Electronic Supplementary Information

Site-specific binding of a water molecule to the sulfa drugs sulfamethoxazole and sulfisoxazole: A laser-desorption isomer-specific UV and IR study

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Table of contents

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Relative energies, RMS values and scaling factors of SMX and SIX conformers

Table S1: Relative energies (kcal/mol) including ZPE correction, RMS values (cm^{-1}) representing the agreement between the scaled calculated harmonic frequencies and the experimental NH stretch frequencies and the scaling factors for the harmonic frequencies of the conformers of the two tautomers of sulfamethoxazole (left) and sulfisoxazole (right). In all cases, the basis set 6-311++G(3df,3pd) was used

SMX	M06-2X	B3LYP	ωB97xD
m-a1	0.00	0.00	0.00
	11	14	15
	0.9517	0.9581	0.9468
m-a3	3.12	2.85	3.29
	19	21	20
	0.9468	0.9532	0.9421
m-i1	10.58	8.37	10.77
	12	3	12
	0.9541	0.9631	0.9502
m-i2	10.49	8.91	10.72
	11	14	10
	0.9542	0.9609	0.9504
m-i3	13.18	11.05	13.45
	20	22	20
	0.9504	0.9583	0.9454

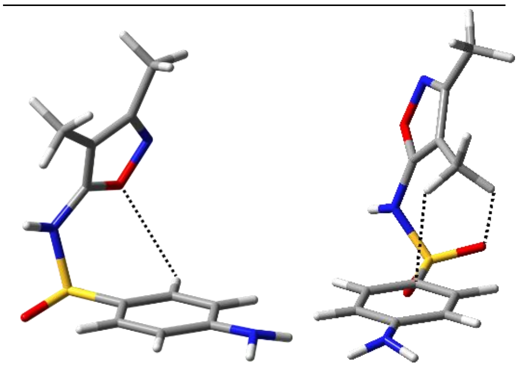

Figure S1: i-a7 (left) and i-a6 (right)

SIX	M06-2X	B3LYP	ωB97xD
i-a1	0.00	0.00	0.00
	7	8	11
	0.9574	0.9578	0.9457
i-a2	1.82	2.41	1.57
	4	3	9
	0.9534	0.9601	0.9479
i-a4	2.15	not conv.	1.81
	16		22
	0.9510		0.9457
i-a5	not conv	not conv	not conv
i-a6	2.94		
	14	not conv.	not conv.
	0.9506		
i-a7		2.60	
	not conv.	21	not conv.
		0.9552	
i-i1	14.11	10.76	14.10
	4	6	4
	0.9566	0.9646	0.9512
i-i2	13.40	11.61	13.85
	3	5	6
	0.9556	0.9639	0.9505
i-i3	13.80	11.47	13.99
	7	9	3
	0.9571	0.9651	0.9518
i-i4	14.22	11.94	14.34
	5	5	5
	0.9574	0.9650	0.9521

Table S2: Relative energies (kcal/mol) including ZPE correction, RMS values (cm^{-1}) representing the agreement between the scaled calculated harmonic frequencies and the experimental NH stretch frequencies and the scaling factors for the harmonic frequencies of the conformers of the two tautomers of sulfamethoxazole using M05-2X in combination with three different basis sets

SMX	6-31+G(d)	6-311++G(d,p)	6-311++G(3df,3pd)
m-a1	0.00	0.00	0.00
	1	3	9
	0.9440	0.9427	0.9424
m-a2	2.04	2.20	
	5	4	not conv.
	0.9455	0.9440	
m-a3	3.52	3.65	3.38
	21	20	20
	0.9391	0.9382	0.9376
m-i1	10.31	9.64	9.92
	7	2	9
	0.9456	0.9458	0.9450
m-i2	10.59	9.99	9.90
	13	3	9
	0.9450	0.9449	0.9450
m-i3	12.98	12.55	12.60
	22	22	21
	0.9407	0.9398	0.9402
m-i4		12.79	12.93
	not conv.	21	21
		0.9396	0.9400

Table S3: Relative energies (kcal/mol) including ZPE correction, RMS values (cm^{-1}) representing the agreement between the scaled calculated harmonic frequencies and the experimental NH stretch frequencies and the scaling factors for the harmonic frequencies of the conformers of the two tautomers of sulfisoxazole using M05-2X in combination with three different basis sets

SIX	6-31+G(d)	6-311++G(d,p)	6-311++G(3df,3pd)
i-a1	0.00	0.00	0.00
	2	5	5
	0.9434	0.9415	0.9415
i-a2	1.66	1.91	1.98
	10	10	3
	0.9464	0.9447	0.9442
i-a3	2.19	2.59	
	2	4	not conv.
	0.9427	0.9410	
i-a4	2.79	3.15	2.62
	12	11	16
	0.9435	0.9417	0.9417
i-a5	3.40	3.68	4.10
	13	12	6
	0.9461	0.9442	0.9442
i-i1	14.55	14.24	13.63
	1	4	1
	0.9473	0.9459	0.9465
i-i2	14.74	14.35	13.27
	2	2	3
	0.9466	0.9449	0.9456
i-i3	14.62	14.49	13.52
	5	8	2
	0.9479	0.9466	0.9469
i-i4	15.16	14.91	13.93
	2	5	0
	0.9483	0.9469	0.9470

Table S4: Relative energies (kcal mol^{-1}) of SMX and SIX conformers calculated at different non-DFT levels of theory. All energies are given without zero-point energy correction. Turbomole[1] was used for the RICC2 calculations

	ΔE^a MP2/6-311++G(d,p) single-point energy	ΔE^a sos-RICC2/TZVPP single-point energy	ΔE sos-RICC2/TZVPP geometry optimization
SMX			
m-a1	0.00	0.00	0.00
m-a2	2.69	2.06	2.11
m-a3	5.08	3.75	3.73
SIX			
i-a1	0.00	0.00	0.00
i-a2	1.59	1.96	1.95
i-a3	3.66	2.98	2.80

^{a} Single-point energies on the M05-2X/6-311++G(d,p) equilibrium geometries.

Table S5: Dihedral angles ω, θ, and τ of the SMX conformer **m-a1** and the four SMX crystal polymorphs. The dihedral angles are defined in Fig. 1 of the main text

	ω	θ	τ
SMX **m-a1**	−86.4	−60.5	134.4
polymorph I[2,a]	−76.6	−56.1	140.8
polymorph II[2,b]	−78.6	−61.6	150.8
polymorph III[3,c]	−70.3	−61.1	152.4
polymorph IV[3,d]	−72.7	−65.7	161.6

CSD Refcodes: ^{a}SLFNMB01, ^{b}SLFNMB02, ^{c}SLFNMB05, ^{d}SLFNMB06.

