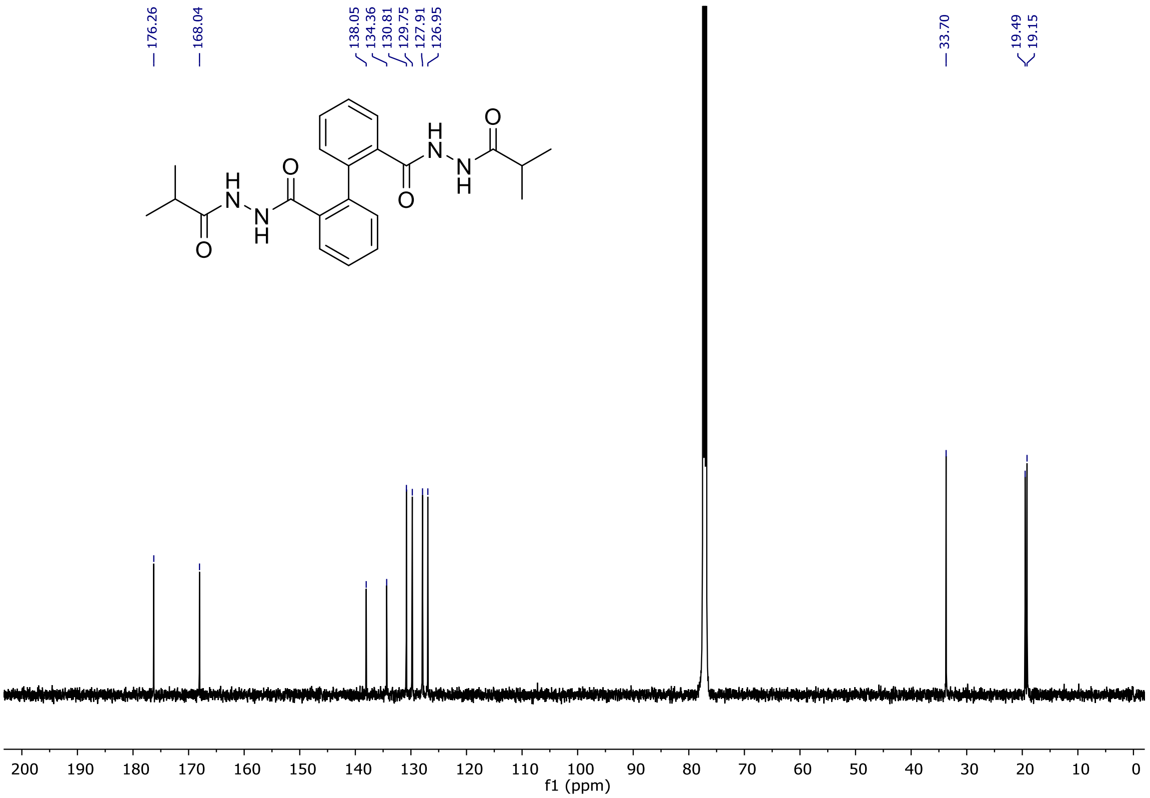


Figure S2. ^{13}C{^{1}H}-NMR spectrum (CDCl$_3$) of biphenyl **1**.

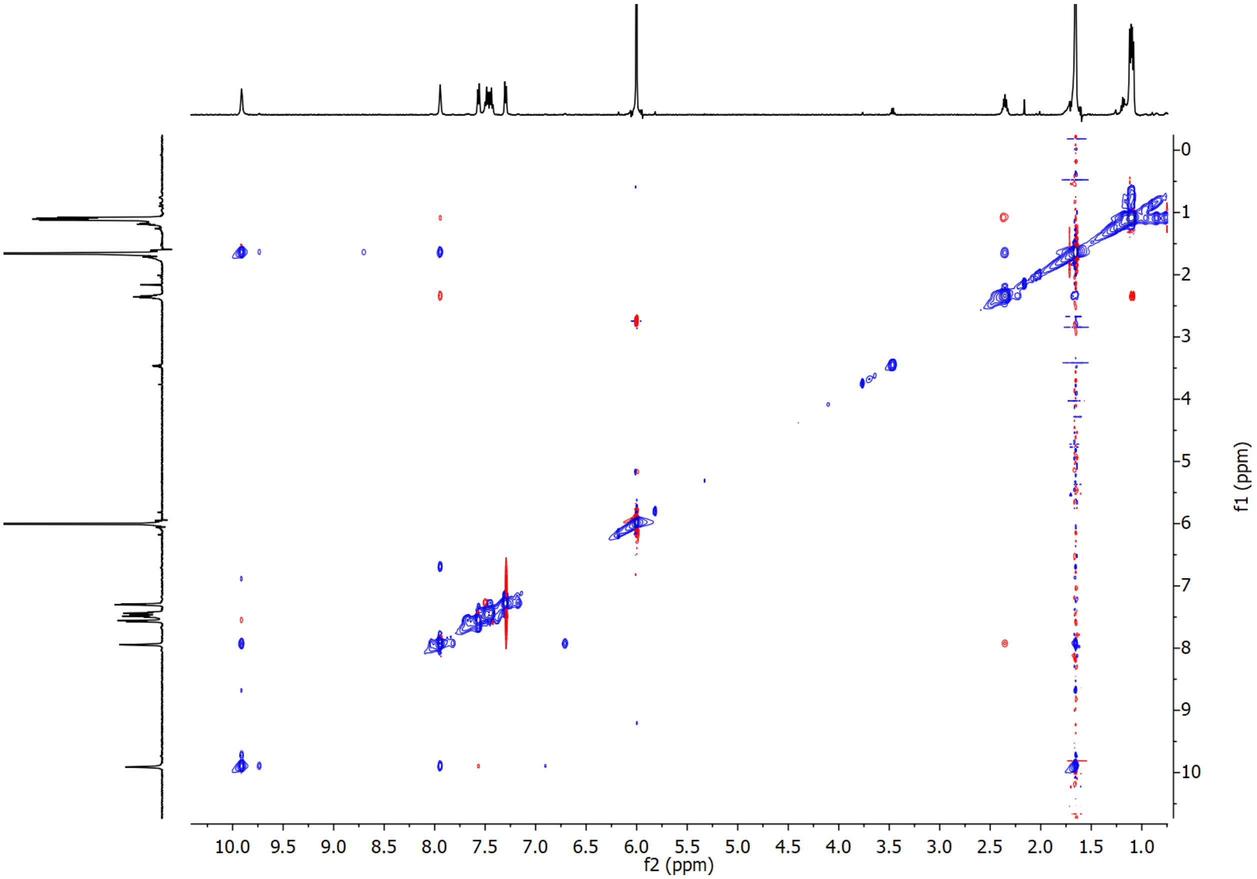


Figure S3. ^{1}H-^{1}H ROESY spectrum (TCE-d^2) of biphenyl **1**.

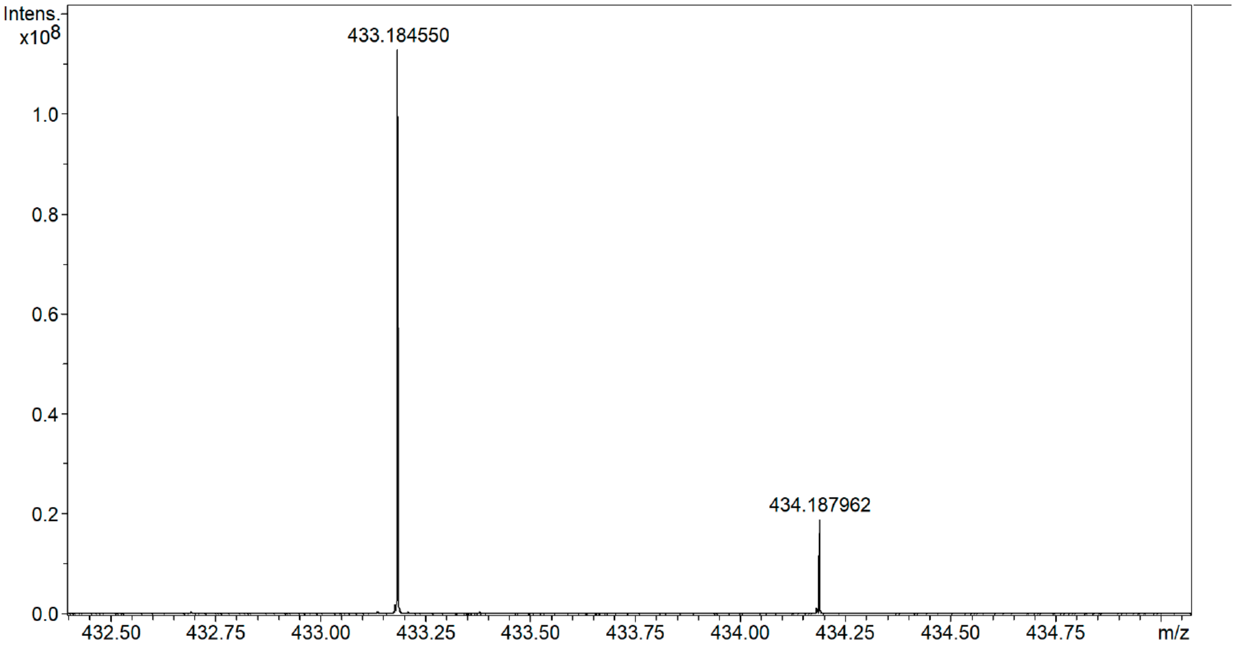


Figure S4. HRMS spectrum of biphenyl **1**.

