Supporting information for

7-Azaindole breaks carboxylic acid dimers and simplifies VCD spectra analyses of natural products

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1. Experimental and computational details

IR and VCD spectroscopy.

The IR and VCD spectra were recorded on a Bruker Vertex FT-IR spectrometer equipped with a PMA 50 module for VCD measurements. Samples were held in a transmission cell with BaF_2 windows and 100 µm path length. Concentrations are given in the main text. Spectra were recorded at room temperature with 4 cm^{-1} spectral resolution by accumulating 32 scans for the IR and ~32000 scans (4 hours accumulation time) for VCD. Baseline correction of the VCD spectra was done by subtraction of the spectra of the solvent recorded under identical conditions.

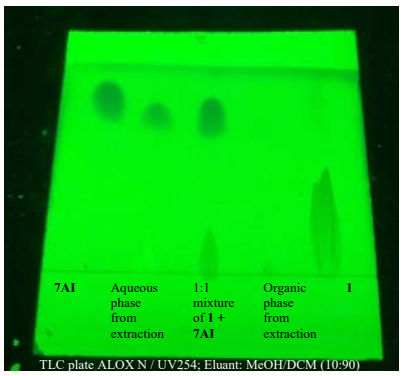
Computational details.

All geometry optimizations and frequency calculations were carried out at B3LYP/6-311++G(2d,p) level of theory using the Gaussian 09 Rev. E software package.[1] Solvent effects were taken into account implicitly by using the integral equation formalism of the polarizable continuum model (IEFPCM)[2, 3] of chloroform. Relative energy differences and Boltzmann populations generally refer to the zero-point corrected energies of the conformers (ΔE_{ZPC}) as we regularly find ΔE_{ZPC}-derived populations to better explain the experimental signatures than Gibbs Free energies (for a detailed discussion see Refs. [4-7], for instance). Vibrational line broadening was simulated by assigning a Lorentzian band shape with half-width at half-height of 6 cm^{-1} (8 cm^{-1} for **4** and **4**··**7AI**) to the calculated dipole and rotational strength. The calculated frequencies were scaled by 0.98 to account for anharmonic effects not captured by the harmonic approximation employed in the frequency calculations. Figures were prepared using CYLview.[8]

Recovery of the carboxylic acid

In order to take full advantage of the proposed methodology for AC determinations of valuable samples, the carboxylic acid needs to be recovered, i.e., separated from **7AI**. For **1**··**7AI**, we succeeded by using simple extraction with HCl (1:1 with 7AI in DCM) followed by another one or two washing steps. The photo below shows a TLC plate which demonstrates that the heterodimer of **1** and **7AI** does not persist on silica and that the two components are easily separable by chromatography. However, note that we did not attempt a quantitative recovery of the carboxylic acids used in this study.

A generally applicable route cannot be given as it depends strongly on the structure of the acid (hydrophilicity, hydrophobicity, …). The TLC suggests, however, that a separation by chromatographic means is generally feasible and that, for instance, HPLC protocols from the initial natural products separation could also be invoked for the purification of the VCD sample.



2. Additional spectra

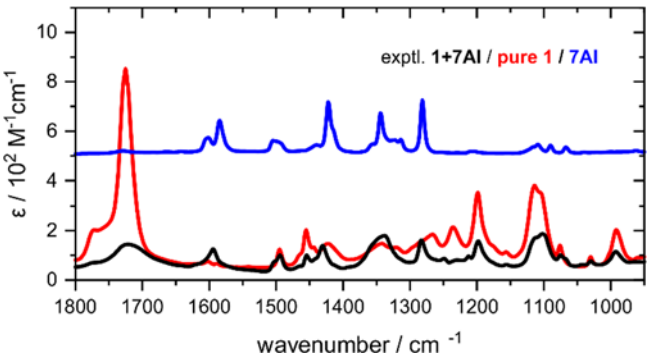


Figure S1. IR spectrum of **7AI** compared to the IR spectra of **1** and **1** + 1eq **7AI**.

