Electronic Supplementary Information

Experimental and theoretical evaluation on the conformational behavior of L-aspartic acid dimethyl ester and its *N*-acetylated derivative

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Synthesis of the compounds

1. L-Aspartic acid dimethyl ester

Activated zinc powder (100.0 mg) was added over a suspension of L-aspartic acid dimethyl ester hydrochloride (197.6 mg, 1.0 mmol), commercially available from Aldrich, in 10 mL of dichloromethane. The reaction mixture was stirred for 3 h at room temperature until deprotonation of the salt. Then, the excess zinc was filtered off and the solvent was removed through evaporation *in vacuo*. Thus, AspOMe was obtained as a white crystalline solid (142.4 mg, 0.9 mmol, 88.4% yield), which was used without further purification. IR (KBr): v = 3306 (m), 3248 (m), 2958 (m), 2856 (w), 1736 (s), 1586 (m), 1441 (s), 1376 (m), 1244 (s), 1214 (s) cm^{-1}. ^{1}H NMR (600.17 MHz, DMSO-d_6, 25 °C, TMS): δ (ppm) = 3.80 (t, ^3J = 6.3 Hz, 1H), 3.64 (s, 3H), 3.60 (s, 3H), 2.73 (dd, ^3J = 6.3 and ^2J = 16.3 Hz, 1H), 2.68 (dd, ^3J = 6.3 and ^2J = 16.3 Hz, 1H). ^{13}C NMR (150.91 MHz, DMSO-d_6, 25 °C, TMS): δ (ppm) = 173.49, 171.25, 52.58, 52.10, 50.85, 37.92. MS (TOF-EI+): calcd for $C_6H_{11}NO_4$, 161.0688; found 102.0561 (corresponding to loss of CH_3O-C=O).

**2. *N*-Acetyl-L-aspartic acid dimethyl ester**

Anhydrous methanol (10 mL) was added to a 25 mL round-bottomed flask and cooled to -5 °C. Thionyl chloride (0.8 mL, 11.4 mmol) was slowly added dropwise with stirring, and the solution was maintained an additional 10 min at -5 °C. Thereafter, 1.0 g (5.7 mmol) of *N*-acetyl-L-aspartic acid was added in small portions, and the reaction mixture was stirred at that temperature for 3 h and then at room temperature for 15 h. The solution was concentrated under reduced pressure and the resulting residue was dissolved in 5 mL of water and 5 mL of dichloromethane. Saturated solution of KHCO$_3$ was added until pH 8 was reached. Aqueous phase was extracted with dichloromethane (3 x 5 mL), the organic extracts were combined, dried with anhydrous MgSO$_4$, filtered, and the solvent was removed with a rotary evaporator to give 801.9 mg of *N*-acetyl-L-aspartic acid dimethyl ester hydrochloride (3.3 mmol, 58.6% yield), which was used without purification. In the next step, the crystalline salt was suspended in 5 mL of chloroform, 0.5 mL of triethylamine was added at room temperature, and the mixture

was stirred for 4 h. The residue was dissolved in 5 mL of water and saturated solution of NaHCO$_3$ (to raise the pH until 8), and the aqueous phase was extracted with chloroform (3 x 5 mL). The organic layer was dried (Na$_2$SO$_4$), filtered, and the solvent was removed *in vacuo* to yield 551.0 mg (2.7 mmol, 80.9% yield) of *N*-acetyl-L-aspartic acid dimethyl ester as white crystals. IR (KBr): ν = 3322 (s), 2958 (m), 2849 (w), 1739 (s), 1651 (s), 1537 (s), 1437 (s), 1375 (s), 1213 (s) cm^{-1}. ^{1}H NMR (600.17 MHz, DMSO-d_6, 25 °C, TMS): δ (ppm) = 8.37 (d, ^3J = 7.8 Hz, 1H), 4.61 (ddd, ^3J = 6.0, 7.3 and 7.8 Hz, 1H), 3.62 (s, 3H), 3.61 (s, 3H), 2.78 (dd, ^3J = 6.0 and ^2J = 16.4 Hz, 1H), 2.69 (dd, ^3J = 7.3 and ^2J = 16.4 Hz, 1H), 1.83 (s, 3H). ^{13}C NMR (150.91 MHz, DMSO-d_6, 25 °C, TMS): δ (ppm) = 171.75, 170.91, 169.72, 52.60, 52.15, 48.94, 36.11, 22.72. MS (TOF-EI+): calcd for C$_8$H$_{13}$NO$_5$, 203.0794; found 144.0639 (corresponding to loss of CH$_3$O-C=O).