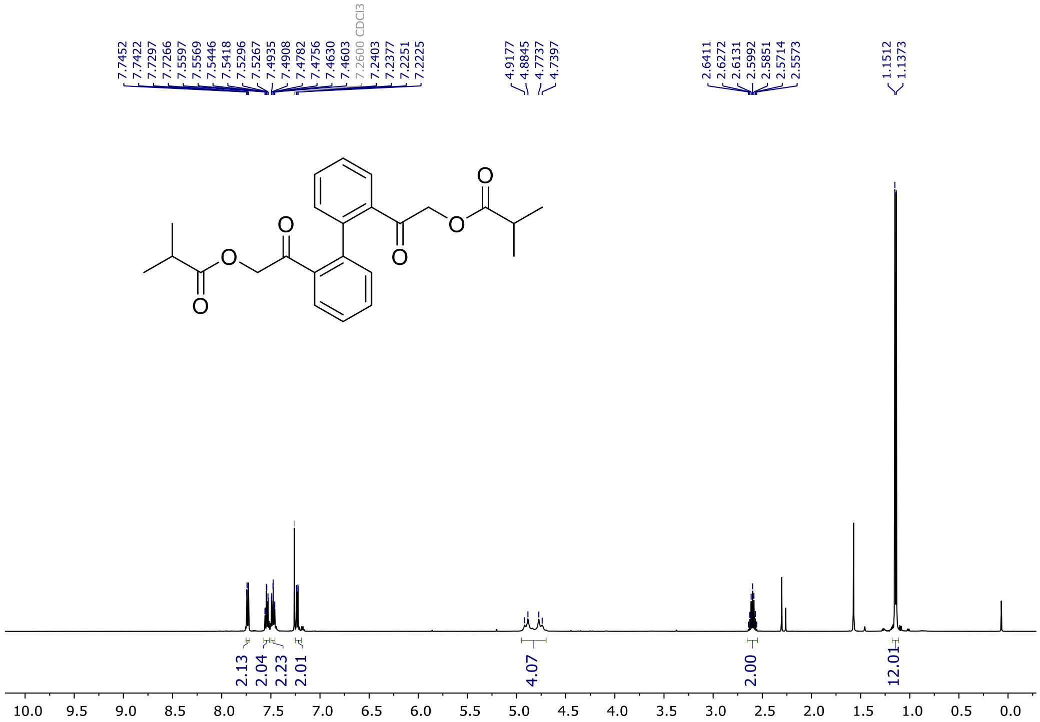


Figure S5. ^{1}H-NMR spectrum (CDCl$_3$) of biphenyl **2**.

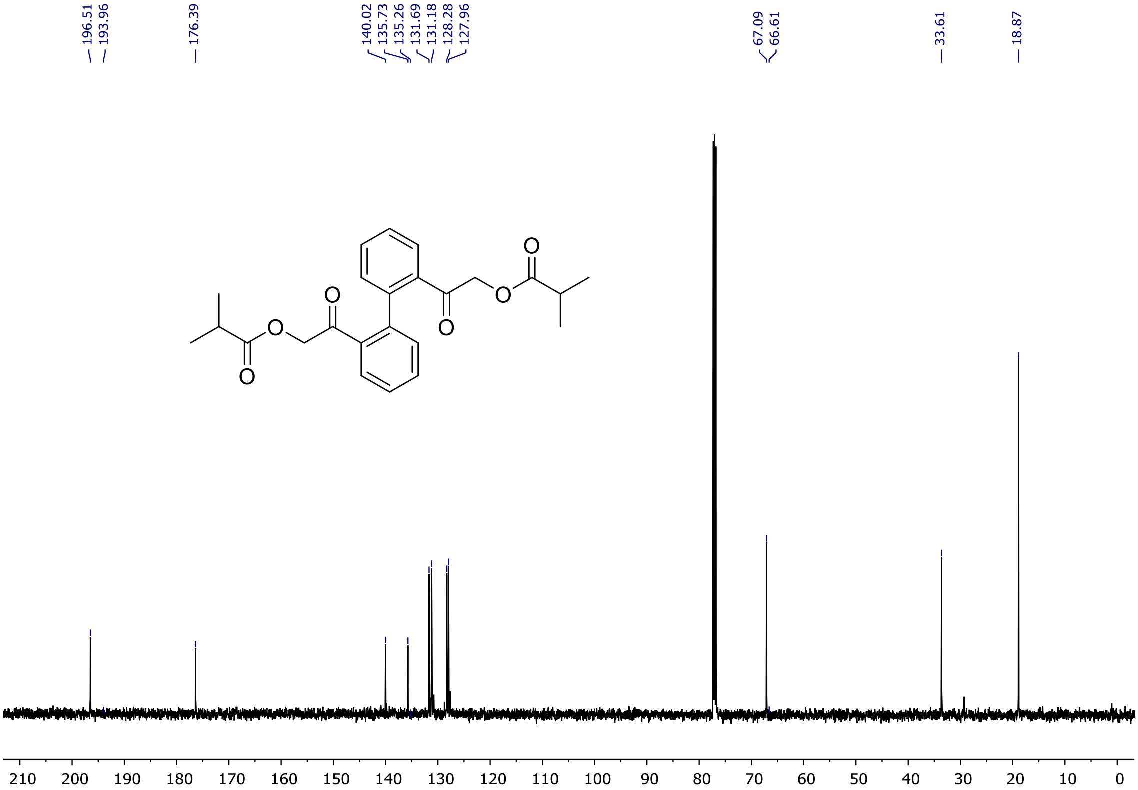


Figure S6. ^{13}C{^{1}H}-NMR spectrum (CDCl$_3$) of biphenyl **2**.

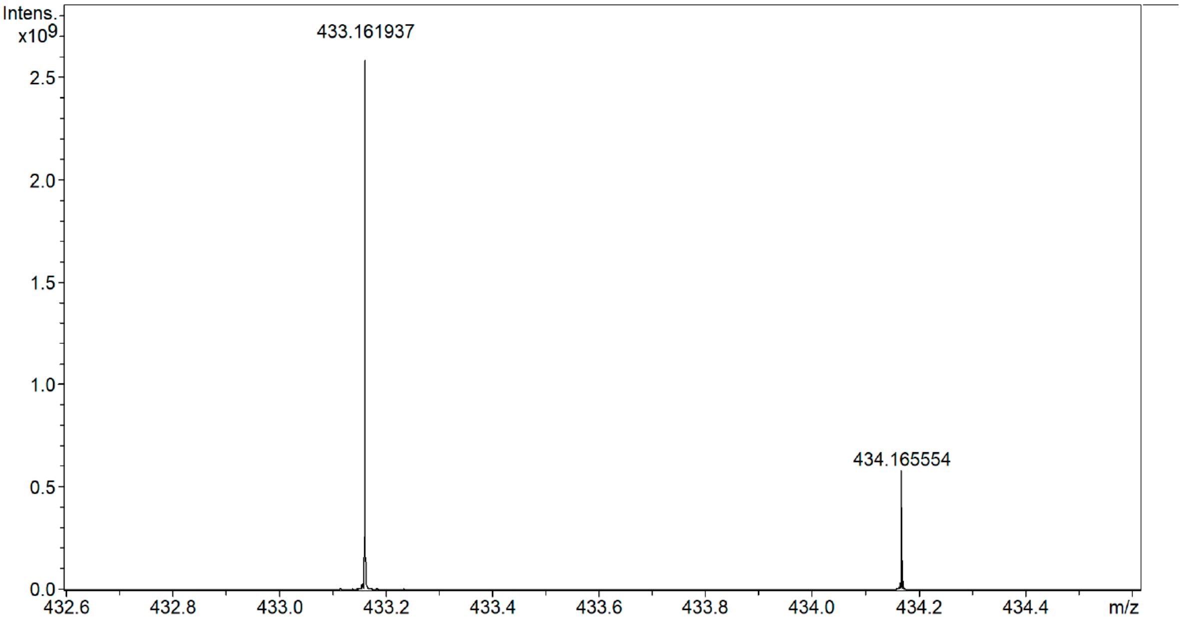


Figure S7. HRMS spectrum of biphenyl **2**.

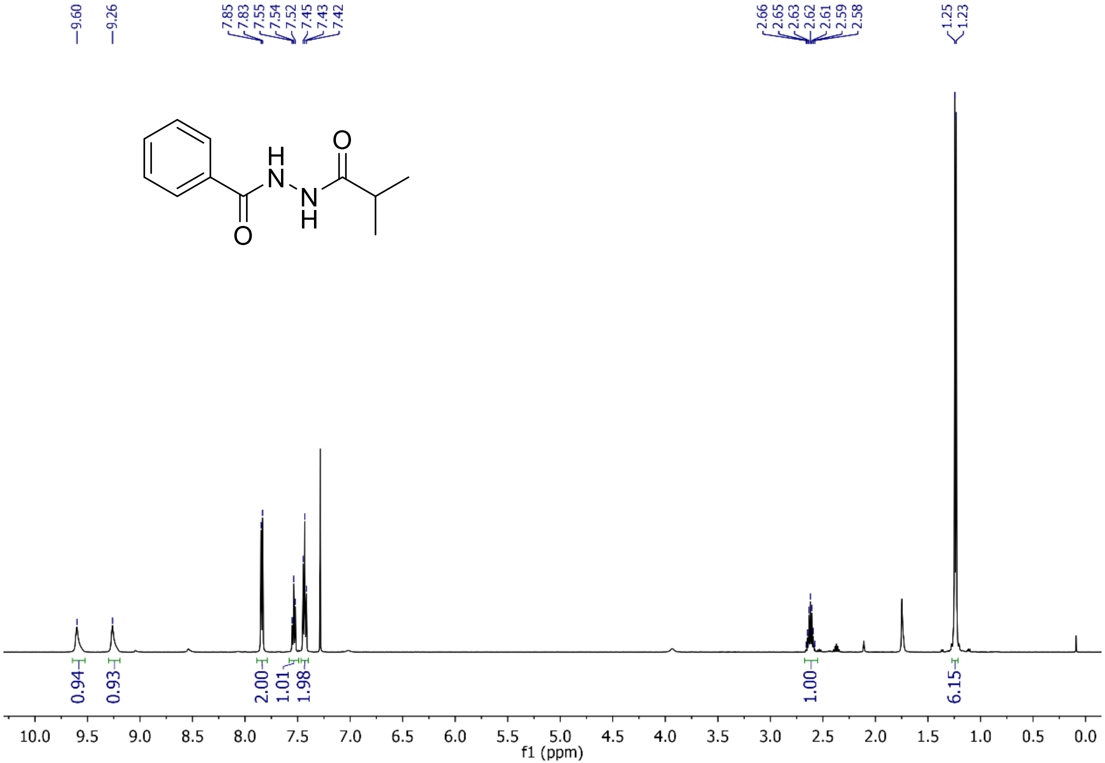


Figure S8. ^{1}H-NMR spectrum ($CDCl_3$) of compound **3**.