Relative energies, RMS values and interaction energies of the monohydrated complexes of SMX and SIX

Table S6: BSSE and ZPE-corrected relative energies, RMS values (cm⁻¹) and scaling factors for the harmonic frequencies, sum of intermolecular EML energies, and complexation energies (kcal/mol) of the monohydrated complexes of sulfamethoxazole. The complexation energies are given in parentheses (raw/corrected). mid = 6-311++G(d,p); big = 6-311++G(3df,3pd). Not conv. = converged to different structure during geometry optimization

	M05-2X			M06-2X		B3LYP		ωB97xD	
	mid	big	big*	mid	big	mid	big	mid	big
m-a1wa	0.00, 8, 0.9408, −11.77 (−12.46/−11.39)	0.00, 10, 0.9418, −11.83 (−10.79/−10.29)	0.00, 12, 0.9413 (−10.79/−10.31)	0.00, 18[a], 0.9447, −12.36 (−12.73/−11.70)	0.00, 18[a], 0.9465, −12.23 (−11.09/−10.54)	0.00**, 11, 0.9605, −10.48 (−9.77/−8.72)	0.00, 13, 0.9616, −10.98 (−8.73/−8.27)	0.00, 17, 0.9445 (−12.69/−11.60)	0.00, 16, 0.9463 (−11.11/−10.57)
m-a1wb	0.04, 15[a], 0.9376, −12.51 (−12.52/−11.32)	0.27, 14[a], 0.9380, −12.61 (−10.63/−10.05)	0.27, 15[a], 0.9373, (−10.57/−10.01)	0.04, 25[a], 0.9412, −12.92 (−12.69/−11.52)	0.22, 25[a], 0.9427, −12.86 (−10.87/−10.24)	0.67, 15[a], 0.9547, −10.99 (−9.34/−8.28)	0.94, 14[a], 0.9552, −10.70 (−7.87/−7.33)	0.62, 22[a], 0.9400 (−11.76/−10.64)	1.09, 18[a], 0.9412 (−10.10/−9.48)
m-a1wc	0.82, 20[a], 0.9402, −10.25 (−11.45/−10.17)	not calc.	0.66, 23[a], 0.9408 (−10.11/−9.44)	0.51, 20[a], 0.9437, −10.58 (−12.10/−10.75)	not calc.	0.47**, 10, 0.9595, −10.33 (−9.09/−8.08)	not calc.	0.68, 16[a], 0.9437 (−11.68/−10.44)	not calc.
m-a3wa	2.78, 13, 0.9391, −12.55 (−12.94/−11.83)	not calc.	2.93, 23, 0.9382, (−11.26/−10.72)	2.78, 19[a], 0.9425, −12.74 (−12.96/−11.81)	not calc.	2.47, 9, 0.9572, −11.60 (−10.11/−9.05)	not calc.	3.41, 20, 0.9424 (−12.27/−11.17)	not calc.
m-a1wf	3.05, 57[a], 0.9335, −4.18 (−9.97/−8.83)	not calc.	2.86, 58[a], 0.9326 (−7.91/−7.40)	2.92, 60[a], 0.9390, −6.53 (−10.96/−9.75)	not calc.	not conv.	not calc.	3.11, 57[a], 0.9351 (−9.05/−7.94)	not calc.
m-a1we	not conv.	not calc.	not calc.	2.74, 63[a], 0.9373, −5.68 (−10.39/−9.14)	not calc	not conv.	not calc.	not conv.	not calc.
m-a1wg	3.65, 63[a], 0.9341, −6.58 (−9.48/−8.33)	not calc.	not calc.	3.63, 64[a], 0.9382, −7.53 (−9.95/−8.71)	not calc.	not conv.	not calc.	3.84, 65[a], 0.9367 (−9.51/−8.36)	not calc.
m-a1wh	not conv.	not calc.	not calc.	not conv.	not calc.	3.67, 56[a], 0.9430, −5.02 (−4.43/−3.88)	not calc.	not conv.	not calc.
m-a1wd	2.98, 56[a], 0.9259, −4.65 (−7.99/−6.67)	not calc.	not calc.	2.88, 56[a], 0.9303, −4.92 (−8.48/−7.10)	not calc.	4.21, 57[a], 0.9420, −2.98 (−4.37/−3.31)	not calc.	3.20, 57[a], 0.9274 (−7.91/−6.64)	not calc.
m-a1wi	5.37, 46[a], 0.9309, −8.06 (−8.96/−7.62)	not calc.	5.65, 52[a], 0.9307 (−7.55/−6.95)	5.68, 46[a], 0.9352, −9.77 (−9.35/−7.93)	not calc.	4.44, 47[a], 0.9481, −7.50 (−6.42/−5.51)	not calc.	5.93, 49[a], 0.9328 (−8.93/−7.58)	not calc.
m-i3wa	10.94, 41[b], 0.9427, −12.37 (−14.15/−12.83)	not calc.	11.19, 48, 0.9429 (−12.20/−11.72)	11.56, 31, 0.9462, −12.55 (−14.30/−12.94)	not calc.	9.66, 35[b], 0.9623, −11.67 (−11.66/−10.44)	not calc.	11.61, 40, 0.9466 (−14.31/−12.99)	not calc.
m-i3wb	11.08, 45[b], 0.9448, −13.15 (−14.88/−13.71)	not calc.	10.86, 50[b], 0.9450 (−13.27/−12.79)	11.42, 40, 0.9485, −13.40 (−15.06/−13.87)	not calc.	not conv.	not calc.	11.39, 45[b], 0.9493 (−15.16/−13.87)	not calc.
m-i3wc	14.04, 78[a,d], 0.9296, −9.19 (−11.10/−9.77)	not calc.	13.91, 71[a,d], 0.9303 (−9.67/−9.16)	14.34, 70[a,d], 0.9343, −9.66 (−11.51/−10.27)	not calc.	not conv.	not calc.	14.84, 68[a,d], 0.9341 (−11.31/−10.09)	not calc.