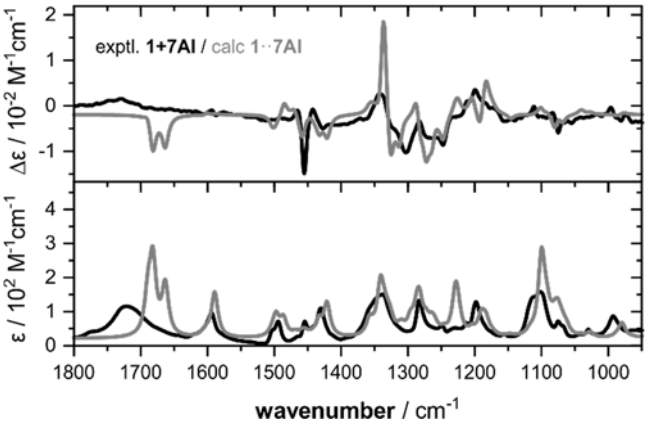


Figure S2. Overlap of the experimental and computed spectra of **1** + 1eq **7AI**.

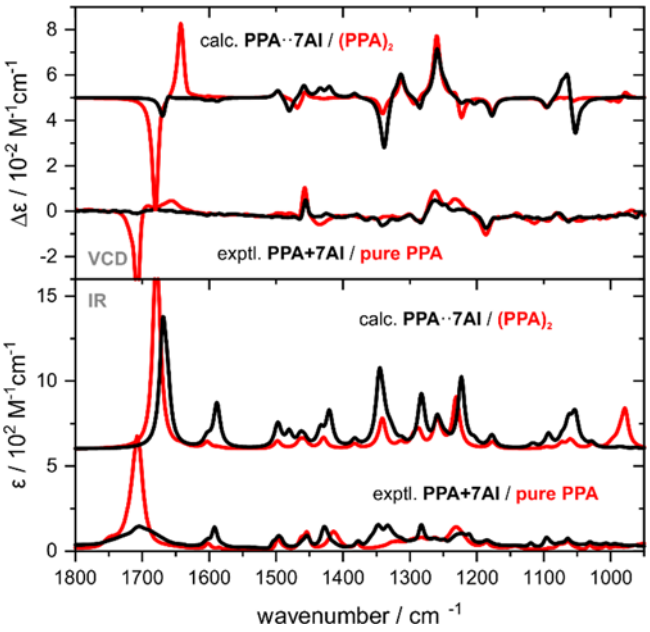


Figure S3. Comparison of the experimental IR and VCD spectra of (R)-2-phenyl propionic acid (PPA) and **PPA** + 1eq **7AI** with the computed spectra of **(PPA)$_2$** (*J. Phys. Chem. B* 2018, **122**, 8056−8064) and **PPA··7AI** (Tab. S6/S7).

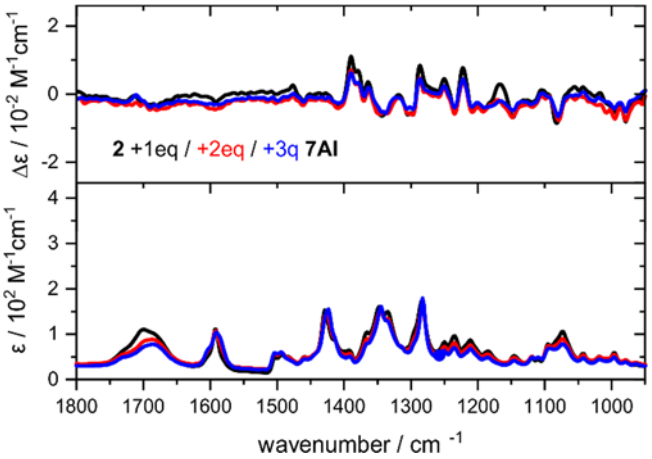


Figure S4. IR and VCD spectra of **2** with different amounts of **7AI**.