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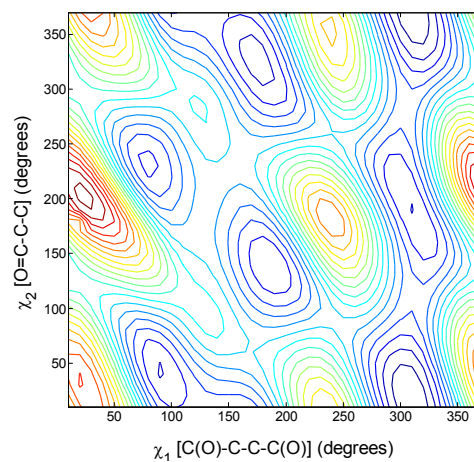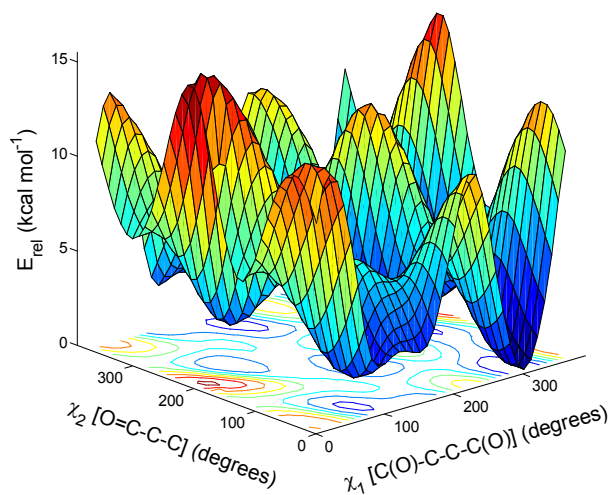
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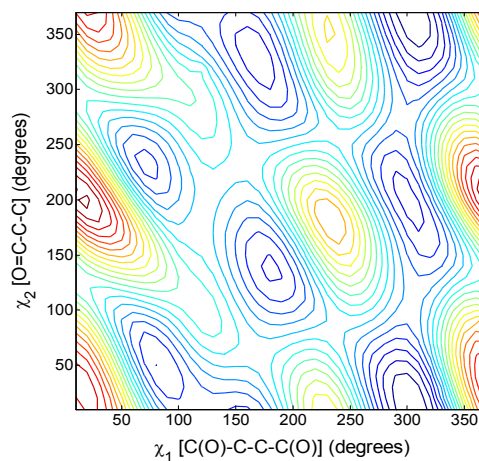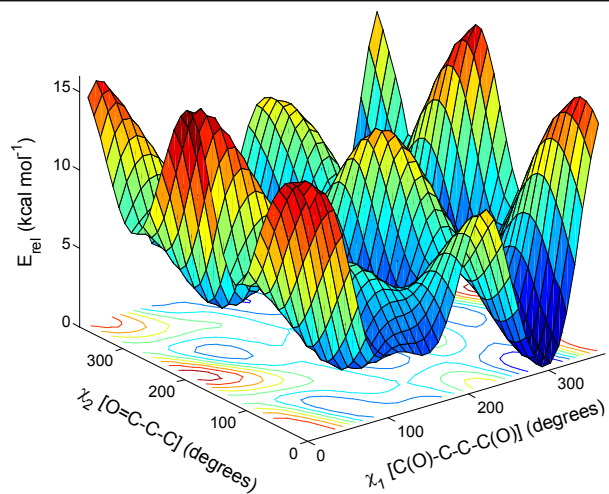
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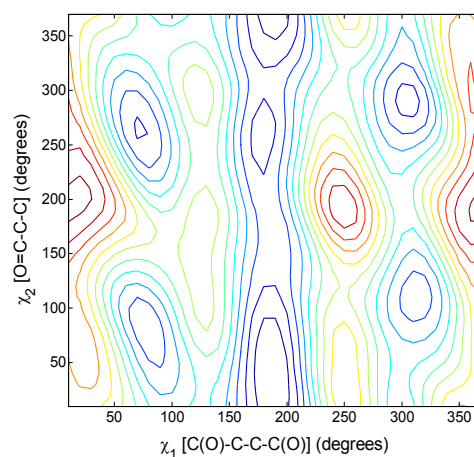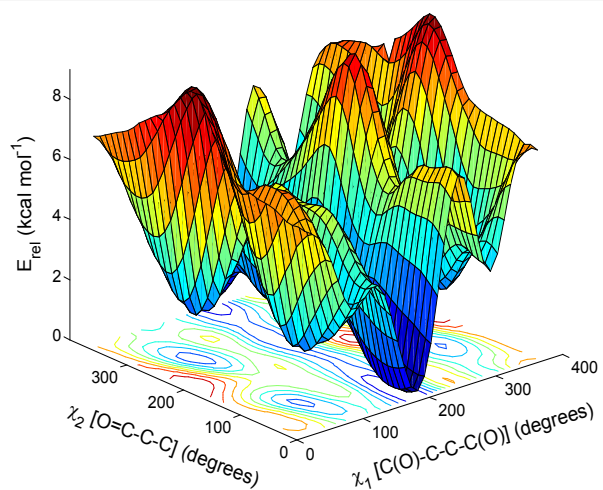
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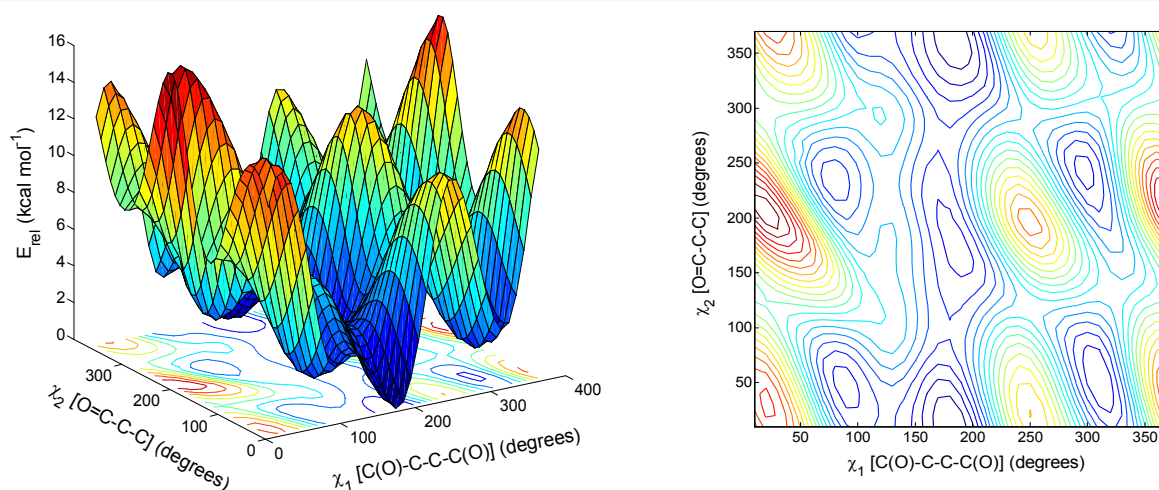