* CP at every step of geometry optimization; ** no CH⋯O or OH⋯π interaction as compared to the structures optimized with the other DFT functionals. [a] transitions (sym. OH and asym. anilinic NH) or [b] sym. OH and sym. anilinic NH or [d] asym. anilinic NH and sulf./heterocycle-NH in wrong order. RMS actually higher

Table S7: BSSE and ZPE-corrected relative energies, RMS values (cm^{-1}) and scaling factors for the harmonic frequencies, sum of intermolecular EML energies, and complexation energies (kcal/mol) of the monohydrated complexes of sulfisoxazole. The complexation energies are given in parentheses (raw/corrected). mid = 6-311++G(d,p); big = 6-311++G(3df,3pd). Not conv. = converged to different structure during geometry optimization

	M05-2X		M06-2X		B3LYP		ωB97xD	
	mid	big	mid	big	mid	big	mid	big
i-a1wb	0.00, 8, 0.9413, −12.52 (−12.32/−11.17)	0.00, 6, 0.9417, −12.61 (−10.49/−9.91)	0.35, 18, 0.9446, −12.90 (−12.56/−11.34)	0.00, 18, 0.9460, −12.90 (−10.73/−10.12)	0.00, 9[a], 0.9589, −11.17 (−9.48/−8.38)	0.00, 8[a], 0.9548, −10.86 (−7.99/−7.45)	0.29, 19, 0.9442 (−11.76/−10.58)	0.00, 13, 0.9453 (−10.03/−9.42)
i-a1wc	0.18, 71[a,d], 0.9451, −9.19 (−13.28/−12.19)	not calc.	0.00, 70[d], 0.9496, 10.45 (−13.89/−12.71)	not calc.	1.53, 76[a], 0.9614, −5.99 (−10.12/−9.18)	not calc.	0.00, 70[a,d], 0.9485 (−13.65/−12.53)	not calc.
i-a1wa	1.47, 21, 0.9371, −9.94 (−10.20/−9.02)	1.30, 24, 0.9375, −9.19 (−8.58/−8.01)	1.52, 32, 0.9414, -10.70 (−10.54/−9.30)	1.27, 35, 0.9426, −9.94 (−8.91/−8.29)	1.21, 23, 0.9541, −8.60 (−7.69/−6.57)	1.08, 22, 0.9548, −7.78 (−6.42/−5.93)*	1.55, 32, 0.9394 (−9.97/−8.78)	1.05, 30, 0.9406 (−8.57/−7.95)
i-a1wd	1.91, 64, 0.9401, −7.69 (−10.61/−9.49)	not calc.	1.93, 59, 0.9446, 8.66 (−11.22/−10.04)	not calc.	not conv.	not calc.	1.35, 69, 0.9435 (−11.07/−9.93)	not calc.
i-a1we	not conv.	not calc.	not conv.	not calc.	1.29, 68[a], 0.9540, 6.46 (−6.64/−6.08)	not calc.	not conv.	not calc.
i-a1wf	2.07, 27, 0.9385, −9.48 (−10.45/−9.05)	not calc.	1.89, 32, 0.9421, −9.88 (−11.06/−9.63)	not calc.	1.31, 26, 0.9525, −8.03 (−7.18/−6.15)	not calc.	2.04, 30, 0.9405 (−10.31/−8.79)	not calc.
i-a2wac	2.22, 51, 0.9362, −9.45 (−11.88/−10.56)	not calc.	1.76, 49, 0.9401, −10.35 (−12.52/−11.14)	not calc.	3.61, 49, 0.9525, −5.78 (−8.12/−6.91)	not calc.	1.76, 55, 0.9375 (−11.48/−10.19)	not calc.
i-a2wb	2.23, 31, 0.9444, −11.74 (−11.50/−10.33)	not calc.	2.25, 38, 0.9478, −11.76 (−11.66/−10.42)	not calc.	2.14, 38, 0.9634, −11.42 (−9.51/−8.29)	not calc.	1.79, 36, 0.9465, (−11.11/−9.95)	not calc.
i-i1wa	10.84, 29[a], 0.9459, −13.80 (−16.85/−15.68)	not calc.	11.57, 26[a], 0.9497, −14.47 (−17.08/−15.86)	not calc.	8.54, 27[a], 0.9625, −11.29 (−13.47/−12.40)	not calc.	11.99, 31[a], 0.9478 (−16.09/−14.90)	not calc.
i-i1wb	16.03, 61, 0.9367, −8.34 (−10.36/−9.01)	not calc.	not conv.	not calc.	not conv.	not calc.	16.16, 62, 0.9386 (−10.24/−8.90)	not calc.
i-i2wa	16.38, 58, 0.9365, −5.59 (−9.43/−8.06)	not calc.	16.38, 51, 0.9414, −5.80 (−9.80/−8.42)	not calc.	not conv.	not calc.	15.98, 58, 0.9394 (−9.89/−8.53)	not calc.
i-i2wb	17.74, 51, 0.9358, −5.74 (−8.05/−6.93)	not calc.	17.91, 43, 0.9413, −6.40 (−8.29/−7.14)	not calc.	14.81, 54[a], 0.9546, −4.14 (−6.37/−5.14)	not calc.	17.45, 53, 0.9386, (−7.96/−6.98)	not calc.
i-i2wc	18.87, 68, 0.9364, −9.42 (−12.04/−10.72)	not calc.	18.84, 62, 0.9409, −9.81 (−12.31/−10.95)	not calc.	17.87, 58, 0.9548, −7.72 (−8.88/−7.62)	not calc.	18.19, 63, 0.9390 (−11.78/−10.40)	not calc.
i-i2wd	19.08, 69, 0.9362, −9.35 (−11.94/−10.62)	not calc.	18.97, 62, 0.9407, −9.79 (−12.21/−10.84)	not calc.	17.93, 59, 0.9542, −7.65 (−8.81/−7.55)	not calc.	18.15, 64, 0.9387 (−11.64/−10.25)	not calc.
i-i2we	21.49, 52, 0.9346, −3.99 (−10.59/−9.21)	not calc.	20.91, 43, 0.9407, −4.33 (−12.59/−11.02)	not calc.	not conv.	not calc.	20.99, 52, 0.9350 (−11.02/−9.56)	not calc.

* no CH···O H-bond; [a] transitions (sym. OH and asym. anilinic NH) or [b] sym. OH and sym. anilinic NH or [d] asym. anilinic NH and sulf.-NH in wrong order. RMS actually higher

Quantum topological key parameters at the bond critical points of the conformers of SMX and SIX

Table S8: Summary of the QTAIM results regarding the non-covalent interactions in the conformers of the amido and imido tautomers of **sulfamethoxazole**. Atomic units are used except for the energy of the hydrogen bonds (kcal/mol). The wave functions were derived at the **B3LYP/6-311++G(3df,3pd)** level of theory for all conformers. All structures were fully optimized at the same level of theory as the wave function used