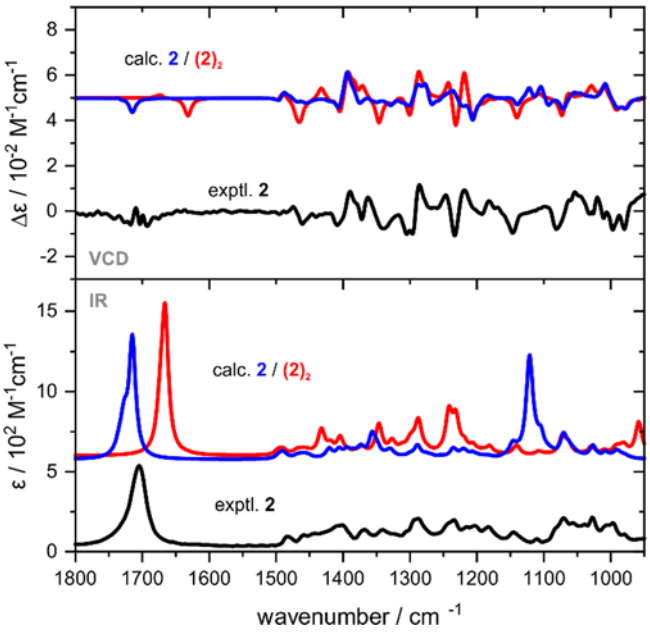


Figure S5. IR and VCD spectra of **2** compared to the computed spectra of monomeric and dimeric **2**.

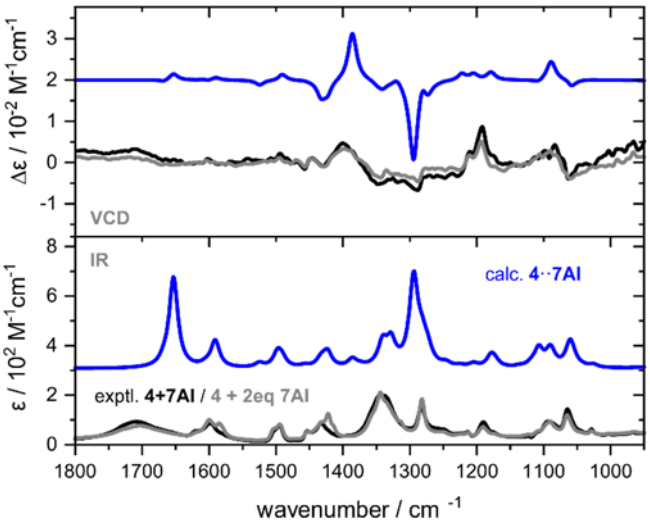
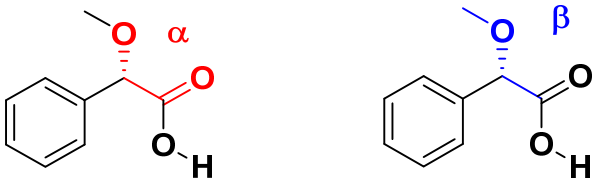


Figure S6. IR and VCD spectra of **4** with 1 and 2 eq of **7AI** compared to the computed spectra of **4··7AI** (cf. Tab. S11). Unlike the other computed spectra, the spectra of **4··7AI** were simulated with 8 cm^{-1} HWHH and the intensities were scaled by 0.5 for better comparison.

3. Computational data



Scheme S1. Torsional angle definitions of *(R)*-**1**.
The COOH moiety is considered in the trans-conformation.

Table S1. Conformers of monomeric *(R)*-**1** as defined by the torsional angles shown in Scheme S1, their relative zero-point corrected and Gibbs free energies (ΔE_{ZPC} and ΔG_{298K}, in kcal/mol) and the corresponding Boltzmann weights χ (in percentage).

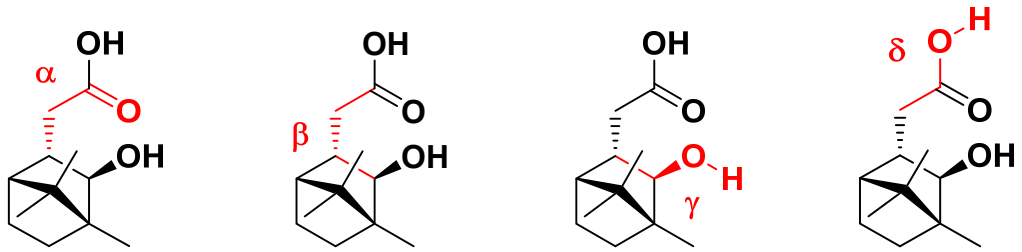
	α / deg	β / deg	ΔE_{ZPC}	ΔG_{298K}	$\chi(\Delta E_{ZPC})$	$\chi(\Delta G_{298K})$
1-c1	-21.9	-71.6	0.0[a]	0.0[b]	44.0	45.7
1-c2	-23.3	-167.2	0.39	0.45	22.9	21.2
1-c3	148.7	-69.5	0.44	0.45	20.8	21.3
1-c4	146.8	-164.9	0.79	0.83	11.6	11.4
1-c5	-16.4	78.1	2.59	2.90	0.6	0.3
1-c6	178.3	78.0	3.58	3.63	0.1	0.1

[a] referenced to E_{ZPC}(**c1**) = -574.661329 hartree. [b] referenced to G(**c1**) = -574.699929 hartree.