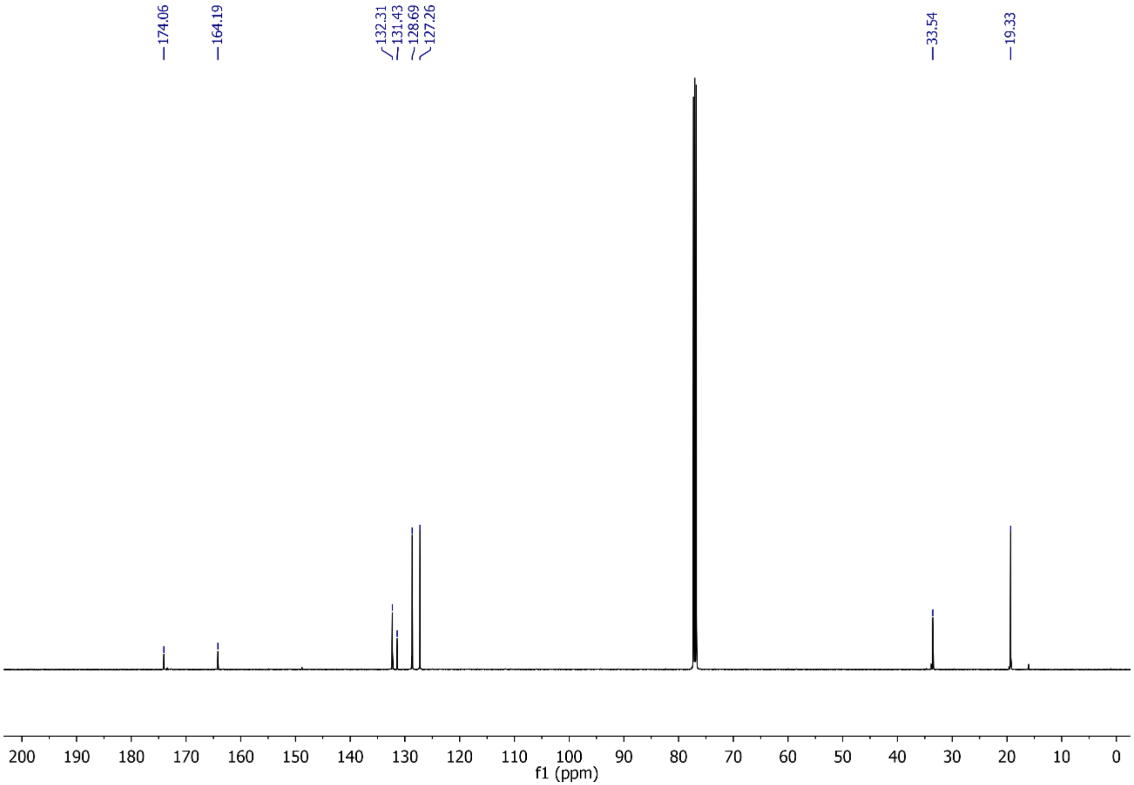


Figure S9. $^{13}C\{^1H\}$-NMR spectrum ($CDCl_3$) of compound **3**.

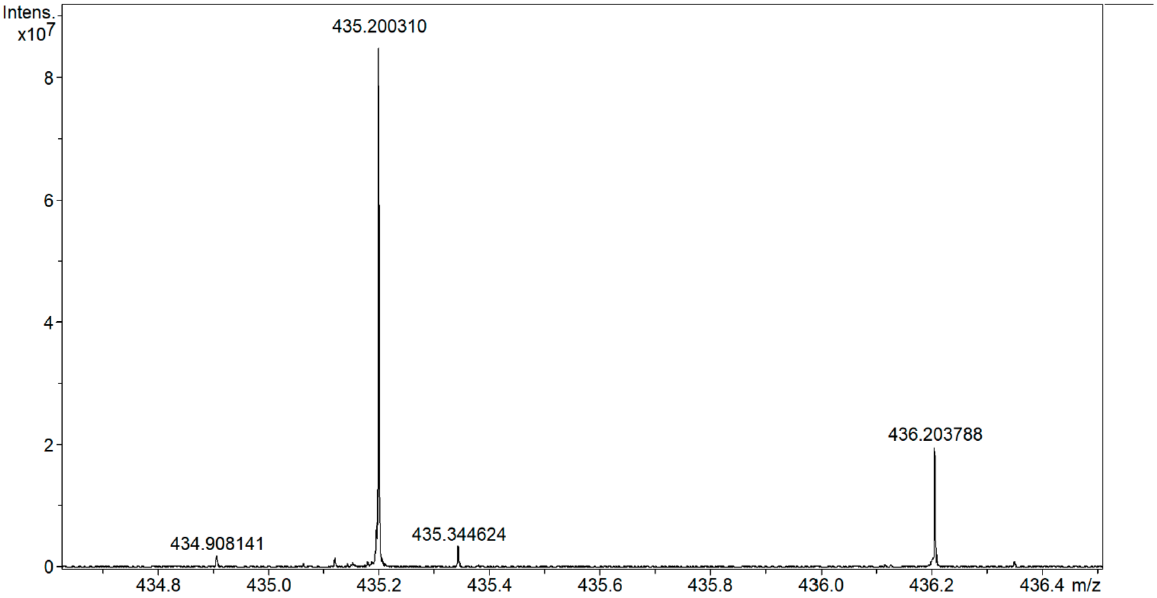


Figure S10. HRMS spectrum of compound **3**.

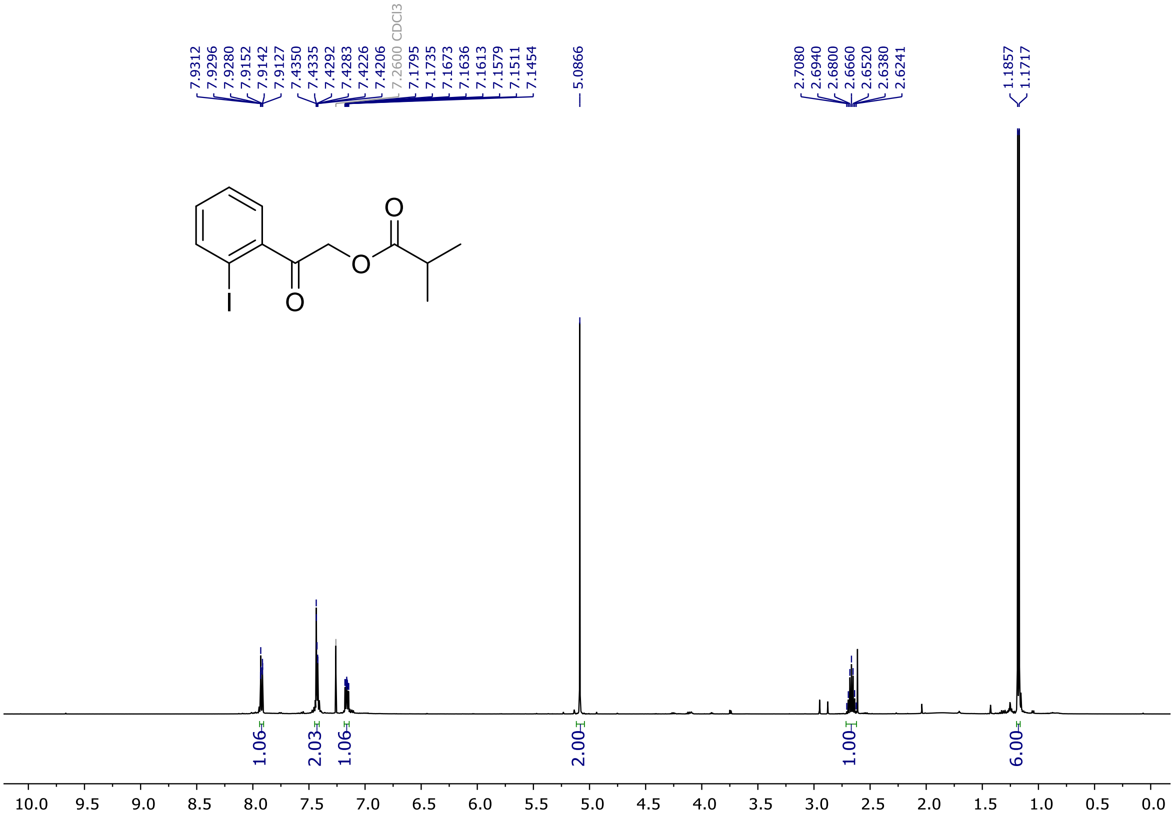


Figure S11. ^{1}H-NMR spectrum (CDCl$_3$) of compound **4**.