Interaction	$\rho(\boldsymbol{r}_{BCP})$	$\nabla^2\rho(\boldsymbol{r}_{BCP})$	$V(\boldsymbol{r}_{BCP})$	$G(\boldsymbol{r}_{BCP})$	$H(\boldsymbol{r}_{BCP})$	E_{HB}	*BPL* (Å)
m-a1							
SO···HC	0.0098	0.0361	−0.0064	0.0077	0.0013	−2.01	2.826
m-a3							
N···HC	0.0067	0.0228	−0.0035	0.0046	0.0011	−1.10	3.127
m-i2							
NH···OS	0.0241	0.0986	−0.0186	0.0216	0.0030	−5.84	2.114
m-i1							
NH···OS	0.0241	0.0952	−0.0183	0.0211	0.0028	−5.74	2.104
m-i3							
CH···OS	0.0141	0.0526	−0.0095	0.0113	0.0018	−2.98	2.509

Table S9: Summary of the QTAIM results regarding the non-covalent interactions in the conformers of the amido and imido tautomers of **sulfamethoxazole**. Atomic units are used except for the energy of the hydrogen bonds (kcal/mol). The wave functions were derived at the **M05-2X/6-311++G(3df,3pd)** level of theory for all conformers but **m-a2**. The wave function for **m-a2** was derived at the **M05-2X/6-311++G(df,pd)** level of theory. All structures were fully optimized at the same level of theory as the wave function used

Interaction	$\rho(\boldsymbol{r}_{BCP})$	$\nabla^2\rho(\boldsymbol{r}_{BCP})$	$V(\boldsymbol{r}_{BCP})$	$G(\boldsymbol{r}_{BCP})$	$H(\boldsymbol{r}_{BCP})$	E_{HB}	*BPL* (Å)
m-a1							
SO···HC	0.0112	0.0419	−0.0079	0.0092	0.0013	−2.48	3.026
m-a2							
CH···CS	0.0075	0.0216	−0.0040	0.0047	0.0007	−1.26	2.984
m-a3							
N···HC[a]	0.0085	0.0296	−0.0048	0.0061	0.0013	−1.51	3.368
m-i2							
NH···OS	0.0256	0.1082	−0.0213	0.0242	0.0029	−6.68	2.096
m-i1							
NH···OS	0.0258	0.1090	−0.0215	0.0244	0.0029	−6.75	2.084
m-i3							
CH···OS	0.0164	0.0634	−0.0119	0.0139	0.0020	−3.73	2.488
m-i4							
CH···OS	0.0169	0.0659	−0.0123	0.0144	0.0021	−3.86	2.463

[a] the bond path does not go to the H atom but the C-atom. However, we assume a H-bond as seen in the results using B3LYP.

Table S10: Summary of the QTAIM results regarding the non-covalent interactions in the conformers of the amido and imido tautomers of **sulfamethoxazole**. Atomic units are used except for the energy of the hydrogen bonds (kcal/mol). The wave functions were derived at the **M06-2X/6-311++G(3df,3pd)** level of theory for all conformers. All structures were fully optimized at the same level of theory as the wave function used

Interaction	$\rho(\boldsymbol{r}_{BCP})$	$\nabla^2\rho(\boldsymbol{r}_{BCP})$	$V(\boldsymbol{r}_{BCP})$	$G(\boldsymbol{r}_{BCP})$	$H(\boldsymbol{r}_{BCP})$	E_{HB}	*BPL* (Å)
m-a1							
SO···HC	0.0113	0.0422	−0.0079	0.0092	0.0013	−2.48	2.889
m-a3							
N···HC[a]	0.0086	0.0301	−0.0049	0.0062	0.0013	−1.54	3.419
m-i2							
NH···OS	0.0245	0.1071	−0.0205	0.0236	0.0031	−6.43	2.106
m-i1							
NH···OS	0.0248	0.1080	−0.0207	0.0238	0.0031	−6.49	2.094
m-i3							
CH···OS	0.0162	0.0649	−0.0118	0.0140	0.0022	−3.07	2.459

[a] the bond path does not go to the H atom but the C-atom. However, we assume a H-bond as seen in the results using B3LYP.

Table S11: Summary of the QTAIM results regarding the non-covalent interactions in the conformers of the amido and imido tautomers of **sulfisoxazole**. Atomic units are used except for the energy of the hydrogen bonds (kcal/mol). The wave functions were derived at the **B3LYP/6-311++G(3df,3pd)** level of theory for all conformers. All structures were fully optimized at the same level of theory as the wave function used

Interaction	$\rho(\boldsymbol{r}_{BCP})$	$\nabla^2\rho(\boldsymbol{r}_{BCP})$	$V(\boldsymbol{r}_{BCP})$	$G(\boldsymbol{r}_{BCP})$	$H(\boldsymbol{r}_{BCP})$	E_{HB}	*BPL* (Å)
i-a1							
CH···OS	0.0064	0.0240	−0.0040	0.0050	0.0010	−1.26	2.9688
i-a2							
CH···CS	0.0042	0.0131	−0.0020	0.0026	0.0006	−0.63	3.1405
i-a7							
CH···ON	0.0047	0.0175	−0.0026	0.0035	0.0009	−0.82	3.3060
i-i1	no non-covalent interaction present						
i-i2							
CH···OS[a]	0.0096	0.0317	−0.0059	0.0069	0.0010	−1.85	2.6343
CH···OS[b]	0.0097	0.0315	−0.0059	0.0069	0.0010	−1.85	2.6036
i-i3	no non-covalent interaction present						
i-i4	no non-covalent interaction present						

[a] opposite side of heterocycle N-H atom; [b] same side

Table S12: Summary of the QTAIM results regarding the non-covalent interactions in the conformers of the amido and imido tautomers of **sulfisoxazole**. Atomic units are used except for the energy of the hydrogen bonds (kcal/mol). The wave functions were derived at the **M05-2X/6-311++G(3df,3pd)** level of theory for all conformers but i-a3. The wave function for i-a3 was derived at the **M05-2X/6-311++G(d,p)** level of theory. All structures were fully optimized at the same level of theory as the wave function used

Interaction	$\rho(\boldsymbol{r}_{BCP})$	$\nabla^2\rho(\boldsymbol{r}_{BCP})$	$V(\boldsymbol{r}_{BCP})$	$G(\boldsymbol{r}_{BCP})$	$H(\boldsymbol{r}_{BCP})$	E_{HB}	*BPL* (Å)
i-a1							
CH···OS	0.0081	0.0316	−0.0056	0.0067	0.0011	−1.76	3.1582
i-a2							
CH···CS	0.0068	0.0211	−0.0036	0.0045	0.0009	−1.13	3.0138
CH···CH	0.0055	0.0175	−0.0029	0.0036	0.0007	−0.91	3.2055
i-a3							
CH···OS	0.0078	0.0276	−0.0051	0.0060	0.0009	−1.60	2.8265
i-a4							
CH···CH	0.0050	0.0150	−0.0026	0.0032	0.0006	−0.82	3.3093
i-a5	no non-covalent interaction present						
i-i1	no non-covalent interaction present						
i-i2							
CH···OS[a]	0.0119	0.0406	−0.0079	0.0090	0.0011	−2.48	2.5646
CH···OS[b]	0.0119	0.0395	−0.0077	0.0088	0.0011	−2.42	2.5147
i-i3	no non-covalent interaction present						
i-i4	no non-covalent interaction present						