Table S2. Conformers of *(R)*-**1**··**7AI**, their relative zero-point corrected and Gibbs free energies (ΔE_{ZPC} and ΔG_{298K}, in kcal/mol) and the corresponding Boltzmann weights χ (in percentage).

	α / deg	β / deg	ΔE_{ZPC}	ΔG_{298K}	$\chi(\Delta E_{ZPC})$	$\chi(\Delta G_{298K})$
1··**7AI** -c1	-24.2	-71.0	0.0[a]	0.0[b]	44.9	67.0
1··**7AI** -c2	-24.5	-166.4	0.40	0.83	22.7	16.4
1··**7AI** -c3	150.5	-69.3	0.43	1.10	21.6	10.6
1··**7AI** -c4	148.0	-165.1	0.87	1.46	10.3	5.7
1··**7AI** -c5	-15.2	78.4	2.77	3.45	0.4	0.2
1··**7AI** -c6	169.2	79.9	3.47	3.99	0.1	0.1

[a] referenced to E_{ZPC}(**c1**) = -954.539472 hartree. [b] referenced to G(**c1**) = -954.59127 hartree.



Scheme S2. Torsional angle definitions of *(1R)*-**2**.

Table S3. Conformers of monomeric *(1R)*-**2** as defined by the torsional angles shown in Scheme S2, their relative zero-point corrected and Gibbs free energies (ΔE_{ZPC} and ΔG_{298K}, in kcal/mol) and the corresponding Boltzmann weights χ (in percentage).

	α / deg	**β** / deg	**γ** / deg	**δ** / deg	ΔE_{ZPC}	ΔG_{298K}	$\chi(\Delta E_{ZPC})$	$\chi(\Delta G_{298K})$
2-c1	9.3	-66.3	-56.1	-178.7	0.0a)	0.0b)	76.74	58.81
2-c2	-161.9	-71.9	-169.0	-0.3	1.45	1.86	6.65	2.52
2-c3	-121.6	-179.3	-169.6	-179.9	1.75	0.96	4.00	11.70
2-c4	105.5	-65.2	-166.4	177.6	1.81	1.30	3.60	6.53
2-c5	-77.6	-70.9	-169.2	-177.8	2.08	1.49	2.28	4.76
2-c6	-132.2	-77.8	-66.1	178.9	2.15	1.77	2.02	2.95
2-c7	23.2	-173.3	-74.3	-177.4	2.31	1.46	1.55	4.97
2-c8	20.8	-172.6	60.2	-177.3	2.46	1.69	1.22	3.36
2-c9	-118.2	-179.7	-77.3	-179.5	2.58	1.77	0.99	2.94
2-c10	8.6	-66.3	-56.0	1.3	3.04	3.11	0.45	0.31
2-c11	-121.0	-179.4	61.7	-180.0	3.06	2.39	0.44	1.05
2-c12	-58.1	54.4	-166.4	177.1	4.79	4.59	0.02	0.03
2-c13	-117.7	-179.3	-169.2	0.7	4.88	4.53	0.02	0.03
2-c14	108.9	-62.9	-164.5	0.4	5.13	4.51	0.01	0.03
2-c15	117.7	63.7	-167.8	-178.3	5.34	5.26	0.01	0.01

a) referenced to E_{ZPC}(**c1**) = -694.924515 hartree. b) referenced to G(**c1**) = -694.965251 hartree.

Table S4. Conformers of dimeric [*(1R)*-**2**]$_2$, their relative zero-point corrected and Gibbs free energies (ΔE_{ZPC} and ΔG_{298K}, in kcal/mol) and the corresponding Boltzmann weights χ (in percentage).