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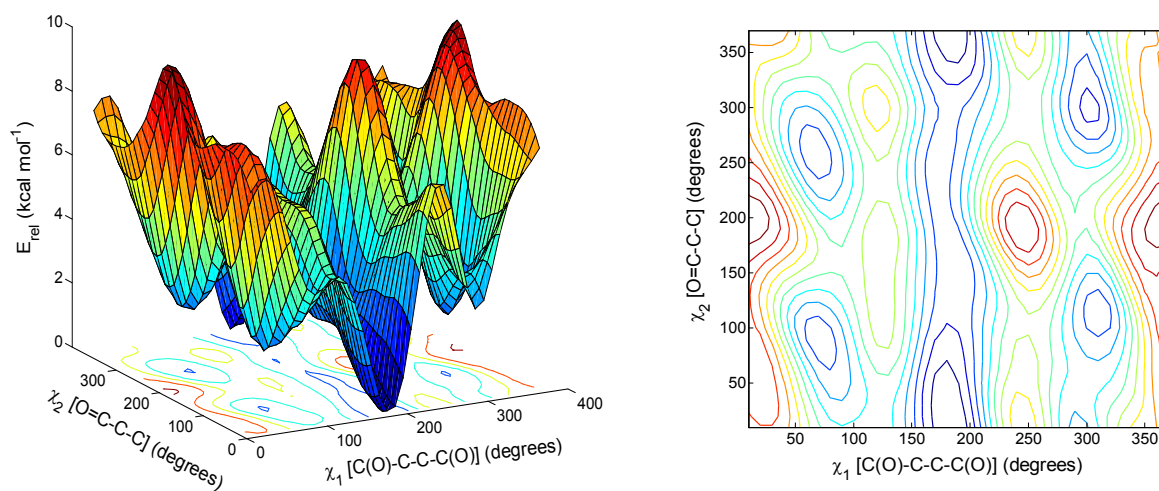
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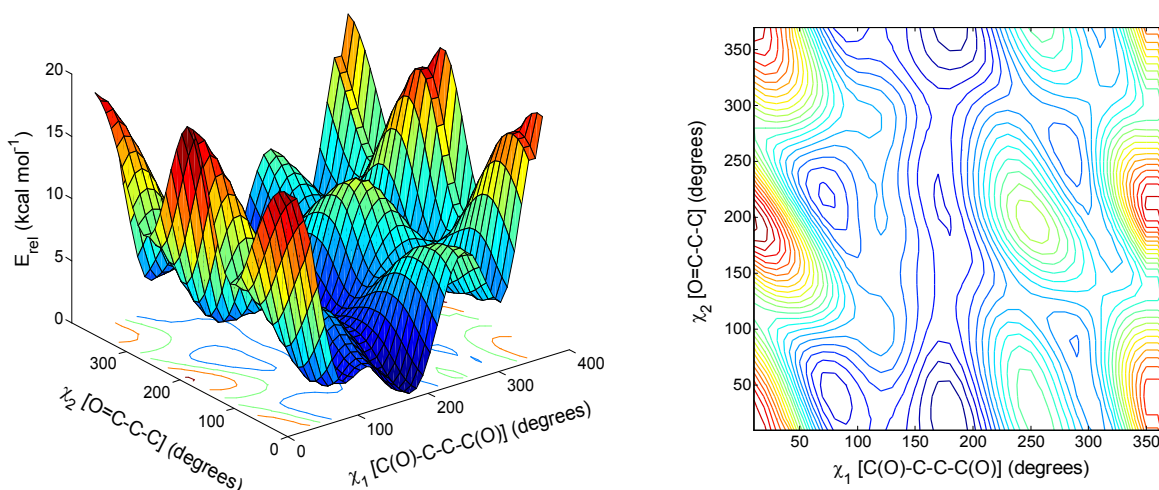
Fig. S1. Potential energy surfaces (PES, at the left) built by varying the χ_1 [C(O)-C-C-C(O)] and χ_2 [O=C-C-C] dihedral angles for AspOMe, calculated at the B3LYP/cc-pVDZ level for the isolated molecule, and their corresponding contour maps (at the right) as a function of the χ_1 and χ_2 dihedral angles.