[a] opposite side of heterocycle N-H atom; [b] same side

Table S13: Summary of the QTAIM results regarding the non-covalent interactions in the conformers of the amido and imido tautomers of **sulfisoxazole**. Atomic units are used except for the energy of the hydrogen bonds (kcal/mol). The wave functions were derived at the **M06-2X/6-311++G(3df,3pd)** level of theory for all conformers. All structures were fully optimized at the same level of theory as the wave function used

Interaction	$\rho(\boldsymbol{r}_{BCP})$	$\nabla^2\rho(\boldsymbol{r}_{BCP})$	$V(\boldsymbol{r}_{BCP})$	$G(\boldsymbol{r}_{BCP})$	$H(\boldsymbol{r}_{BCP})$	E_{HB}	*BPL* (Å)
i-a1							
CH···OS[a]	0.0086	0.0335	−0.0060	0.0072	0.0012	−1.88	3.3749
i-a2							
CH···CS	0.0066	0.0209	−0.0035	0.0043	0.0008	−1.10	3.3783
CH···CH	0.0066	0.0199	−0.0034	0.0042	0.0008	−1.07	3.1133
i-a4							
CH···CH	0.0060	0.0176	−0.0031	0.0038	0.0007	−0.97	3.0676
CH···CS[a]	0.0059	0.0194	−0.0032	0.0040	0.0008	−1.00	3.7777
i-a6							
CH···CS	0.0079	0.0238	−0.0041	0.0050	0.0009	−1.29	2.9890
CH···OS	0.0066	0.0230	−0.0043	0.0050	0.0007	−1.35	2.9928
i-i1	no non-covalent interaction present						
i-i2							
CH···OS[b]	0.0118	0.0411	−0.0079	0.0091	0.0012	−2.48	2.5624
CH···OS[c]	0.0119	0.0401	−0.0078	0.0089	0.0011	−2.45	2.4988
i-i3	no non-covalent interaction present						
i-i4	no non-covalent interaction present						

[a] bond path actually goes to the C atom. However, we assume that it is a tracing error (cf. B3LYP results). [b] opposite side of heterocycle N-H atom; [c] same side

Potential energy scans and transition states

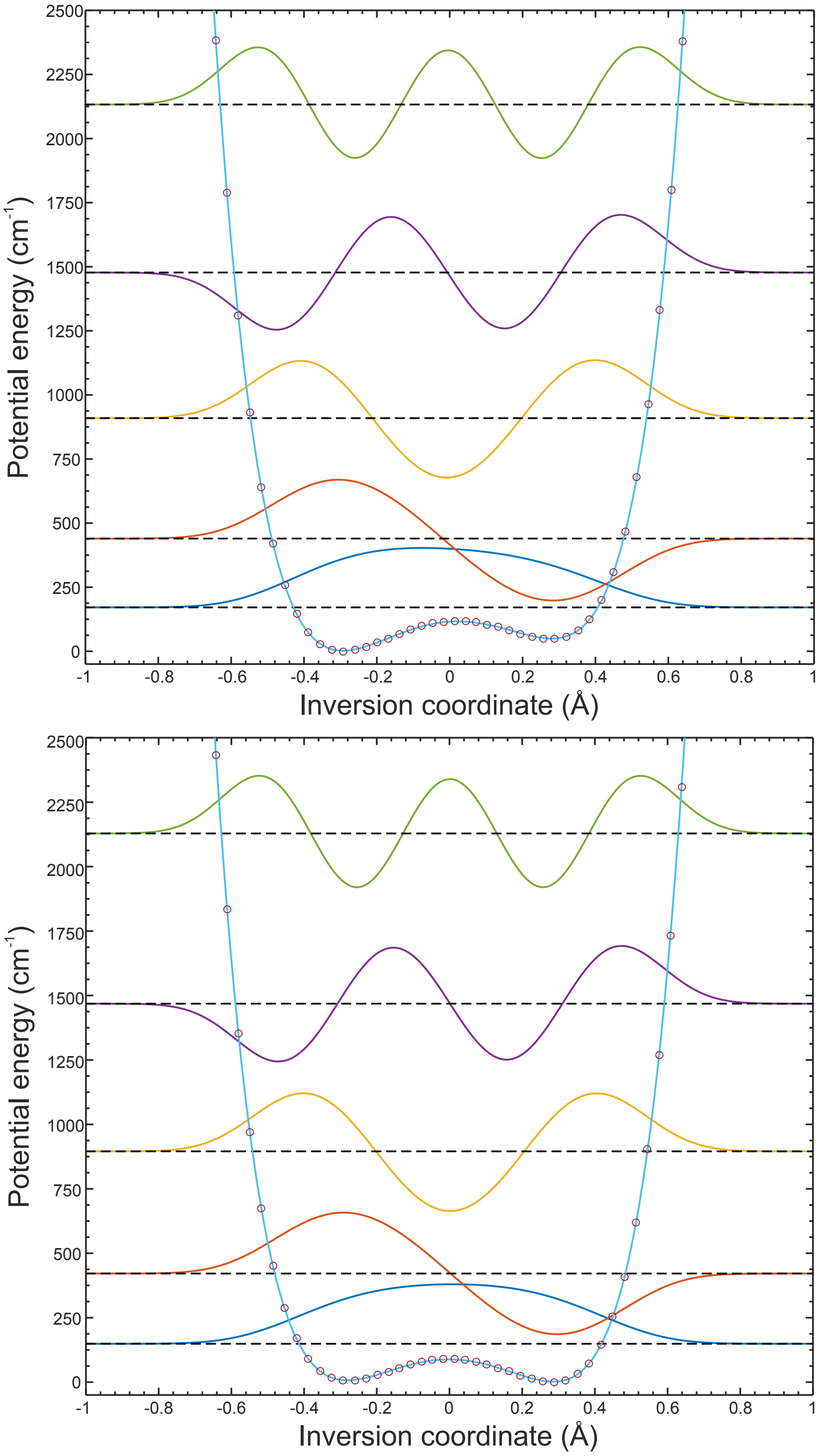

Figure S2: Inversion potential (M05-2X/6-311++G(3df,3pd)) for the anilinic group in SMX (top) and SIX (bottom). The inversion coordinate is given as the distance along the line that intersects both the CN bond direction at right angle and the midpoint between the two hydrogen atoms. A negative value for the inversion coordinate translates to the hydrogen atoms being on the same side of the phenyl plane as the oxygen atoms of the sulfonamide group. The reduced masses used were 1.234 amu and 1.223 amu, respectively. The vibrational eigenvalues and eigenfunctions of the potential energy curves were determined numerically using the Numerov method[4,5].