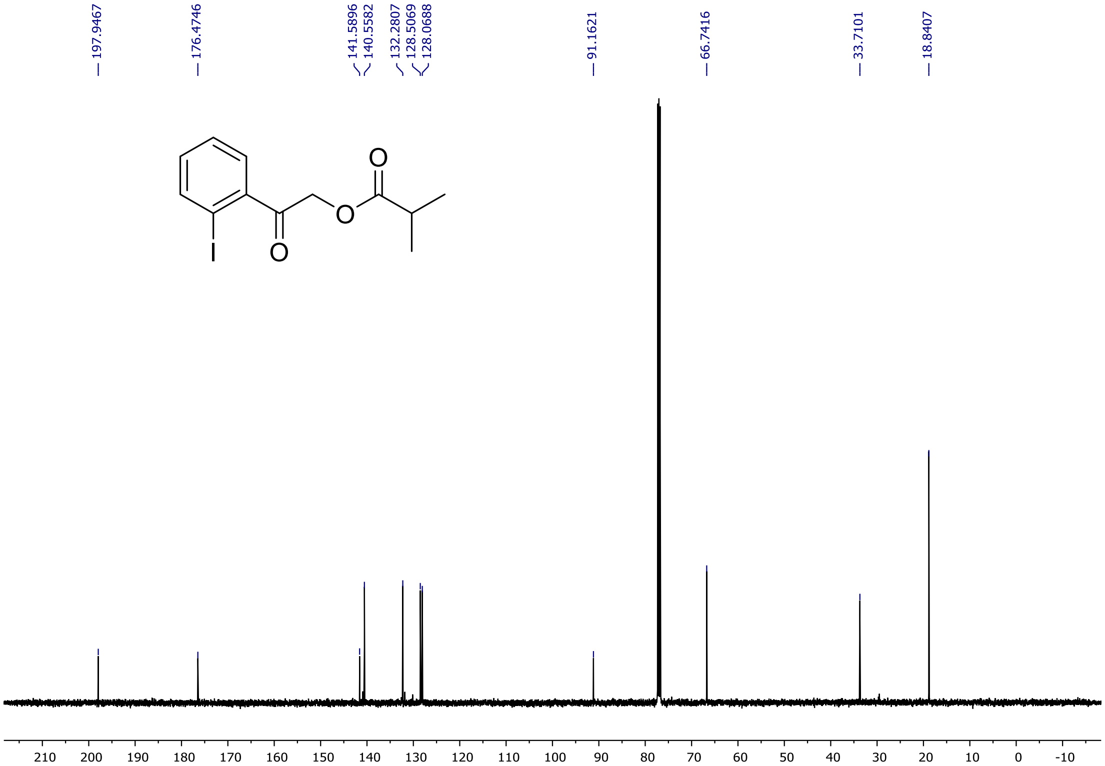


Figure S12. ^{13}C{^{1}H}-NMR spectrum (CDCl$_3$) of compound **4**.

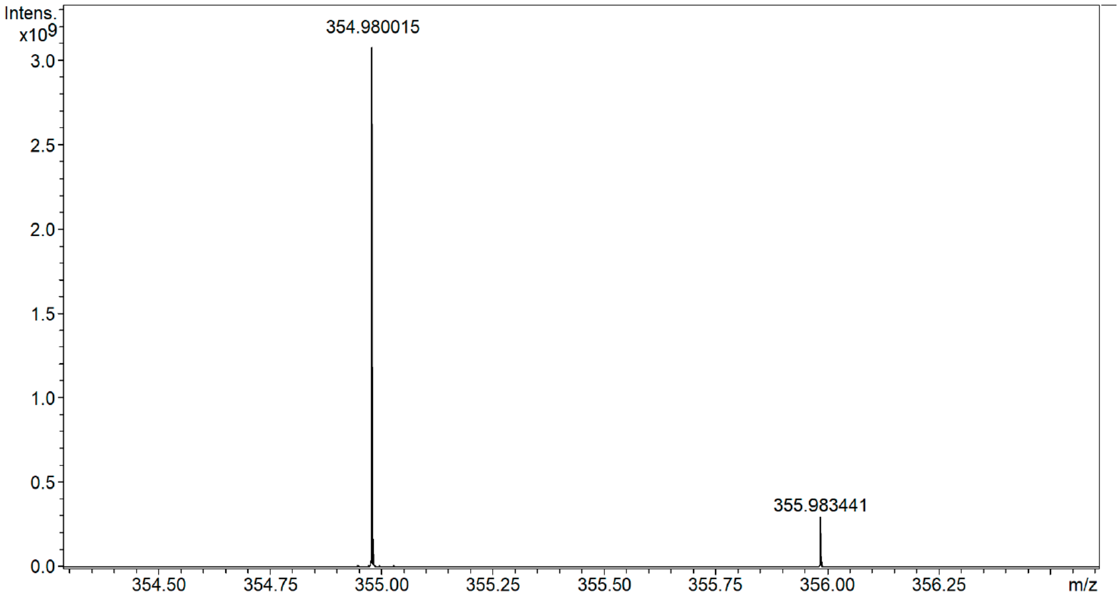


Figure S13. HRMS spectrum of compound **4**.

4. Determination of torsional barriers

Demonstration of equation (8). In an ideal mixture of two solvents, the concentration of solvent B can be obtained from the concentration of solvent A, the molar masses of both solvents M_{A} and M_{B}, and the density of both solvents (ρ_{A} and ρ_{B}; see equations 1 – 3).

$$[\mathrm{A}] = \frac{\rho_{\mathrm{A}} V_{\mathrm{A}}}{M_{\mathrm{A}}(V_{\mathrm{A}} + V_{\mathrm{B}})} \qquad (1)$$

$$V_{\mathrm{B}} = \frac{\rho_{\mathrm{A}} V_{\mathrm{A}}}{M_{\mathrm{A}}[\mathrm{A}]} - V_{\mathrm{A}} \qquad (2)$$

$$[\mathrm{B}] = \frac{\rho_{\mathrm{B}} V_{\mathrm{B}}}{M_{\mathrm{B}}(V_{\mathrm{A}} + V_{\mathrm{B}})} = \frac{\rho_{\mathrm{B}}\left(\frac{\rho_{\mathrm{A}} V_{\mathrm{A}}}{M_{\mathrm{A}}[\mathrm{A}]} - V_{\mathrm{A}}\right)}{M_{\mathrm{B}}\left(V_{\mathrm{A}} + \frac{\rho_{\mathrm{A}} V_{\mathrm{A}}}{M_{\mathrm{A}}[\mathrm{A}]} - V_{\mathrm{A}}\right)} = \frac{\rho_{\mathrm{B}}}{M_{\mathrm{B}}} - [\mathrm{A}]\frac{\rho_{\mathrm{B}} M_{\mathrm{A}}}{\rho_{\mathrm{A}} M_{\mathrm{B}}} \qquad (3)$$

Demonstration for the linear relationship between free energies of activation and coalescence temperatures (see article, Figure 4, insert c). The rate of torsion at coalescence temperature T_{c} is given by equation (4) and is related to the free activation energy of torsion using Eyring equation (5).

$$k = \frac{\pi \cdot \Delta\nu}{\sqrt{2}} \qquad (4)$$

$$k = \frac{k_B T_{\mathrm{c}}}{h} e^{-\Delta G^{\ddagger}/RT_{\mathrm{c}}} \qquad (5)$$

And thus:

$$\Delta G^{\ddagger} = -RT_{\mathrm{c}} \ln \frac{\pi\, \Delta\nu\, h}{\sqrt{2}\, k_B\, T_{\mathrm{c}}} \qquad (6)$$

Equation (6) can be rewritten in a linear combination of 3 distinct terms:

$$\Delta G^{\ddagger} = -RT_{\mathrm{c}} \ln \frac{\pi\, h}{\sqrt{2}\, k_B} - RT_{\mathrm{c}} \ln \Delta\nu + RT_{\mathrm{c}} \ln T_{\mathrm{c}} \qquad (7)$$

$\Delta G^{\ddagger}$ varies linearly with T_{c} if each term in equation 7 varies linearly with T_{c}.

$-RT \ln \frac{\pi\, h}{\sqrt{2}\, k_B}$ is proportional to T_{c}, as all other terms are constants.

$-RT_{\mathrm{c}} \ln \Delta\nu$ varies linearly with T_{c}, as long as $\Delta\nu$ (i.e. the difference in resonance frequencies of the diastereotopic nuclei in a slow exchange regime) does not undergo large changes. If $\Delta\nu$ had been constant in different solvent mixtures, $-RT_{\mathrm{c}} \ln \Delta\nu$ would have been strictly proportional to T_{c}. As $\Delta\nu$ varies with the solvent mixture, and thus with the measured coalescence temperatures, but changes are mild (see Figure S14a), $-RT_{\mathrm{c}} \ln \Delta\nu$ still varies linearly with T_{c}, but the intersection of the regression line with the y-axis is non-zero (see Figure S14b, red series).

$RT_\mathrm{c}\ln T_\mathrm{c}$ varies linearly with T_c over the relatively narrow temperature range of the VT NMR experiments, as shown in equation 8 and Figure S14b (blue series).

$$\frac{d(RT_\mathrm{c}\ln T_\mathrm{c})}{dT_\mathrm{c}} = R(\ln T_\mathrm{c} + 1) \qquad (8)$$

Therefore $\Delta G^\ddagger$ varies linearly with T_c within the relatively narrow range of coalescence temperatures T_c.

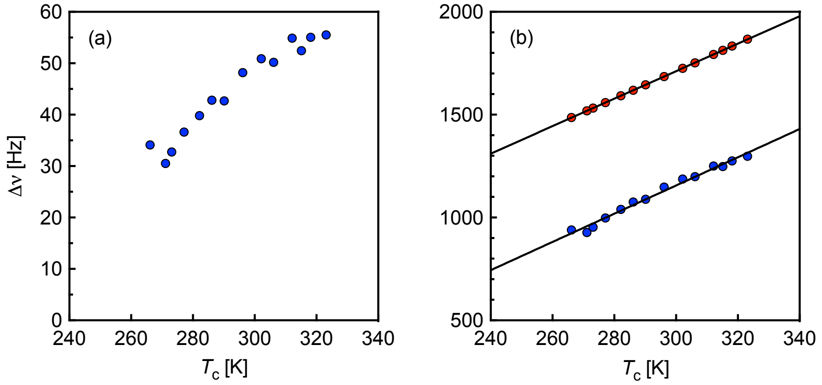


Figure S14. (a) Difference in resonance frequencies $\Delta\nu$ of the isopropyl diastereotopic nuclei of biphenyl **1** in a slow exchange regime as a function of coalescence temperature T_c. (b) $RT_\mathrm{c}\ln T_\mathrm{c}$ as a function of coalescence temperature T_c. (c) $RT_\mathrm{c}\ln\Delta\nu$ as a function of coalescence temperature T_c.