Ia **IIa** **IIIb**

IVb **Vc** **VIb**

VIIb **VIIIa**
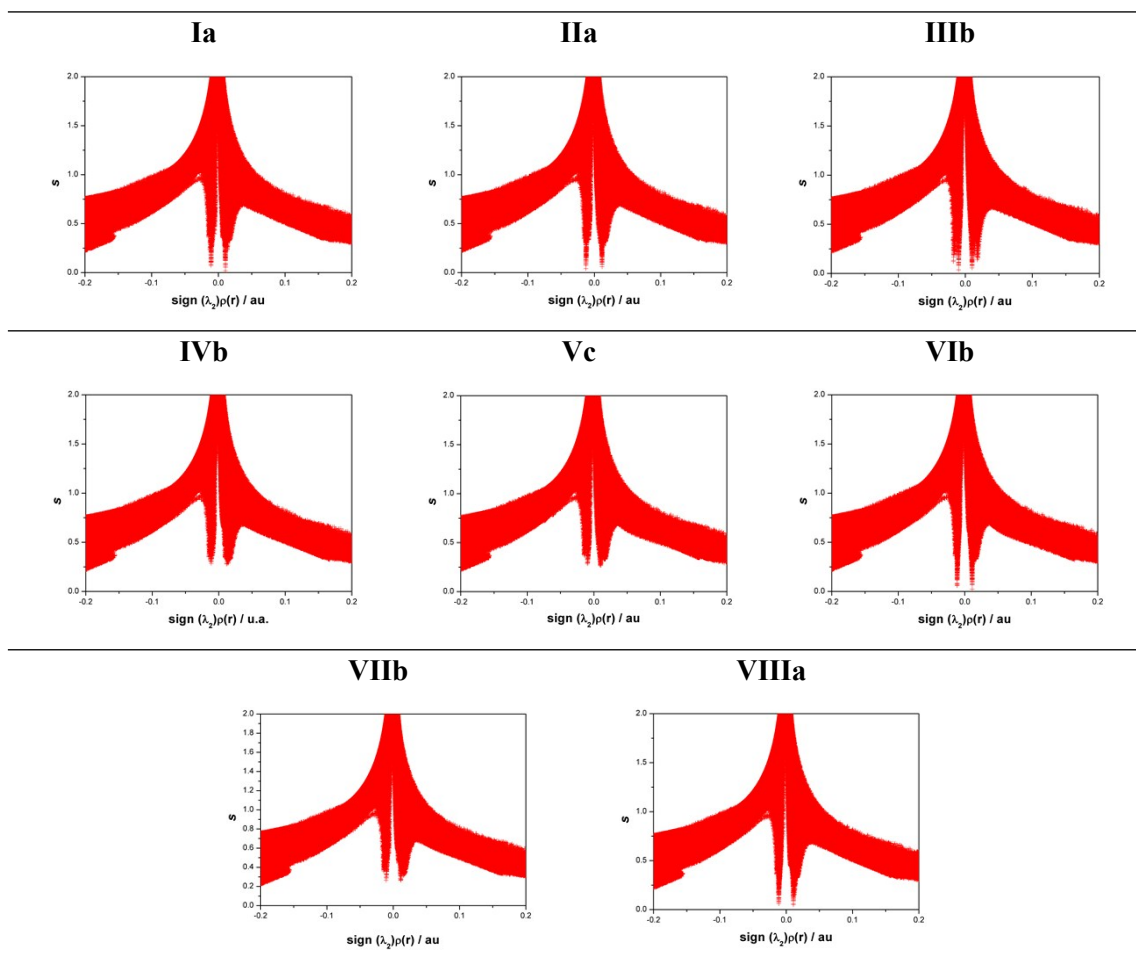
Fig. S2. NCI plots of the reduced density gradients [$s(r)$] versus sign $(\lambda_2)\rho(r)$ for the AspOMe conformers.

Ia	IIa	IIIb

IVb	Vc	VIb

VIIb	VIIIa
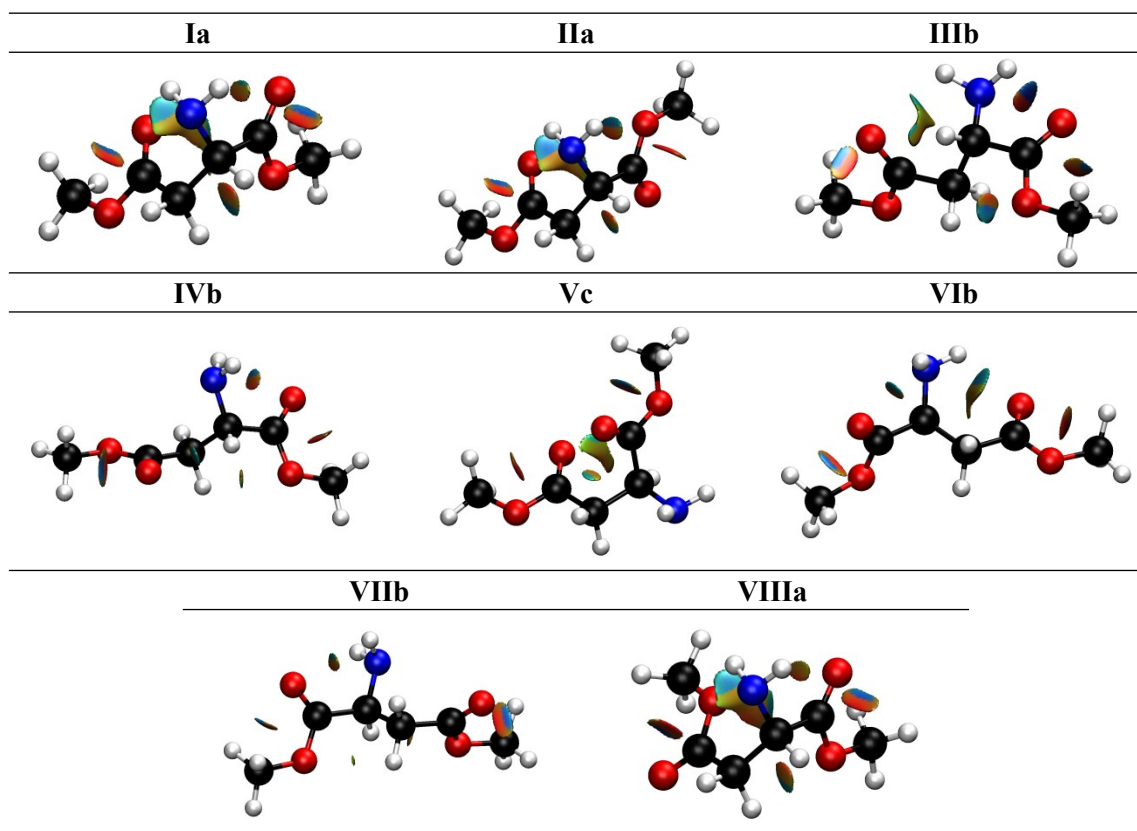
Fig. S3. NCI isosurfaces of AspOMe conformers, which were generated with $s = 0.5$ au and blue-green-red scaling from -2 au $< (\lambda_2)\rho(r) < 2$ au.