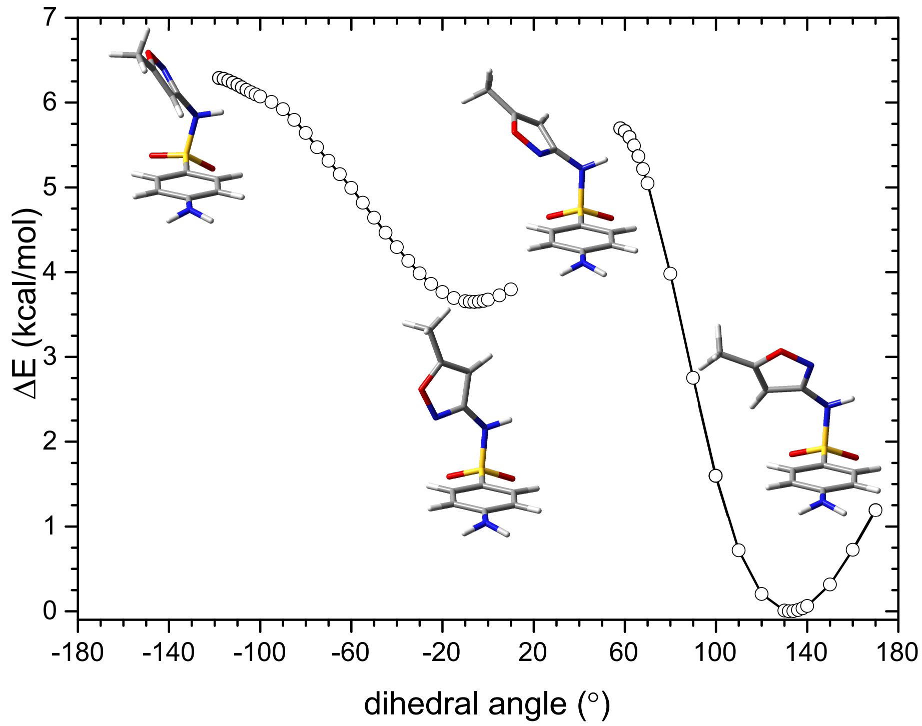

Figure S3: Relaxed potential energy scan connecting the conformers m-a3 and m-a1 of sulfamethoxazole. The N-C-N-S dihedral angle was scanned. The structures of the minima and transition states are given. M05-2X/6-311++G(3df,3pd) was used for all calculations.

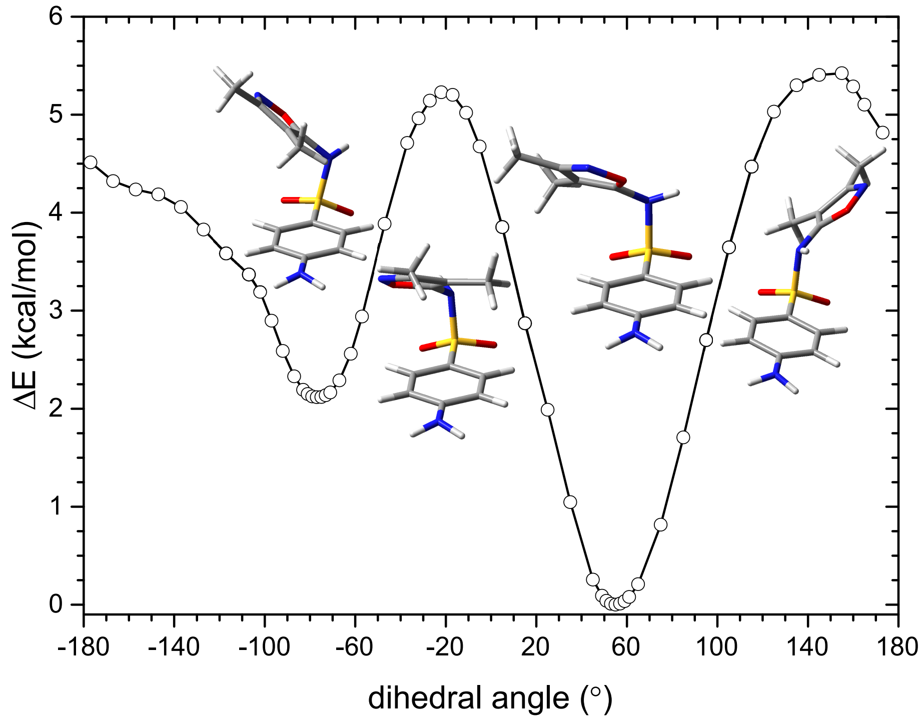

Figure S4: Relaxed potential energy scan connecting the conformers i-a2 and i-a1 of sulfisoxazole. The C-N-S-C dihedral angle was scanned. The structures of the minima and transition states are given. M05-2X/6-311++G(3df,3pd) was used for all calculations.

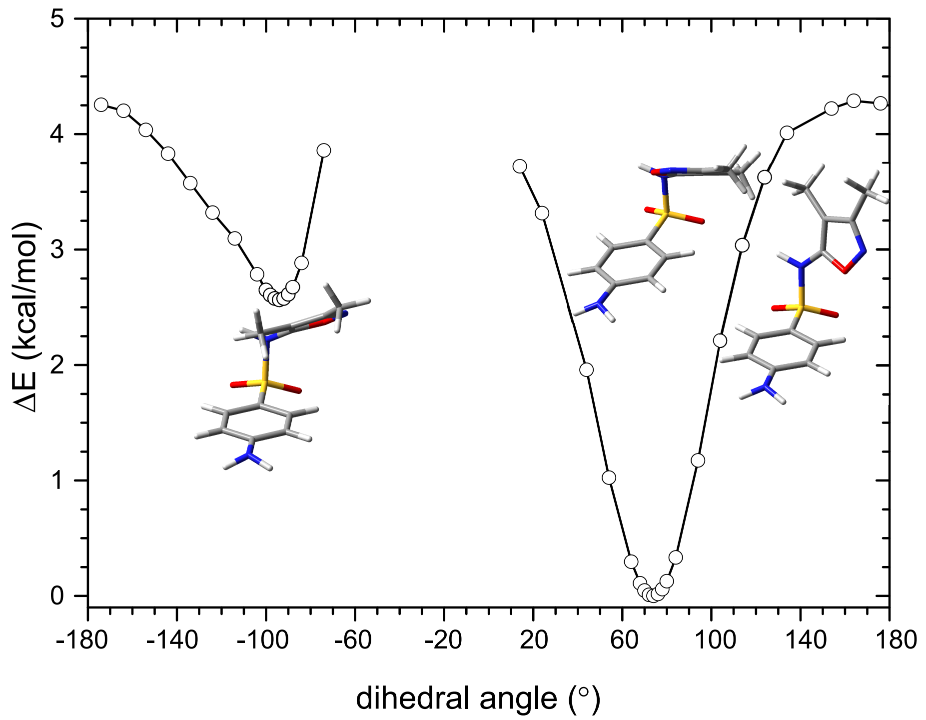

Figure S5: Relaxed potential energy scan connecting the conformers i-a4 and i-a1 of sulfisoxazole. The C-C-N-S dihedral angle was scanned. The structures of the minima and transition states are given. M05-2X/6-311++G(3df,3pd) was used for all calculations.