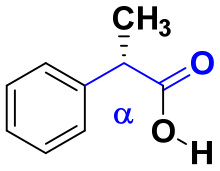
	α / deg	β / deg	γ / deg	α / deg	β / deg	γ / deg	ΔE_{ZPC}	ΔG_{298K}	$\chi(\Delta E_{ZPC})$	$\chi(\Delta G_{298K})$
2-c1-c1	7.8	-67.1	-55.6	7.8	-67.1	-55.6	0.00	0.00	64.45	32.84
2-c1-c3	10.1	-67.7	-55.8	-120.9	-178.8	-169.7	1.22	0.53	8.25	13.51
2-c1-c4	8.4	-67.1	-55.4	103.4	-67.0	-167.8	1.26	0.53	7.68	13.33
2-c1-c5	10.7	-67.5	-55.9	-178.4	-77.3	-68.4	1.32	0.68	6.99	10.42
2-c1-c6	11.4	-68.4	-55.8	-143.2	-76.6	-63.6	1.39	0.64	6.15	11.13
2-c3-c3	-120.8	-178.9	-169.9	-120.8	-178.9	-169.9	2.65	1.37	0.73	3.26
2-c3-c4	-122.1	-178.7	-169.9	104.9	-66.0	-167.0	2.67	1.56	0.71	2.37
2-c3-c5	-124.0	-179.0	-170.1	-77.0	-69.6	-168.1	2.84	1.66	0.53	2.01
2-c3-c6	-124.3	-178.0	-169.8	-151.1	-75.3	-61.6	2.56	1.37	0.86	3.27
2-c4-c4	104.7	-65.7	-164.3	104.7	-65.7	-164.3	2.71	1.62	0.66	2.13
2-c4-c5	104.4	-67.2	-167.6	-76.2	-69.5	-167.9	2.88	1.85	0.50	1.43
2-c4-c6	102.3	-66.8	-168.0	-151.5	-75.4	-61.0	2.64	1.94	0.75	1.25
2-c5-c5	-75.4	-68.7	-165.2	-75.4	-68.7	-165.2	2.93	1.89	0.46	1.36
2-c5-c6	-76.9	-69.6	-168.3	-151.2	-75.2	-61.1	2.76	2.14	0.61	0.89
2-c6-c6	-149.1	-75.9	-62.0	-149.1	-75.9	-62.0	2.70	2.20	0.67	0.80

[a] referenced to E_{ZPC}(**c1**) = -1389.865499 hartree. [b] referenced to G(**c1**) = -1389.928613 hartree.

Table S5. Conformers of monomeric *(1R)*-**2**··**7AI**, their relative zero-point corrected and Gibbs free energies (ΔE_{ZPC} and ΔG_{298K}, in kcal/mol) and the corresponding Boltzmann weights χ (in percentage).

	α / deg	β / deg	γ / deg	ΔE_{ZPC}	ΔG_{298K}	$\chi(\Delta E_{ZPC})$	$\chi(\Delta G_{298K})$
2-c1	9.6	-67.3	-54.4	0.0[a]	0.0[b]	83.3	61.8
2-c2	n/a						
2-c3	-125.4	-178.7	-169.2	1.94	1.01	3.1	11.2
2-c4	104.6	-67.2	-166.8	2.20	1.55	2.0	4.5
2-c5	-73.3	-70.2	-167.3	2.27	1.54	1.8	4.6
2-c6	-153.2	-74.8	-58.9	1.48	1.03	6.8	10.9
2-c7	31.0	-173.4	-72.2	2.50	1.81	1.3	2.9
2-c8	24.3	-172.2	58.9	2.74	2.15	0.8	1.6
2-c9	-120.9	-178.7	-74.1	2.71	1.91	0.9	2.5

[a] referenced to E_{ZPC}(**c1**) = - 1074.801672 hartree. [b] referenced to G(**c1**) = -1074.854694 hartree.



Scheme S3. Torsional angle definitions of **2-phenyl propionic acid (PPA)**.
The COOH moiety is considered in the trans-conformation.

Table S6. Conformers of monomeric *(S)*-**PPA** as defined by the torsional angles shown in Scheme S3, their relative zero-point corrected and Gibbs free energies (ΔE_{ZPC} and ΔG_{298K}, in kcal/mol) and the corresponding Boltzmann weights χ (in percentage).