(a)

(b)
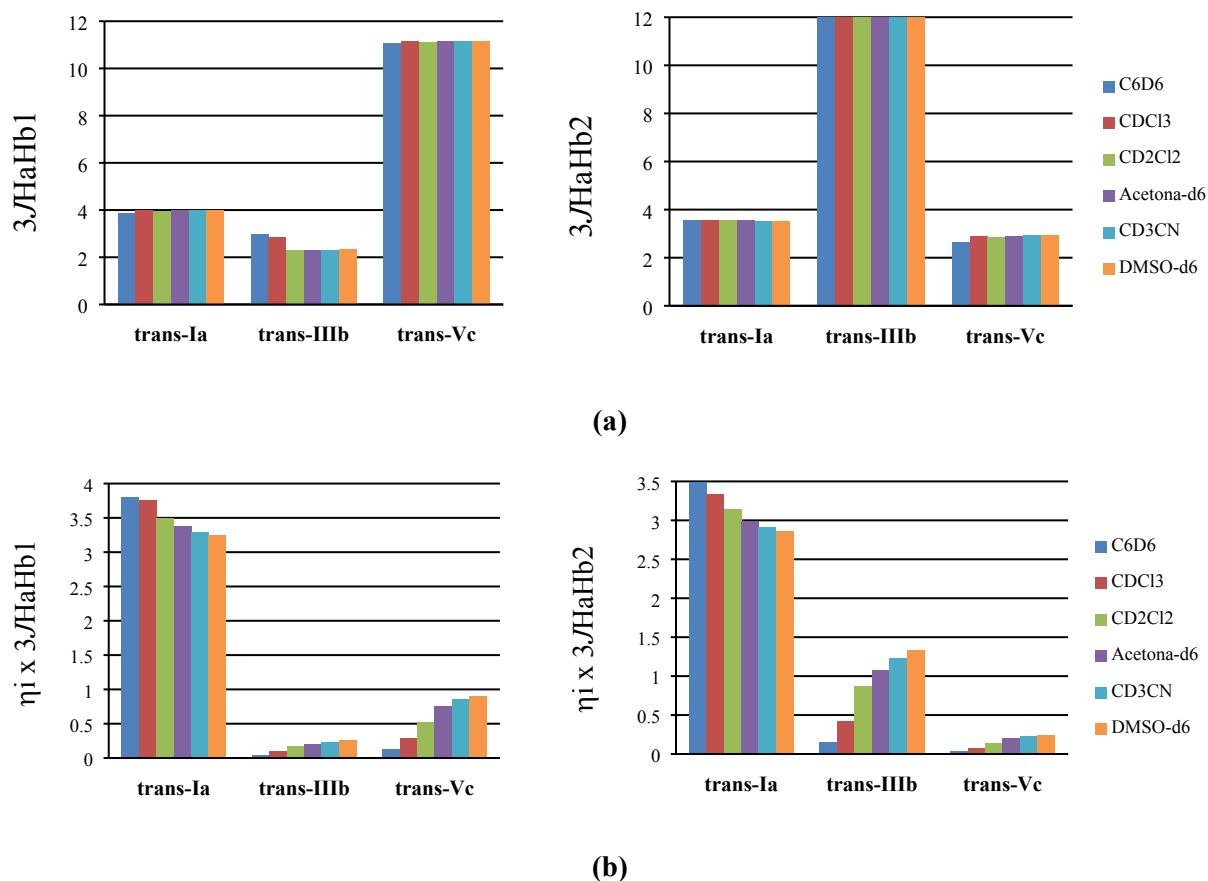
Fig. S4. (a) Individual coupling constants $^3J_{HaHb,i}$ for the AcAspOMe conformers and (b) conformational contributions ($\eta_i \times {}^3J_{HaHb,i}$) for the observed $^3J_{HaHb,obs}$ coupling constants, calculated at the ωB97X-D/EPR-III level of theory, by using the IEF-PCM in several solvents. The values are presented in Hz.

Table S1. Conformer energies, relative energies, populations, investigated dihedral angles[a] and dipole moments in isolated phase for the most stable conformers of AspOMe, optimized using different methods. In all cases the aug-cc-pVTZ basis set was used.[(*)]