Activation parameters

Table S1. Torsional barriers of isomerization for biphenyl **1** in mixtures of DMSO-d^6 and PhNO$_2$-d^5, obtained by variable-temperature NMR spectroscopy and DFT calculations.

c_DMSO [a]	$c_{\mathrm{PhNO_2}}$ [a]	T_c [b]	$\Delta G^\ddagger_\mathrm{exp}(T_c)$ [c,d]	$\Delta G^\ddagger_\mathrm{exp}(25\ \mathrm{°C})$ [c,e]	$\Delta G^\ddagger_\mathrm{calc}(25\ \mathrm{°C})$ [c,f]	$\Delta\Delta G^\ddagger$ [c,f,g]
0.0	9.8	50	15.88	15.58	15.39	–0.19
0.1	9.7	45	15.62	15.41	15.35	–0.06
0.3	9.6	42	15.50	15.27	15.19	–0.08
0.4	9.5	39	15.32	15.15	15.06	–0.09
0.7	9.3	33	15.07	14.95	14.87	–0.08
0.9	9.1	29	14.86	14.79	14.73	–0.06
1.2	9.0	23	14.58	14.66	14.62	–0.04
1.6	8.7	17	14.34	14.46	14.45	–0.02
2.1	8.4	13	14.14	14.32	14.32	0.00
2.5	8.1	9	13.97	14.21	14.21	0.01
3.2	7.6	4	13.76	14.05	14.06	0.00
3.9	7.1	0	13.61	13.94	13.92	–0.01
4.5	6.7	–2	13.55	13.86	13.83	–0.03
5.4	6.0	–7	13.23	13.77	13.69	–0.08

[a] Concentrations in mol/L. [b] Coalescence temperature in °C. [c] in kcal/mol. [d] Free energy of torsion at coalescence temperature. [e] Free energy of torsion at 25 °C; see article for the calculation of the enthalpic and entropic corrections. [f] Calculated free energy of torsion at 25 °C (see section 7 for details). [g] Relative to the experimental torsional barrier.

5. Variable temperature NMR experiments

Variable temperature (VT) NMR experiments were carried out for solutions of biphenyls **1** and **2** in TCE-d^2, PhNO$_2$-d^5, 1.6 M DMSO-d^6 in PhNO$_2$-d^5 (biphenyl **1**) and pure DMSO-d^6 (biphenyl **2**). Temperature ranges allowed the observation of slow, intermediate and fast exchange regimes.

The DNMR module (ver 1.1.2) built-in Bruker TopSpin software package[6] was used to simulate 1D temperature-dependent NMR spectra of coupled half spin nuclei. Line shape analysis is based on the average density matrix theory.[7–9] Chemical shifts (δ), coupling constants (J) and rotational constants (k) were refined altogether. Temperature-dependence of the chemical shifts as well as natural width was taken into account by including the residual HDO signal in the fitting. Constants k were calculated for each individual spectrum.

Relevant portions of the VT NMR spectra of biphenyl **1** and their fitting are presented in the manuscript; the corresponding experiments with biphenyl **2** are shown below (see Figure S15).

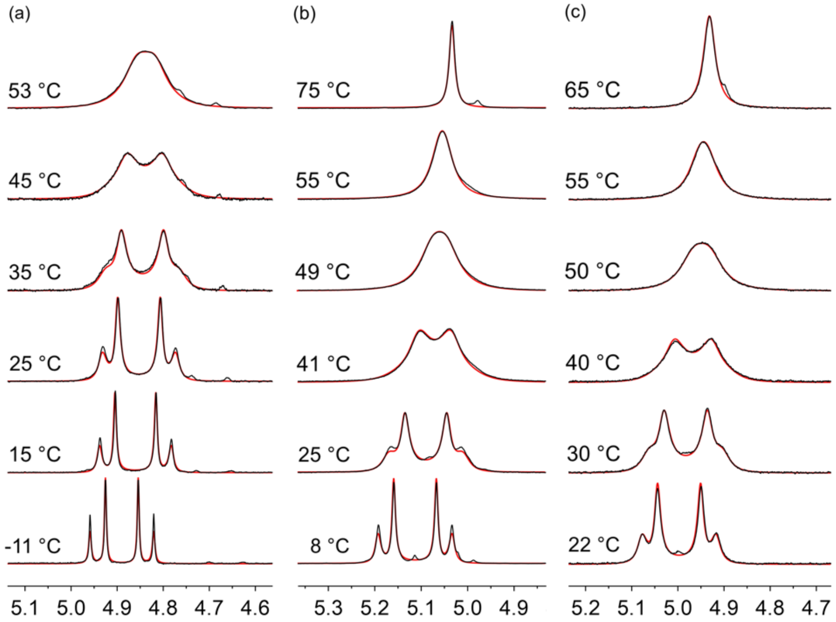


Figure S15. ^{1}H NMR signals of the α-methylene signal in biphenyl **2** as a function of temperature in (a) TCE-d^2, (b) PhNO$_2$-d^5 and (c) DMSO-d^6. Line shape fitting in red.

6. Chemical shifts as a function of temperature

Chemical shift gradients were obtained by recording ^{1}H-NMR spectra of compounds **1** and **3** in TCE-d^2, PhNO$_2$-d^5 and DMSO-d^6 within a temperature range of 15 ºC – 65 ºC. Chemical shifts of protons NHα and NHβ were measured by using tetramethylsilane (TMS) as external standard and plotted against temperature. The slopes of the regression lines afford the chemical shift gradients.

Table S2. NHα and NHβ chemical shifts and temperature gradients.

			δ [a]	δ_{rel} [b]	$\Delta\delta/\Delta T$ [c]	$(\Delta\delta/\Delta T)_{rel}$ [d]
NHα	TCE-d^2	**1**	9.87	+1.12	–6.7 ± 0.1	–2.8 ± 0.1
		3	8.75		–3.9 ± 0.1	
	PhNO$_2$-d^5	**1**	10.84	+1.79	–11.6 ± 0.1	–4.6 ± 0.3
		3	9.05		–7.0 ± 0.3	
	DMSO-d^6	**1**	10.12	–0.16	–4.6 ± 0.1	–0.2 ± 0.1
		3	10.27		–4.9 ± 0.1	
NHβ	TCE-d^2	**1**	7.91	–0.46	–5.1 ± 0.3	–1.2 ± 0.3
		3	8.37		–3.9 ± 0.1	
	PhNO2-d^5	**1**	8.45	–0.25	–7.1 ± 0.3	–0.6 ± 0.4
		3	8.70		–6.5 ± 0.3	
	DMSO-d^6	**1**	9.76	–0.04	–5.0 ± 0.1	0.0 ± 0.1
		3	9.81		–5.0 ± 0.1	

[a] NH chemical shift in biphenyl **1** at 25 ºC [ppm]. [b] NH chemical shift in biphenyl **1** relative to reference scaffold **3** [ppm]. [c] NH chemical shift gradient in biphenyl **1** [ppb/K]. [d] NH chemical shift gradient in biphenyl **1** relative to reference scaffold **3** [ppb/K].

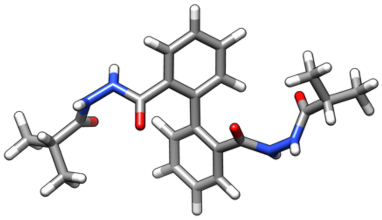
7. Computational details

All density functional theory (DFT) calculations were carried out with Gaussian 16 Rev. C.01[10] and the Turbomole suite of programs (version 7.2.1)[11–15] on the OSC Owens and Pitzer Clusters of the Ohio Supercomputer Center in Columbus, OH (23,392-core Dell Intel Xeon E5-2680 v4 and 10,240-core Dell Intel Gold 6148 machines, respectively). Solvation energies were calculated with COSMO*therm* X18.[16] The program Goodvibes 3.0[17] was used to compute enthalpic and entropic contributions to the torsional barriers.

Solvation energies were calculated using a close variant of the procedure described by Klamt and coworkers.[18] All ground and transition states were optimized (a) in the gas phase, at the BP86/def-TZVP level of theory, and (b) in solution at the same level of theory using the CPCM continuum solvation model[19,20] with tabulated dielectric constants and refractive indexes.[21,22] Energies were then refined in single-point calculations at the BP86/def2-TZVPD level. The COSMO solvation model[23] was applied to structures optimized in solution. The output from these single-point calculations in the gas phase and in solution was then treated with COSMO*therm* X18[16] and the BP_TZVPD_FINE_18 parametrization model to extract free Gibbs energies of solvation. Optimizing structures in solution with the CPCM solvation model instead of the COSMO model is a minor variation of the procedure recommended by Klamt and coworkers,[18] as convergence failed when COSMO was used during the optimization of transition states. We verified the validity of our method by comparing the solvation free energies of ground state conformers obtained with both CPCM and COSMO methods; differences were insignificant (< 0.2 kcal/mol in all cases).