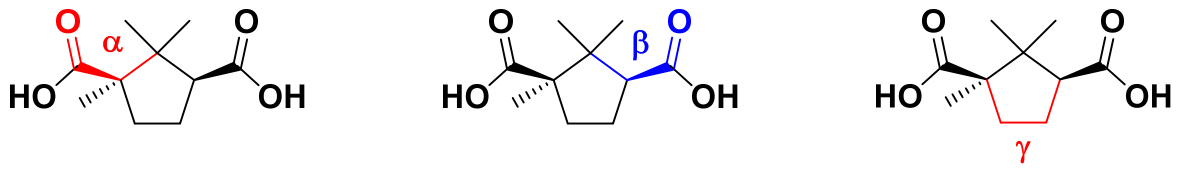
	α	**ΔE_{ZPC}**	**ΔG_{298K}**	**$\chi(\Delta E_{ZPC})$**	**$\chi(\Delta G_{298K})$**
PPA-c1	-96.9	0.0[a)]	0.0[b)]	80.7	78.6
PPA-c2	97.5	0.85	0.77	19.3	21.4

[a)] referenced to E_{ZPC}(**c1**) = -499.440249 hartree. [b)] referenced to G(**c1**) = -499.477101 hartree.

Table S7. Conformers of *(S)*-**PPA··7AI**, their relative zero-point corrected and Gibbs free energies (ΔE_{ZPC} and ΔG_{298K}, in kcal/mol) and the corresponding Boltzmann weights χ (in percentage).

	α	**ΔE_{ZPC}**	**ΔG_{298K}**	**$\chi(\Delta E_{ZPC})$**	**$\chi(\Delta G_{298K})$**
PPA··7AI-c1	-94.7	0.0[a)]	0.0[b)]	73.7	80.4
PPA··7AI-c2	95.3	0.61	0.84	26.3	19.6

[a)] referenced to E_{ZPC}(**c1**) = -879.317294 hartree. [b)] referenced to G(**c1**) = -879.367061 hartree.



Scheme S4. Torsional angle definitions of **3**.
The COOH moiety is considered in the trans-conformation.

Table S8. Conformers of monomeric **3** as defined by the torsional angles shown in Scheme S4, their relative zero-point corrected and Gibbs free energies (ΔE_{ZPC} and ΔG_{298K}, in kcal/mol) and the corresponding Boltzmann weights χ (in percentage).

	α / deg	β / deg	γ / deg	ΔE_{ZPC}	ΔG_{298K}	$\chi(\Delta E_{ZPC})$	$\chi(\Delta G_{298K})$
3-c1	-112.2	98.4	11.2	0.0[a)]	0.0[b)]	54.2	51.7
3-c2	71.5	100.6	16.6	0.50	0.43	23.3	25.2
3-c3	-112.0	-83.9	1.3	1.03	1.05	9.4	8.8
3-c4	-111.7	-14.3	1.3	1.22	1.25	6.9	6.3
3-c5	71.0	-82.8	14.3	1.52	1.29	4.2	5.9
3-c6	72.3	-17.9	6.4	1.95	1.88	2.0	2.1

[a)] referenced to E_{ZPC}(**c1**) = -691.612329 hartree. [b)] referenced to G(**c1**) = -691.653728 hartree.

Table S9. Conformers of **7AI··3··7AI**, their relative zero-point corrected and Gibbs free energies (ΔE_{ZPC} and ΔG_{298K}, in kcal/mol) and the corresponding Boltzmann weights χ (in percentage).

	α / deg	β / deg	γ / deg	ΔE_{ZPC}	ΔG_{298K}	$\chi(\Delta E_{ZPC})$	$\chi(\Delta G_{298K})$
7AI··3··7AI-c1	-111.2	98.3	11.1	0.0[a)]	0.0[b)]	50.9	59.8
7AI··3··7AI-c2	70.4	99.8	16.0	0.48	0.65	22.8	20.0
7AI··3··7AI-c3	-111.9	-83.7	9.4	0.78	1.05	13.6	10.1
7AI··3··7AI-c4	-111.0	-21.9	3.9	1.44	1.66	4.5	3.6
7AI··3··7AI-c5	69.8	-82.2	14.7	1.24	1.52	6.2	4.6
7AI··3··7AI-c6	71.8	-27.7	8.3	1.92	2.03	2.0	1.9

[a)] referenced to E_{ZPC}(**c1**) = -1451.366086 hartree. [b)] referenced to G(**c1**) = -1451.432812 hartree.