| Conformer	Parameters	MP2	B3LYP	CAM-B3LYP	M05-2X	M06-2X	B97-D	ωB97X-D
	E (hartrees)	-589.93943	-591.16201	-590.91311	-591.09986	-590.92884	-590.78160	-590.97001
	E_{rel} (kcal mol^{-1}) [b]	0.00	0.00	0.09	0.00	0.00	0.00	0.00
	ZPE (hartrees)	--	0.17869	0.180973	0.182885	0.181463	0.174122	0.181599
	E + ZPE (hartrees)	--	-590.98332	-590.73214	-590.91697	-590.74738	-590.60747	-590.78841
	E_{rel} + ZPE (kcal mol^{-1})	--	0.00	0.26	0.03	0.00	0.00	0.00
Ia	%P (E_{rel} + ZPE)	--	20.8	20.8	32.5	44.7	29.9	30.4
	ω [O=C$_1$-O-C]	2.6	1.2	1.4	2.5	2.3	1.9	1.7
	ψ [N-C-C=O]	21.3	19.6	20.8	21.3	21.3	19.3	21.2
	χ_1 [C(O)-C-C-C(O)]	57.1	62.6	61.7	58.5	58.1	60.0	60.1
	χ_2 [O=C$_{16}$-C-C]	0.5	2.2	2.3	2.1	2.5	0.5	0.1
	μ (debyes)	3.29	3.13	3.16	3.19	3.06	3.09	3.19
	E (hartrees)	-589.93901	-591.16185	-590.91309	-591.09979	-590.92863	-590.78112	-590.96977
	E_{rel} (kcal mol^{-1})	0.26	0.10	0.11	0.04	0.13	0.30	0.15
	ZPE (hartrees)	--	0.178732	0.181037	0.182772	0.181743	0.174066	0.181481
	E + ZPE (hartrees)	--	-590.98311	-590.73205	-590.91702	-590.74689	-590.60706	-590.78829
	E_{rel} + ZPE (kcal mol^{-1})	--	0.13	0.31	0.00	0.31	0.26	0.01
IIa	%P (E_{rel} + ZPE)	--	16.7	19.1	34.0	26.5	19.3	26.8
	ω [O=C$_1$-O-C]	2.6	1.6	1.8	2.7	2.5	2.1	1.8
	ψ [N-C-C=O]	161.4	161.1	160.2	161.9	162.5	164.2	161.1
	χ_1 [C(O)-C-C-C(O)]	61.8	66.2	65.4	62.5	63.2	64.8	64.8
	χ_2 [O=C$_{16}$-C-C]	1.6	1.1	0.6	0.9	3.8	0.7	1.5
	μ (debyes)	0.52	0.40	0.40	0.48	0.52	0.47	0.41

	E (hartrees)	-589.93797	-591.16221	-590.91326	-591.09879	-590.92765	-590.77994	-590.96901
	E_{rel} (kcal mol⁻¹)	0.92	0.13	0.00	0.67	0.75	1.04	0.63
	ZPE (hartrees)	--	0.178359	0.180711	0.182545	0.181279	0.173760	0.181306
	E + ZPE (hartrees)	--	-590.98385	-590.73255	-590.91625	-590.74637	-590.60618	-590.78770
	E_{rel} + ZPE (kcal mol⁻¹)	--	0.33	0.00	0.48	0.64	0.81	0.44
IIIb	%P (E_{rel} + ZPE)	--	11.9	32.3	15.1	15.2	7.6	14.4
	ω [O=C$_1$-O-C]	0.8	0.8	0.8	0.7	0.8	0.3	0.5
	ψ [N-C-C=O]	17.2	15.3	15.9	16.0	16.4	13.5	16.5
	χ_1 [C(O)-C-C-C(O)]	177.3	173.0	173.7	175.3	175.7	172.4	175.2
	χ_2 [O=C$_{16}$-C-C]	16.6	11.9	10.9	13.6	11.1	12.5	14.4
	μ (debyes)	2.84	2.81	2.86	2.81	2.79	2.76	2.79
	E (hartrees)	-589.93705	-591.16160	-590.91202	-591.09740	-590.92591	-590.78045	-590.96825
	E_{rel} (kcal mol⁻¹)	1.50	0.26	0.78	1.54	1.84	0.72	1.10
	ZPE (hartrees)	--	0.178386	0.180621	0.182356	0.181337	0.173849	0.181059
	E + ZPE (hartrees)	--	-590.98321	-590.73140	-590.91504	-590.74457	-590.60660	-590.78719
	E_{rel} + ZPE (kcal mol⁻¹)	--	0.07	0.72	1.24	1.76	0.55	0.76
IVb	%P (E_{rel} + ZPE)	--	18.6	9.6	4.2	2.3	11.8	8.4
	ω [O=C$_1$-O-C]	1.1	0.8	0.5	0.5	0.5	1.1	0.2
	ψ [N-C-C=O]	22.0	18.0	15.3	14.4	14.3	21.6	13.6
	χ_1 [C(O)-C-C-C(O)]	174.1	166.8	166.8	170.1	169.9	170.4	166.5
	χ_2 [O=C$_{16}$-C-C]	53.7	42.4	40.5	45.4	45.9	53.5	44.2
	μ (debyes)	1.53	1.63	1.72	1.66	1.62	1.36	1.69
	E (hartrees)	-589.93744	-591.16147	-590.91194	-591.09790	-590.92656	-590.78071	-590.96852
	E_{rel} (kcal mol⁻¹)	1.25	0.34	0.83	1.23	1.43	0.55	0.93
	ZPE (hartrees)	--	0.178417	0.180690	0.182466	0.181382	0.173789	0.181400
	E + ZPE (hartrees)	--	-590.98305	-590.73125	-590.91543	-590.74518	-590.60692	-590.78712
	E_{rel} + ZPE (kcal mol⁻¹)	--	0.17	0.82	1.00	1.38	0.35	0.80
Vc	%P (E_{rel} + ZPE)	--	15.7	8.1	6.3	4.3	16.6	7.8
	ω [O=C$_1$-O-C]	1.9	1.0	1.3	2.1	2.1	1.2	2.0
	ψ [N-C-C=O]	85.7	87.6	89.1	86.8	87.3	84.4	85.9
	χ_1 [C(O)-C-C-C(O)]	60.0	65.4	64.0	61.6	60.9	65.0	62.8
	χ_2 [O=C$_{16}$-C-C]	4.8	4.0	4.0	3.5	3.3	3.3	3.8
	μ (debyes)	0.45	0.49	0.48	0.36	0.37	0.39	0.39