Hunter's parameters α and β of N'-acylcarbohydrazide groups were calculated by truncating the B3LYP-optimized structure of biphenyl **1a** at the C_{aryl}-C_{aryl} bond, and by re-optimizing the *N'*-isobutyrylbenzohydrazide fragment with the semi-empirical method AM1, while freezing the NHα and Cγ=O atoms involved in the hydrogen bonding interactions. The maximum and minimum electrostatic potentials generated by a positive point-charge were obtained on the 0.002 au isodensity surface of the molecule. AM1 calculations were carried out with the Spartan 18 package.[24]

Coordinates of optimized structures



1a

H	-0.80760	-4.56228	-0.87620
C	-0.61674	-3.49797	-0.82567
C	-0.12428	-0.73463	-0.65375
C	0.54243	-3.02822	-0.22506
C	-1.52838	-2.59122	-1.34838
C	-1.27854	-1.22892	-1.26424
C	0.79947	-1.65787	-0.13109
H	1.24245	-3.72929	0.21091
H	-2.43894	-2.93708	-1.82034
H	-2.00065	-0.53709	-1.67788
C	0.12428	0.73464	-0.65375
C	0.61674	3.49797	-0.82565
C	1.27854	1.22892	-1.26423
C	-0.79947	1.65787	-0.13108
C	-0.54243	3.02823	-0.22504
C	1.52837	2.59123	-1.34837
H	2.00064	0.53710	-1.67788
H	-1.24245	3.72929	0.21093
H	2.43893	2.93709	-1.82032
H	0.80760	4.56229	-0.87617
C	2.03515	-1.20171	0.58463
O	2.06649	-0.33157	1.42575
N	3.17260	-1.92958	0.24785
N	4.40384	-1.48101	0.68519
C	-2.03515	1.20171	0.58464
O	-2.06649	0.33156	1.42576
N	-3.17260	1.92958	0.24787
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C	5.01883	-0.42221	0.04961
C	-5.01883	0.42221	0.04962
O	-4.64180	0.01846	-1.03160
C	-6.21968	-0.15315	0.78952
H	-6.41824	0.46479	1.67141
O	4.64180	-0.01845	-1.03161
C	6.21968	0.15314	0.78952
H	6.41824	-0.46480	1.67140
C	5.87883	1.57577	1.25608
H	5.67531	2.21518	0.39634
H	6.71812	1.99914	1.81082
H	4.99923	1.58593	1.90147
C	7.45587	0.13123	-0.11435
H	7.26814	0.70283	-1.02357
H	7.72318	-0.88699	-0.40331
H	8.30961	0.57227	0.40329
C	-7.45587	-0.13123	-0.11434
H	-8.30961	-0.57227	0.40329
H	-7.26814	-0.70283	-1.02356
H	-7.72318	0.88699	-0.40329
C	-5.87883	-1.57578	1.25608
H	-4.99923	-1.58594	1.90146
H	-5.67531	-2.21518	0.39633
H	-6.71812	-1.99915	1.81081
H	3.19388	-2.40188	-0.64259
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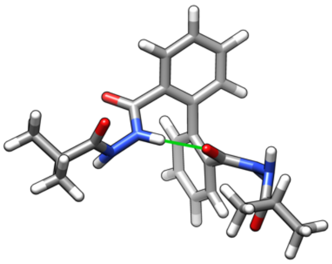

1b

N	3.78769	-0.03794	-0.72345
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O	-3.76396	-0.89117	-0.06774
O	-2.82213	2.41581	-1.25489
O	4.20556	1.21357	1.12045
C	-0.16445	-2.27759	0.87986
C	0.98811	-1.53325	1.17649
C	-0.65365	-2.48221	-0.51852
C	-0.82503	-2.91775	1.92859
H	-1.71105	-3.50009	1.71026
C	1.45928	-1.45229	2.48858
H	2.33095	-0.84587	2.70430
C	-1.79436	-1.84719	-1.02840
C	1.65798	-0.70346	0.12642
C	-0.36066	-2.82580	3.23571
H	-0.89541	-3.32957	4.03096
C	-2.56837	-0.79698	-0.27827
C	-3.01689	2.33070	-0.06278
N	3.00102	-0.92802	-0.02089
C	-2.26392	-2.17771	-2.29984
H	-3.15595	-1.68705	-2.66619
C	0.00372	-3.42117	-1.31843
H	0.87375	-3.93114	-0.92325
C	4.25480	1.09908	-0.08535
C	0.78589	-2.09543	3.51863
H	1.14984	-2.01620	4.53476
N	-1.81727	0.26808	0.12724
C	-3.89463	3.30811	0.71343
H	-3.82185	3.07912	1.78184
C	-0.45451	-3.72662	-2.59260
H	0.07214	-4.45761	-3.19316
C	-1.59684	-3.10633	-3.08402
H	-1.96706	-3.34497	-4.07278
C	4.85811	2.14502	-1.01216
H	4.88977	1.73804	-2.02811
C	-3.40818	4.74235	0.48545
H	-2.38713	4.88044	0.84624
H	-4.05314	5.44914	1.01114
H	-3.42611	4.98047	-0.57841
C	-5.35268	3.12404	0.27043
H	-5.45090	3.33626	-0.79486
H	-6.00293	3.80647	0.82123
H	-5.69801	2.10374	0.44502
C	3.95535	3.38766	-1.00981
H	2.94216	3.14967	-1.33753
H	4.36212	4.14583	-1.68106
H	3.89769	3.80978	-0.00591
C	6.28652	2.47779	-0.57044
H	6.28819	2.84609	0.45563
H	6.70979	3.24845	-1.21681
H	6.93546	1.60126	-0.61776
H	-0.85021	0.37631	-0.16920
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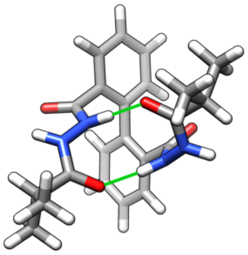

1c

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C	-2.20188	-1.36332	-0.38174
C	-2.45159	-0.57618	-2.66242
C	-4.36618	-0.66416	-1.21784
C	-3.56999	-1.15719	-0.19420
C	-1.64380	-1.05360	-1.63039
H	-2.00594	-0.36072	-3.62526
H	-5.42368	-0.50728	-1.04682
H	-4.00528	-1.38325	0.76982
C	-1.39215	-1.99942	0.70499
C	0.11049	-3.31036	2.68195
C	-1.18445	-3.37900	0.65673
C	-0.82065	-1.27633	1.76310
C	-0.06697	-1.93438	2.73422
C	-0.44807	-4.03315	1.63692
H	-1.60556	-3.94160	-0.16658
H	0.37618	-1.36182	3.53898
H	-0.30955	-5.10533	1.57855
H	0.68649	-3.81111	3.44957
C	-0.18171	-1.25402	-1.90873
O	0.25384	-2.13187	-2.64052
N	0.63692	-0.36309	-1.28399
H	0.30925	0.55502	-0.96502
N	1.99347	-0.46402	-1.54733
H	2.19482	-1.00108	-2.38013
C	2.91459	-0.31630	-0.56216
O	2.62973	0.07489	0.56459
C	4.34921	-0.61627	-0.97677
H	4.34981	-0.95116	-2.01860
C	-1.01288	0.20877	1.86547
O	-2.09573	0.74096	2.00845
N	0.16759	0.91748	1.82736
H	1.02325	0.50205	1.45007
N	0.10164	2.29473	1.74115
H	-0.11184	2.78089	2.59713
C	-0.11842	2.91302	0.54551
O	-0.07762	2.31412	-0.52001
C	-0.38679	4.40806	0.62813
H	-0.28123	4.72480	1.67074
C	-1.82895	4.68050	0.17714
H	-2.54938	4.13986	0.79273
H	-1.96605	4.36778	-0.85846
H	-2.04706	5.74747	0.24875
C	0.63125	5.17421	-0.22268
H	0.42702	6.24535	-0.17821
H	0.57203	4.85339	-1.26293
H	1.65179	5.00806	0.12717
C	4.90976	-1.74062	-0.09716
H	4.32653	-2.65756	-0.19868
H	4.89622	-1.44313	0.95173
H	5.94007	-1.96075	-0.38187
C	5.19542	0.65858	-0.87374
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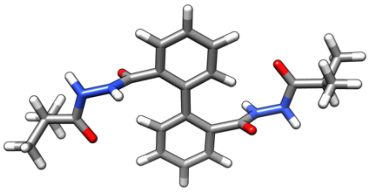

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C	-0.07523	-0.74761	0.00146
C	0.77712	-3.04289	0.01158
C	-1.56889	-2.69554	0.14731
C	-1.34901	-1.32847	0.08765
C	1.00515	-1.66727	-0.08055
H	1.62721	-3.71138	-0.04908
H	-2.58767	-3.05561	0.20069
H	-2.23425	-0.72300	0.09795
C	0.07523	0.74761	-0.00146
C	0.49767	3.57104	-0.13303
C	1.34901	1.32847	-0.08765
C	-1.00515	1.66727	0.08055
C	-0.77712	3.04289	-0.01158
C	1.56889	2.69554	-0.14731
H	2.23425	0.72300	-0.09795
H	-1.62721	3.71138	0.04908
H	2.58767	3.05561	-0.20069
H	0.64450	4.64176	-0.19123
C	2.44853	-1.37647	-0.41525
O	2.84797	-1.17308	-1.54171
N	3.31090	-1.53379	0.64951
H	2.95777	-1.54384	1.59322
N	4.66891	-1.35332	0.49351
H	5.14424	-2.10966	0.02548
C	5.20908	-0.08379	0.40007
O	4.58002	0.90871	0.69635
C	6.65885	-0.05036	-0.06845
H	7.02881	-1.07797	-0.14743
C	-2.44853	1.37647	0.41525
O	-2.84797	1.17308	1.54171
N	-3.31090	1.53379	-0.64951
H	-2.95777	1.54384	-1.59322
N	-4.66891	1.35332	-0.49351
H	-5.14424	2.10966	-0.02548
C	-5.20908	0.08379	-0.40007
O	-4.58002	-0.90871	-0.69635
C	-6.65885	0.05036	0.06845
H	-7.02881	1.07797	0.14743
C	-6.71454	-0.59806	1.45940
H	-6.10088	-0.05550	2.18016
H	-6.35056	-1.62496	1.41077
H	-7.74289	-0.61282	1.82483
C	-7.52125	-0.70507	-0.94698
H	-8.55416	-0.75809	-0.59846
H	-7.14669	-1.72042	-1.07845
H	-7.51655	-0.21338	-1.92158
C	7.52125	0.70507	0.94698
H	7.51655	0.21338	1.92158
H	7.14669	1.72042	1.07845
H	8.55416	0.75809	0.59846
C	6.71454	0.59806	-1.45940
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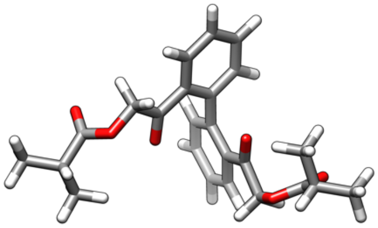