Molecular graphs of all calculated monohydrated complexes of SMX and SIX

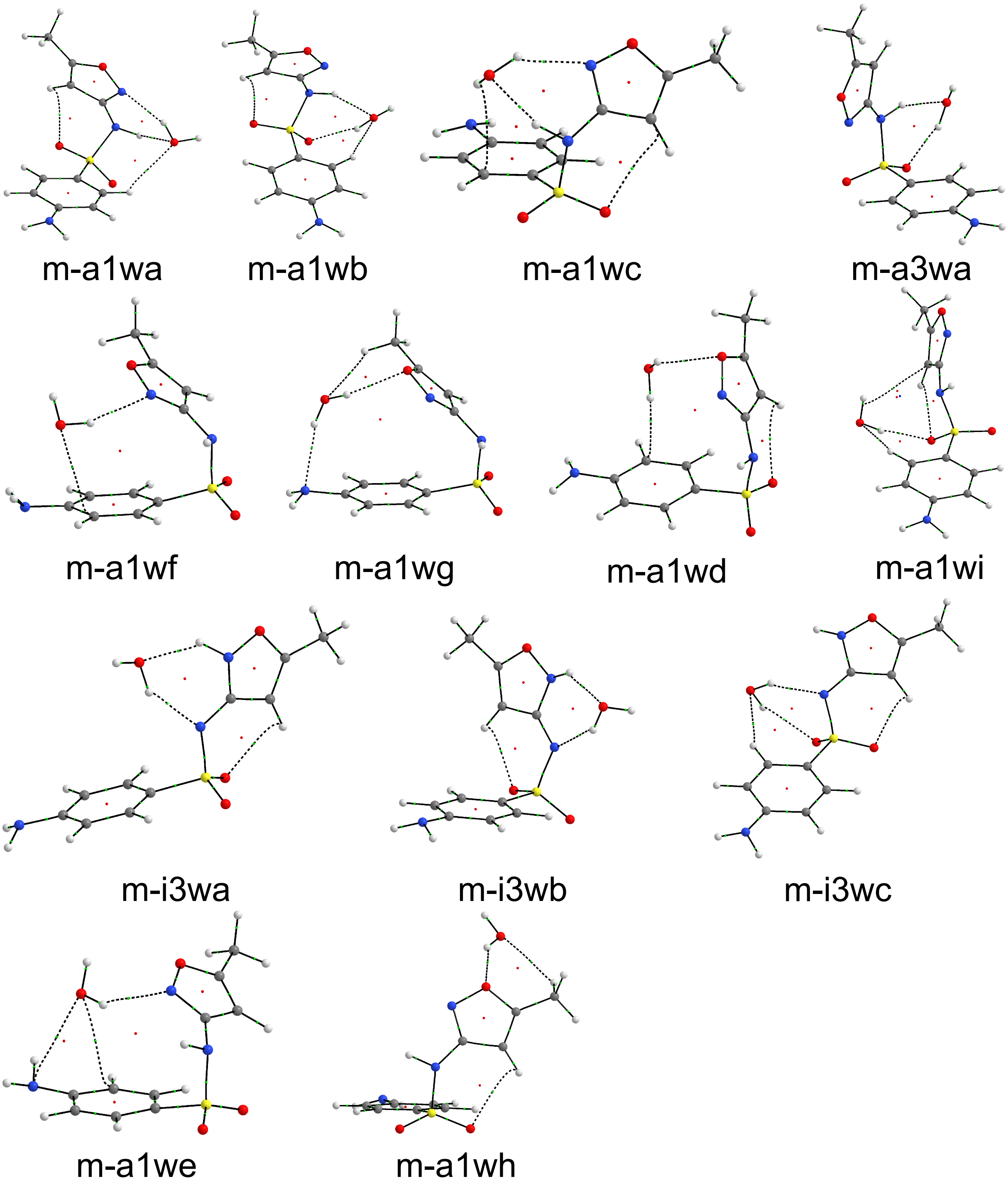

Figure S6: The molecular graphs of all SMX isomers. All geometries were optimized using M05-2X/6-311++G(d,p) unless for the last two isomers that were only stable using M06-2X or B3LYP, respectively.