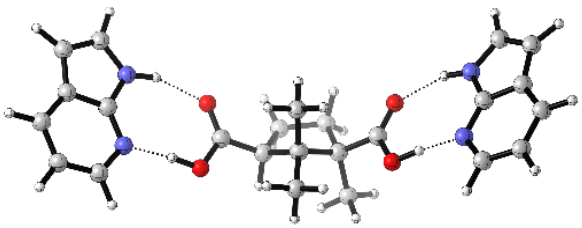
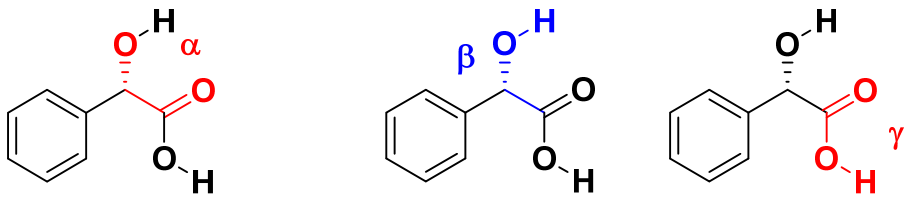


Figure S7. Structure of the lowest energy conformer **7AI··3··7AI**-*c1*.



Scheme S5. Torsional angle definitions of **4**.

Table S10. Conformers of monomeric *(S)*-**4** as defined by the torsional angles shown in Scheme S5, their relative zero-point corrected and Gibbs free energies (ΔE_{ZPC} and ΔG_{298K}, in kcal/mol) and the corresponding Boltzmann weights χ (in percentage).

	α / deg	**β** / deg	**γ** / deg	ΔE_{ZPC}	ΔG_{298K}	$\chi(\Delta E_{ZPC})$	$\chi(\Delta G_{298K})$
4-c1	-7.4	4.1	-1.2	0.0[a)]	0.0[b)]	78.6	77.0
4-c2	168.9	151.9	-177.3	0.98	0.89	15.0	17.0
4-c3	-22.1	174.3	-2.5	2.13	2.20	2.2	1.9
4-c4	10.8	-12.7	-174.0	2.21	2.69	1.9	0.8
4-c5	147.6	64.3	0.5	2.44	2.36	1.3	1.4
4-c6	164.8	-47.8	0.5	2.56	2.18	1.0	1.9

[a)] referenced to E_{ZPC}(**c1**) = -535.382145 hartree. [b)] referenced to G(**c1**) = -535.418706 hartree.

Table S11. Conformers of *(S)*-**4··7AI**, their relative zero-point corrected and Gibbs free energies (ΔE_{ZPC} and ΔG_{298K}, in kcal/mol) and the corresponding Boltzmann weights χ (in percentage).

	α / deg	**β** / deg	ΔE_{ZPC}	ΔG_{298K}	$\chi(\Delta E_{ZPC})$	$\chi(\Delta G_{298K})$
4··7AI -c1	-7.6	4.4	0.0	0.0	94.0	91.5
4··7AI -c2	n/a					
4··7AI -c3	-21.6	175.2	2.87	2.60	0.7	1.1
4··7AI -c4	n/a					
4··7AI -c5	n/a					
4··7AI -c6	159.3	20.6[c)]	1.70	1.49	5.3	7.4

[a)] referenced to E_{ZPC}(**c1**) = -915.261443 hartree. [b)] referenced to G(**c1**) = -915.309966 hartree.
[c)] When 7AI, the heterodimers of both c5 and c6 converge to an identical structure, in which β is an intermediate angle between both monomeric structures

4 . References

1. *Gaussian 09, Rev E.01*, 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. J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, 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, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, Wallingford CT, USA, 2013
2. B. Mennucci, C. Cappelli, R. Cammi and J. Tomasi, *Chirality*, 2011, **23**, 717-729.
3. J. Tomasi, B. Mennucci and R. Cammi, *Chem. Rev.*, 2005, **105**, 2999-3094.
4. K. Scholten and C. Merten, *Phys. Chem. Chem. Phys.*, 2022, **24**, 3611-3617.
5. K. Scholten and C. Merten, *Phys. Chem. Chem. Phys.*, 2022, **24**, 4042-4050.
6. M. Kemper, E. Engelage and C. Merten, *Angew. Chem. Int. Ed.*, 2021, **60**, 2958-2962.
7. K. Bünnemann and C. Merten, *Phys. Chem. Chem. Phys.*, 2017, **19**, 18948-18956.
8. *CYLview 1.0b*, C. Y. Legault, Université de Sherbrooke, 2009