2a

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C	0.92651	1.34829	-2.89378
C	-0.69502	3.10481	-2.79477
C	-0.73696	2.97336	-1.41356
C	0.89512	1.19876	-1.50189
H	1.57979	0.72581	-3.48861
H	-1.31500	3.84620	-3.28291
H	-1.39302	3.61071	-0.83468
C	-0.03709	2.02480	0.74818
C	-0.14078	2.28396	3.54431
C	0.73777	2.97157	1.41632
C	-0.89502	1.19753	1.50281
C	-0.92633	1.34560	2.89485
C	0.69588	3.10159	2.79768
H	1.39409	3.60927	0.83812
H	-1.57986	0.72274	3.48901
H	1.31616	3.84222	3.28660
H	-0.18521	2.37749	4.62146
C	1.74337	0.16268	-0.84625
O	1.79851	0.01748	0.35402
C	2.56504	-0.76397	-1.75404
O	3.26867	-1.73544	-0.99457
C	-1.74362	0.16243	0.84606
O	-1.79948	0.01911	-0.35440
C	-2.56463	-0.76571	1.75292
O	-3.26838	-1.73626	0.99238
H	1.90117	-1.32258	-2.41400
H	3.26222	-0.17713	-2.35351
C	4.45433	-1.34439	-0.46123
H	-1.90031	-1.32507	2.41178
H	-3.26170	-0.17989	2.35353
C	-4.45447	-1.34481	0.46029
O	-4.95954	-0.27758	0.69385
C	-5.02070	-2.41240	-0.45426
H	-4.64189	-3.37355	-0.09917
O	4.95916	-0.27664	-0.69289
C	5.02042	-2.41318	0.45202
H	4.64204	-3.37391	0.09536
C	4.47825	-2.18210	1.87380
H	4.83037	-1.22684	2.26716
H	4.82940	-2.97567	2.53582
H	3.38865	-2.17322	1.88672
C	6.54799	-2.41133	0.41682
H	6.93990	-1.44440	0.73311
H	6.92604	-2.61272	-0.58688
H	6.93784	-3.17941	1.08715
C	-6.54825	-2.41102	-0.41837
H	-6.93820	-3.17823	-1.08963
H	-6.94056	-1.44374	-0.73307
H	-6.92579	-2.61396	0.58522
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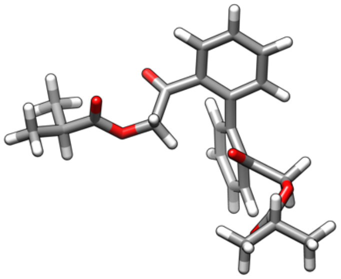

2b

C	-5.27787	2.11447	1.01415
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H	-3.89161	3.78676	1.14043
H	-5.53199	4.14786	1.69247
H	-5.18285	4.00990	-0.03783
C	-6.77436	1.84382	0.77679
H	-7.07908	2.19661	-0.21071
H	-7.36887	2.37387	1.52248
H	-7.00535	0.78074	0.85144
C	-4.46396	1.33414	0.00217
O	-4.01975	1.76101	-1.03248
O	-4.32060	0.03781	0.38081
C	-3.54553	-0.77286	-0.48873
H	-3.85255	-0.63787	-1.52490
H	-3.74966	-1.80666	-0.20073
C	-2.04573	-0.52988	-0.32552
O	-1.61043	0.10243	0.60584
C	-1.14832	-1.13584	-1.36296
C	0.01742	-1.83820	-0.99843
C	0.88635	-2.25383	-2.00880
H	1.77532	-2.80968	-1.73948
C	0.62251	-1.98167	-3.34605
H	1.31730	-2.31211	-4.10754
C	-0.53021	-1.29513	-3.70052
H	-0.73974	-1.07269	-4.73866
C	-1.41341	-0.88334	-2.71145
H	-2.29014	-0.31171	-2.98636
C	0.31907	-2.22539	0.40975
C	1.50034	-1.83459	1.05900
C	1.79624	-2.33628	2.32819
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C	0.92134	-3.19606	2.97434
H	1.15804	-3.56729	3.96304
C	-0.25439	-3.58023	2.34115
H	-0.94093	-4.25981	2.82989
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C	1.98501	0.53855	0.18514
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H	1.67144	0.98214	1.13333
O	2.97408	1.33795	-0.44837
C	3.87702	1.94749	0.36225
O	3.80984	1.92042	1.56332
C	4.95978	2.63245	-0.44818
H	4.51826	2.90380	-1.40986
C	5.46549	3.88676	0.26282
H	4.66483	4.61319	0.41122
H	6.24984	4.36137	-0.32958
H	5.87445	3.63664	1.24199
C	6.09268	1.62353	-0.70742
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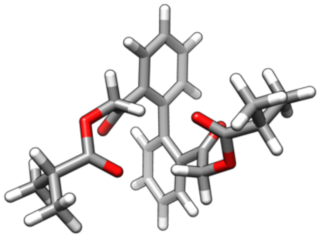
H	6.85868	2.08170	-1.33570
H	5.72204	0.72886	-1.20729



2c

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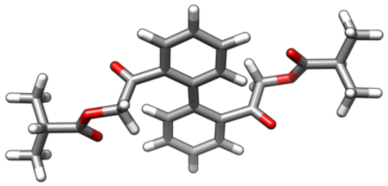
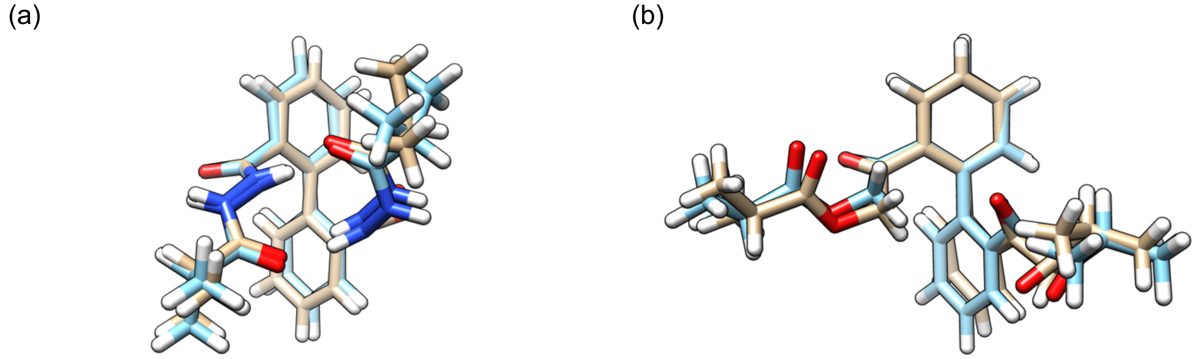
C	2.28279	1.91209	1.66254
C	2.86067	0.56037	3.55541
C	1.60550	-0.03103	3.50634
C	1.00696	1.34173	1.61843
H	2.55038	2.68796	0.95790
H	3.57193	0.25070	4.31060
H	1.35173	-0.81381	4.20933
C	-0.66522	-0.34080	2.54779
C	-3.20372	-1.53475	2.62840
C	-1.60550	0.03103	3.50634
C	-1.00696	-1.34173	1.61843
C	-2.28279	-1.91209	1.66254
C	-2.86067	-0.56037	3.55541
H	-1.35173	0.81381	4.20933
H	-2.55038	-2.68796	0.95790
H	-3.57193	-0.25070	4.31060
H	-4.18028	-2.00050	2.65627
C	-0.00081	1.86842	0.64087
O	-1.14687	2.08704	0.95767
C	0.47298	2.10160	-0.79029
O	-0.50444	2.80047	-1.55612
C	0.00081	-1.86842	0.64087
O	1.14687	-2.08704	0.95767
C	-0.47298	-2.10160	-0.79029
O	0.50444	-2.80047	-1.55612
H	1.36599	2.72386	-0.81250

H	0.72048	1.13705	-1.24156
C	-1.53119	2.07839	-2.05825
H	-1.36599	-2.72386	-0.81250
H	-0.72048	-1.13705	-1.24156
C	1.53119	-2.07839	-2.05825
O	1.60550	-0.87818	-1.97592
C	2.56189	-2.97757	-2.71284
H	2.03569	-3.86994	-3.05926
O	-1.60550	0.87818	-1.97592
C	-2.56189	2.97757	-2.71284
H	-2.03569	3.86994	-3.05926
C	-3.58705	3.40745	-1.64856
H	-4.12916	2.54083	-1.26629
H	-4.30930	4.09693	-2.08937
H	-3.10311	3.90201	-0.80672
C	-3.22854	2.27768	-3.89619
H	-3.73023	1.36548	-3.57234
H	-2.50075	2.00495	-4.66218
H	-3.96967	2.93745	-4.35087
C	3.22854	-2.27768	-3.89619
H	3.96967	-2.93745	-4.35087
H	3.73023	-1.36548	-3.57234
H	2.50075	-2.00495	-4.66218
C	3.58705	-3.40745	-1.64856
H	3.10311	-3.90201	-0.80672
H	4.12916	-2.54083	-1.26629
H	4.30930	-4.09693	-2.08937