VIb	E (hartrees)	-589.93646	-591.16086	-590.91154	-591.09714	-590.92595	-590.77984	-590.96782
	E_{rel} (kcal mol^{-1})	1.87	0.72	1.08	1.71	1.82	1.10	1.37
	ZPE (hartrees)	--	0.178333	0.180602	0.182143	0.181136	0.173905	0.181036
	E + ZPE (hartrees)	--	-590.98253	-590.73093	-590.91499	-590.74481	-590.60593	-590.78678
	E_{rel} + ZPE (kcal mol^{-1})	--	0.50	1.02	1.24	1.61	0.97	1.02
	%P (E_{rel} + ZPE)	--	8.9	5.8	4.2	2.9	5.9	5.5
	ω [O=C$_1$-O-C]	0.6	0.4	0.3	0.3	0.2	0.7	0.9
	ψ [N-C-C=O]	36.3	34.6	32.2	31.6	29.4	36.1	35.0
	χ_1 [C(O)-C-C-C(O)]	176.4	174.8	175.2	175.5	175.5	174.9	175.4
	χ_2 [O=C$_{16}$-C-C]	6.9	1.3	0.6	4.1	1.2	6.1	2.5
	μ (debyes)	3.49	3.38	3.48	3.50	3.49	3.28	3.42
VIIb	E (hartrees)	-589.93657	-591.16054	-590.91098	-591.09674	-590.92539	-590.77972	-590.96761
	E_{rel} (kcal mol^{-1})	1.80	0.92	1.43	1.96	2.17	1.18	1.50
	ZPE (hartrees)	--	0.178345	0.180608	0.182315	0.181217	0.173827	0.181208
	E + ZPE (hartrees)	--	-590.98219	-590.73037	-590.91443	-590.74417	-590.60589	-590.78640
	E_{rel} + ZPE (kcal mol^{-1})	--	0.71	1.37	1.63	2.01	0.99	1.26
	%P (E_{rel} + ZPE)	--	6.2	3.2	2.2	1.5	5.6	3.5
	ω [O=C$_1$-O-C]	1.2	1.0	0.8	0.6	0.4	1.4	1.4
	ψ [N-C-C=O]	22.3	19.4	15.4	13.1	10.7	23.2	19.9
	χ_1 [C(O)-C-C-C(O)]	178.1	176.5	176.6	179.5	180.0	178.5	178.2
	χ_2 [O=C$_{16}$-C-C]	124.6	129.6	130.9	127.2	127.4	124.8	129.1
	μ (debyes)	3.74	3.49	3.45	3.41	3.25	3.43	3.49
VIIIa	E (hartrees)	-589.93736	-591.15920	-590.91024	-591.09680	-590.92606	-590.77931	-590.96773
	E_{rel} (kcal mol^{-1})	1.30	1.76	1.90	1.92	1.75	1.44	1.43
	ZPE (hartrees)	--	0.178505	0.180834	0.182699	0.181357	0.173901	0.181434
	E + ZPE (hartrees)	--	-590.98070	-590.72940	-590.91410	-590.74470	-590.60541	-590.78630
	E_{rel} + ZPE (kcal mol^{-1})	--	1.65	1.98	1.83	1.68	1.30	1.32
	%P (E_{rel} + ZPE)	--	1.2	1.1	1.5	2.6	3.3	3.2
	ω [O=C$_1$-O-C]	1.6	0.1	0.2	1.1	1.4	1.1	1.1
	ψ [N-C-C=O]	19.0	12.8	14.4	16.3	16.8	12.9	15.0
	χ_1 [C(O)-C-C-C(O)]	48.3	62.6	61.9	58.2	57.8	59.2	59.7
	χ_2 [O=C$_{16}$-C-C]	163.2	176.0	176.0	178.5	179.3	179.2	177.9
	μ (debyes)	1.48	2.11	2.13	2.09	1.99	2.05	2.07

[a] Dihedral angles in degrees; [b] 1 au = 627.5095 kcal mol^{-1}; [*] The numbering of atoms is in Fig. 2.

Table S2. Comparison of significant NBO interactions and the corresponding energies (in kcal mol^{-1}) for the AspOMe conformers, calculated at ωB97X-D/aug-cc-pVTZ.
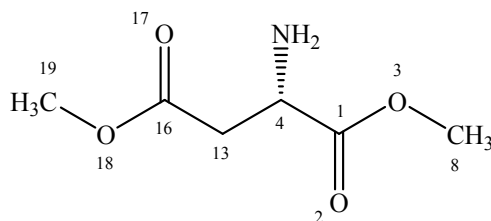
Interaction	Ia	IIa	IIIb	IVb	Vc	VIb	VIIb	VIIIa
LP2(O18) → π*$_{C16=O17}$	70.69	71.24	69.35	66.56	69.90	69.91	66.79	65.89
LP2(O3) → π*$_{C1=O2}$	65.27	63.65	67.29	68.84	69.78	69.67	69.11	66.74
LP2(O2) → σ*$_{C1-O3}$	43.71	43.00	42.41	42.80	42.98	43.15	43.10	43.49
LP2(O17) → σ*$_{C16-O18}$	42.38	41.95	42.24	43.23	42.70	42.49	43.89	45.30
LP2(O2) → σ*$_{C1-C4}$	26.31	25.58	25.58	25.57	25.45	25.41	25.70	26.33
LP2(O17) → σ*$_{C13-C16}$	24.97	24.76	25.31	25.65	25.33	25.54	25.18	24.39
LP2(N) → σ*$_{C1-C4}$	11.97	13.61	--[a]	11.17	9.73	1.11	12.05	12.08
LP2(O18) → σ*$_{C16-O17}$	10.30	10.40	10.15	10.00	10.25	10.14	9.77	9.33
LP2(O3) → σ*$_{C1-O2}$	9.94	10.04	9.90	10.37	10.77	10.50	10.42	10.08
LP2(O17) → σ*$_{N5-H7}$	0.50	0.72	--	--	--	--	--	--
LP2(O2) → σ*$_{N5-H7}$	--	--	0.85	--	--	--	--	--

[a] Hyperconjugation energy smaller than 0.5 kcal mol^{-1}.