2^{TS}

H	0.54144	-4.64674	-0.15984
C	0.41157	-3.57237	-0.15402
C	0.04863	-0.74514	-0.06873
C	-0.83725	-3.01940	0.07863
C	1.47414	-2.71955	-0.39969
C	1.28139	-1.34792	-0.36081
C	-1.04393	-1.63702	0.09850
H	-1.68801	-3.66963	0.24221
H	2.46378	-3.10111	-0.61179
H	2.14802	-0.75216	-0.58076
C	-0.04863	0.74514	0.06873
C	-0.41157	3.57237	0.15401
C	-1.28139	1.34792	0.36081
C	1.04393	1.63702	-0.09850
C	0.83725	3.01940	-0.07863
C	-1.47414	2.71955	0.39969
H	-2.14802	0.75216	0.58076
H	1.68801	3.66964	-0.24221
H	-2.46378	3.10111	0.61179
H	-0.54144	4.64674	0.15984
C	-2.51672	-1.32265	0.22286
O	-3.13772	-1.48813	1.24301
C	-3.22065	-0.99080	-1.09644
O	-4.63553	-0.96257	-0.96171
C	2.51672	1.32266	-0.22286
O	3.13772	1.48814	-1.24301
C	3.22065	0.99081	1.09644
O	4.63553	0.96257	0.96170
H	-2.83924	-0.05128	-1.49977
H	-3.00323	-1.78699	-1.80954
C	-5.18448	0.15608	-0.42861
H	3.00323	1.78699	1.80954
H	2.83924	0.05129	1.49977
C	5.18448	-0.15608	0.42861
O	4.54229	-1.14043	0.16419
C	6.67282	0.01693	0.20469
H	7.02712	0.73827	0.94455
O	-4.54229	1.14043	-0.16419
C	-6.67282	-0.01693	-0.20469
H	-7.02712	-0.73823	-0.94458
C	-7.41148	1.30938	-0.37796
H	-7.04561	2.05112	0.33234
H	-8.47982	1.16552	-0.20803
H	-7.27879	1.71413	-1.38260
C	-6.89233	-0.61828	1.19534
H	-6.54309	0.06953	1.96734
H	-6.35748	-1.56041	1.31307
H	-7.95647	-0.80022	1.35478
C	7.41149	-1.30937	0.37800
H	8.47983	-1.16551	0.20807
H	7.04562	-2.05113	-0.33227
H	7.27880	-1.71408	1.38266
C	6.89233	0.61823	-1.19537
H	6.35747	1.56036	-1.31313
H	6.54309	-0.06960	-1.96735
H	7.95646	0.80017	-1.35481



(a) (b)

Figure S16. Superimposition of the X-ray crystal structure of (a) biphenyl **1c** and (b) biphenyl **2b** (in pale brown) with the corresponding B3LYP-optimized structures (in pale blue).

8. X-ray crystallographic analysis

Biphenyl 1. A specimen of $C_{24}H_{28}Cl_4N_4O_4$, approximate dimensions 0.090 mm x 0.090 mm x 0.110 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. The integration of the data using a monoclinic unit cell yielded a total of 15222 reflections to a maximum θ angle of 28.81° (0.74 Å resolution), of which 5967 were independent (average redundancy 2.551, completeness = 80.9%, R_{int} = 3.62%, R_{sig} = 3.28%) and 5011 (83.98%) were greater than $2\sigma(F^2)$. The final cell constants of a = 9.8228(4) Å, b = 15.9940(8) Å, c = 18.5143(11) Å, β = 104.008(2)°, volume = 2822.2(2) Å^3, are based upon the refinement of the XYZ-centroids of reflections above 20 σ(I). The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9500 and 0.9680. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 1 21/c 1, with Z = 4 for the formula unit, $C_{24}H_{28}Cl_4N_4O_4$. Residual peaks pertaining to 1,1,2,2-tetrachloroethane could not be modeled. The final anisotropic full-matrix least-squares refinement on F^2 with 329 variables converged at R1 = 5.29%, for the observed data and wR2 = 16.24% for all data. The goodness-of-fit was 1.000. The largest peak in the final difference electron density synthesis was 1.352 e^-

/Å^3 and the largest hole was -0.709 e$^-$/Å^3 with an RMS deviation of 0.064 e$^-$/Å^3. On the basis of the final model, the calculated density was 1.361 g/cm^3 and F(000), 1200 e$^-$.

Sample and crystal data

Identification code	e4622a_a	
Chemical formula	$C_{24}H_{28}Cl_4N_4O_4$ C22 H26 N4 O4, C2 H2 Cl4	
Formula weight	578.30 g/mol	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal size	0.090 x 0.090 x 0.110 mm	
Crystal system	monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 9.8228(4) Å	α = 90°
	b = 15.9940(8) Å	β = 104.008(2)°
	c = 18.5143(11) Å	γ = 90°
Volume	2822.2(2) Å^3	
Z	4	
Density (calculated)	1.361 g/cm^3	
Absorption coefficient	0.456 mm^{-1}	
F(000)	1200	

Data collection and structure refinement

Theta range for data collection	2.27 to 28.81°	
Index ranges	-11<=h<=9, -20<=k<=21, -23<=l<=18	
Reflections collected	15222	
Independent reflections	5967 [R(int) = 0.0362]	
Max. and min. transmission	0.9680 and 0.9500	
Structure solution technique	direct methods	
Structure solution program	SHELXS-97 (Sheldrick 2008)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2014 (Sheldrick 2014)	
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	5967 / 0 / 329	
Goodness-of-fit on F^2	1.000	
Final R indices	5011 data; I>2σ(I)	R1 = 0.0529, wR2 = 0.1511
	all data	R1 = 0.0624, wR2 = 0.1624
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0898P)^2+2.8186P]$ where $P=(F_o^2+2F_c^2)/3$	
Largest diff. peak and hole	1.352 and -0.709 eÅ^{-3}	
R.M.S. deviation from mean	0.064 eÅ^{-3}	

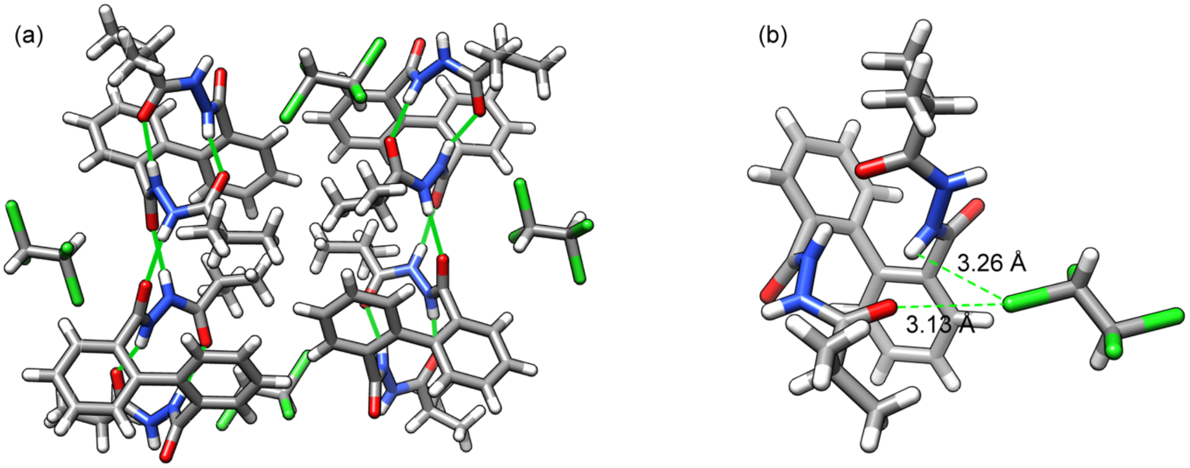


Figure S17. (a) Unit cell of biphenyl **1** crystallized in TCE-d^2; intra- and intermolecular hydrogen bonding interactions are highlighted in green. (b) Short contacts between biphenyl **1** and TCE-d^2 in the unit cell.

Biphenyl 2. A specimen of $C_{48}H_{52}O_{12}$, approximate dimensions 0.080 mm x 0.090 mm x 0.120 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured (λ = 0.71073 Å). The integration of the data using a triclinic unit cell yielded a total of 30510 reflections to a maximum θ angle of 28.72° (0.74 Å resolution), of which 10379 were independent (average redundancy 2.940, completeness = 93.1%, R_{int} =4.34%, R_{sig} = 4.22%) and 7939 (76.49%) were greater than 2σ(F^2). The final cell constants of a = 9.6496(5) Å, b = 12.0424(8) Å, c = 19.8345(13) Å, α = 81.278(2)°, β = 82.463(2)°, γ = 70.074(2)°, volume = 2134.0(2) Å^3, are based upon the refinement of the XYZ-centroids of reflections above 20 σ(I). The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9810 and 0.9990. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P -1, with Z = 2 for the formula unit, $C_{48}H_{52}O_{12}$. The final anisotropic full-matrix least-squares refinement on F^2 with 549variables converged at R1 = 4.57%, for the observed data and wR2 = 13.36% for all data. The goodness-of-fit was 1.007. The largest peak in the final difference electron density synthesis was 0.265 e$^-$/Å^3 and the largest hole was-0.219 e$^-$/Å^3 with an RMS deviation of 0.043 e$^-$/Å^3. On the basis of the final model, the calculated density was 1.278 g/cm^3 and F(000), 872 e$^-$.

Sample and crystal data

Identification code	e4700a_a	
Chemical formula	$C_{48}H_{52}O_{12}$	
Formula weight	820.89 g/mol	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal size	0.080 x 0.090 x 0.120 mm	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 9.6496(5) Å	α = 81.278(2)°
	b = 12.0424(8) Å	β = 82.463(2)°
	c = 19.8345(13) Å	γ = 70.074(2)°
Volume	2134.0(2) Å^3	

Z	2
Density (calculated)	1.278 g/cm^3
Absorption coefficient	0.091 mm^{-1}
F(000)	872

Data collection and structure refinement

Theta range for data collection	1.81 to 28.72°	
Index ranges	-9<=h<=12, -16<=k<=16, -26<=l<=26	
Reflections collected	30510	
Independent reflections	10379 [R(int) = 0.0434]	
Max. and min. transmission	0.9990 and 0.9810	
Structure solution technique	direct methods	
Structure solution program	SHELXS-97 (Sheldrick 2008)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2014 (Sheldrick 2014)	
Function minimized	Σ w(F$_o^2$ - F$_c^2$)^2	
Data / restraints / parameters	10379 / 0 / 549	
Goodness-of-fit on F^2	1.007	
Final R indices	7939 data; I>2σ(I)	R1 = 0.0457, wR2 = 0.1208
	all data	R1 = 0.0631, wR2 = 0.1336
Weighting scheme	w=1/[σ^2(F$_o^2$)+(0.0653P)^2+0.5311P] where P=(F$_o^2$+2F$_c^2$)/3	
Largest diff. peak and hole	0.265 and -0.219 eÅ^{-3}	
R.M.S. deviation from mean	0.043 eÅ^{-3}	

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