Table S3. Comparison between calculated and experimental $^3J_{HaHb1}$ coupling constant for AspOMe compound.

	Benzene	Chloroform	Dichloromethane	Acetone	Acetonitrile	DMSO
Ia	0.92[a]	0.99	1.25	1.05	1.02	1.02
IIa	0.77	0.67	0.60	0.56	0.53	0.54
IIIb	0.24	0.21	0.17	0.16	0.16	0.16
IVb	0.28	0.33	0.29	0.33	0.34	0.34
Vc	1.05	1.01	0.90	0.97	0.98	0.98
VIb	0.13	0.12	0.10	0.15	0.16	0.16
VIIb	0.21	0.24	0.24	0.28	0.29	0.30
VIIIa	0.20	0.23	0.23	0.28	0.30	0.30
Theoretical[b]	3.8	3.8	3.8	3.8	3.8	3.8
Experimental[c]	4.2	4.2	4.1	4.8	4.8	6.3

[a] Conformational contributions values (η_i x $^3J_{HaHb1,i}$) for the observed $^3J_{HaHb1,obs}$ coupling constant, calculated at the ωB97X-D/EPR-III level of theory.

[b] Predicted $^3J_{HaHb1}$ coupling constant.

[c] Experimental $^3J_{HaHb1}$ coupling constant.

Table S4. Comparison between calculated and experimental $^3J_{HaHb2}$ coupling constant for AspOMe compound.

	Benzene	Chloroform	Dichloromethane	Acetone	Acetonitrile	DMSO
Ia	1.26	1.34	1.7	1.46	1.42	1.42
IIa	0.88	0.76	0.68	0.65	0.63	0.59
IIIb	1.11	0.98	0.79	0.73	0.72	0.72
IVb	1.52	1.71	1.48	1.68	1.71	1.74
Vc	0.3	0.29	0.26	0.28	0.29	0.29
VIb	0.69	0.63	0.57	0.79	0.86	0.85
VIIb	0.75	0.87	0.86	1.01	1.06	1.08
VIIIa	0.25	0.28	0.28	0.33	0.35	0.35
Theoretical[b]	6.8	6.9	6.6	6.9	7.0	7.0
Experimental[c]	6.0	5.6	5.8	5.2	5.7	6.3

[a] Conformational contributions values (η_i x $^3J_{HaHb2,i}$) for the observed $^3J_{HaHb2,obs}$ coupling constant, calculated at the ωB97X-D/EPR-III level of theory.

[b] Predicted $^3J_{HaHb2}$ coupling constant.

[c] Experimental $^3J_{HaHb2}$ coupling constant.

Table S5. Relative total energy of the system $(E_{rel,Tot})$[a], relative energy of the steric $(E_{rel,Lewis})$ and hyperconjugative $(E_{rel,Hyper})$ interactions for the AspOMe conformers, taking into account the solvent effects (IEF-PCM), calculated at ωB97X-D/aug-cc-pVTZ level of theory.

Conformer	$E_{rel,Tot}$			$E_{rel,Lewis}$			$E_{rel,Hyper}$		
	Isolated	CHCl₃	DMSO	Isolated	CHCl₃	DMSO	Isolated	CHCl₃	DMSO
Ia	0.00	0.00	0.00	5.67	6.58	7.12	7.12	7.48	7.80
IIa	0.15	0.41	0.56	6.94	7.82	8.75	8.25	8.31	8.87
IIIb	0.63	0.97	1.11	0.27	0.64	0.61	1.10	0.57	0.19
IVb	1.10	0.71	0.55	0.00	0.46	0.59	0.36	0.65	0.72
Vc	0.93	0.79	0.79	4.60	4.87	5.23	5.13	4.97	5.12
VIb	1.37	1.22	1.08	3.59	2.14	1.21	3.67	1.82	0.81
VIIb	1.50	0.90	0.68	0.05	0.00	0.00	0.00	0.00	0.00
VIIIa	1.42	0.95	0.88	7.24	8.00	8.60	7.27	7.95	8.40

[a] Relative energies in kcal mol⁻¹.

Table S6. Relative total energy of the system $(E_{rel,Tot})$[a], relative energy of the steric $(E_{rel,Lewis})$ and hyperconjugative $(E_{rel,Hyper})$ interactions for the AcAspOMe conformers, taking into account the solvent effects (IEF-PCM), calculated at ωB97X-D/aug-cc-pVTZ.

Conformer	$E_{rel,Tot}$			$E_{rel,Lewis}$			$E_{rel,Hyper}$		
	Isolated	CHCl₃	DMSO	Isolated	CHCl₃	DMSO	Isolated	CHCl₃	DMSO
trans-**Ia**	0.00	0.00	0.00	16.18	13.14	11.79	20.00	15.56	13.07
trans-**IIIb**	3.81	2.43	1.29	0.00	0.00	0.00	0.00	0.00	0.00
trans-**Vc**	3.59	2.28	1.36	16.25	15.64	14.69	16.47	15.79	14.62

[a] Relative energies in kcal mol⁻¹.