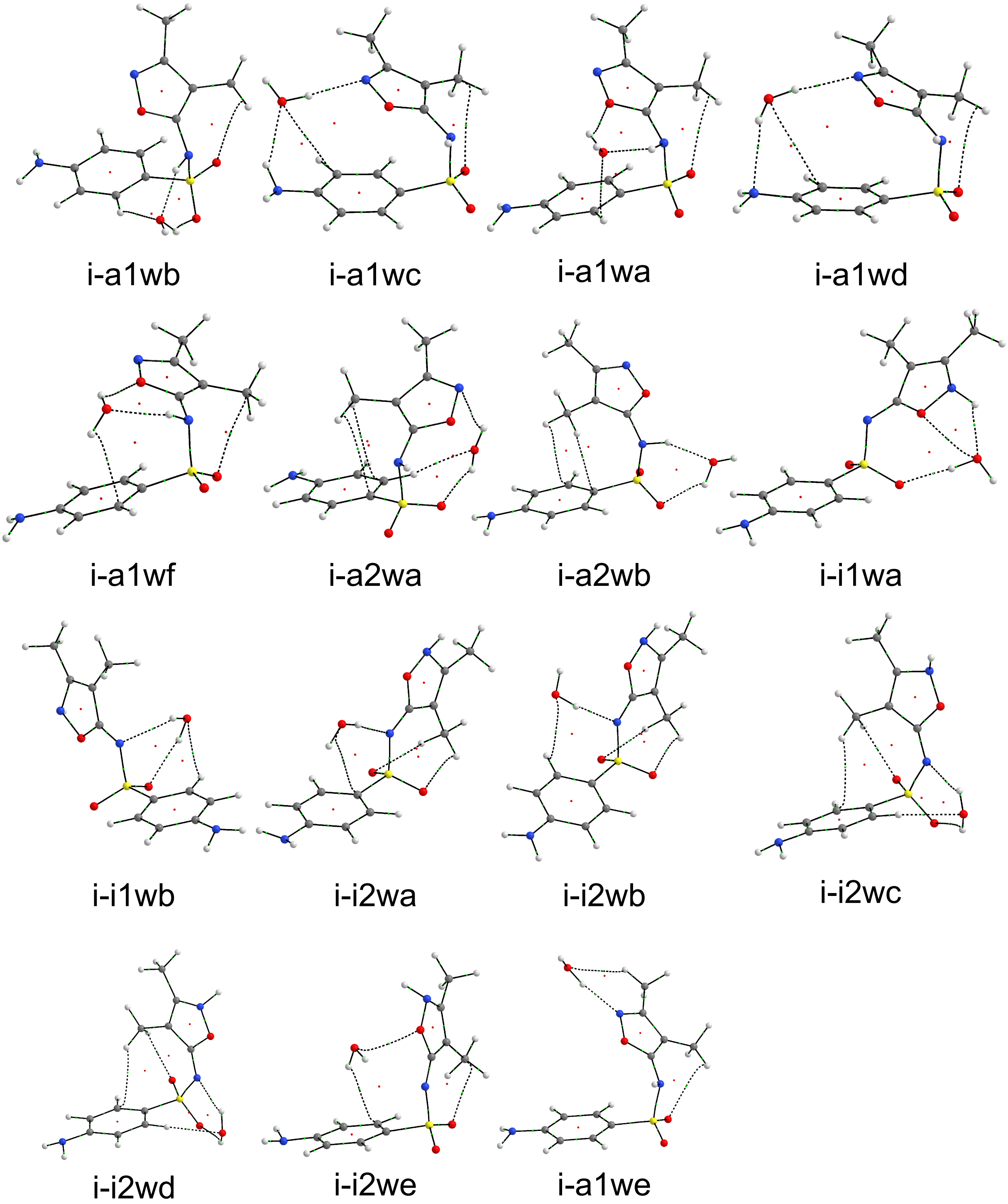

Figure S7: The molecular graphs of all SIX isomers. All geometries were optimized using M05-2X/6-311++G(d,p) unless for the last isomer that was only stable using B3LYP.

Tentative assignment of the R2PI spectra of SMX and SIX

The most prominent vibronic progressions in the RIDIR spectra of the SMX and SIX monomers are based on an S_1 excited state vibration with a frequency of $+72\,\mathrm{cm}^{-1}$ and $+69\,\mathrm{cm}^{-1}$, respectively. Using harmonic S_1 state frequencies calculated at the TD-B3LYP/6-31+G(d) and CIS/6-31+G(d) level of theory, we tentatively assign the asymmetric butterfly motion with a calculated unscaled frequency of $80\,\mathrm{cm}^{-1}$ (CIS: $66\,\mathrm{cm}^{-1}$) in SMX and $63\,\mathrm{cm}^{-1}$ (CIS: $75\,\mathrm{cm}^{-1}$) in SIX as the origin of these progressions. Additionally, we observed a very prominent vibronic progression built upon a mode with a frequency of $+34\,\mathrm{cm}^{-1}$ in the R2PI spectrum of SIX. Based on our S_1 state harmonic frequency calculations at the CIS/6-31+G(d) and TD-B3LYP/6-31+G(d) levels of theory, we tentatively suggest that this transition is either due to a normal mode consisting of γ(NH2) and τ(N–heterocycle) (CIS: $32\,\mathrm{cm}^{-1}$) or a normal mode consisting of τ(N–heterocycle) and τ(S–phenyl) (TD-B3LYP: $35\,\mathrm{cm}^{-1}$). A similar transition is present in the R2PI spectrum of SIX at $+31\,\mathrm{cm}^{-1}$ but with much lower relative intensity. Therefore, only in the R2PI spectrum of SIX a hot band originating from the corresponding vibrationally excited ground state is present $-33\,\mathrm{cm}^{-1}$ red-shifted with respect to the electronic origin. Assuming a Boltzmann distribution and using the integrated intensities of the transitions at $+34\,\mathrm{cm}^{-1}$ and $-33\,\mathrm{cm}^{-1}$ the vibrational temperature of SIX under our experimental conditions is estimated to be 21 K. The very same pattern ($+34\,\mathrm{cm}^{-1}$ and $+69\,\mathrm{cm}^{-1}$ as well as $+31\,\mathrm{cm}^{-1}$ and $+72\,\mathrm{cm}^{-1}$) as around the electronic origin can be observed $+815\,\mathrm{cm}^{-1}$ (for SIX) and $+816\,\mathrm{cm}^{-1}$ (for SMX) blue-shifted as combination bands, building the same vibronic progression upon a vibration tentatively assigned to a mode similar to mode 1, sometimes denoted as mode 12, of aniline. This aniline normal mode mainly consists of three in-phase stretching contributions, namely $\nu(C_1\text{–}N)$, $\nu(C_1\text{–}C_2)$ and $\nu(C_1\text{–}C_6)$. The assignment was based on harmonic frequency calculations and comparison to published and assigned vibronic spectra of aniline's S_1 ($^1B_2$) excited state.[6,7] Depending on the theoretical method and the molecule the mode has some contribution from ν(NO), γ(CH) or inversion at the sulfonamide nitrogen atom. The unscaled harmonic frequencies are for SMX $842\,\mathrm{cm}^{-1}$ (CIS and TD-B3LYP), and for SIX $849\,\mathrm{cm}^{-1}$ (CIS) and $835\,\mathrm{cm}^{-1}$ (TD-B3LYP).

Quantum topological key parameters at the bond critical points of the monohydrated complexes of SMX and SIX

Table S14: Summary of the QTAIM results regarding the non-covalent interactions in the isomers of the amido and imido tautomers of **sulfamethoxazole–H_2O**. Atomic units are used except for the energy of the hydrogen bonds (kcal/mol). The geometries were optimized and the wave functions were derived at the **M05-2X/6-311++G(d,p)** level of theory

Interaction	$\rho(\boldsymbol{r}_{\mathrm{BCP}})$	$\nabla^2\rho(\boldsymbol{r}_{\mathrm{BCP}})$	$V(\boldsymbol{r}_{\mathrm{BCP}})$	$G(\boldsymbol{r}_{\mathrm{BCP}})$	$H(\boldsymbol{r}_{\mathrm{BCP}})$	E_{HB}	$\sum_i E_{\mathrm{HB}}^{\mathrm{inter,i}}$	*BPL* (Å)
m-a1wa								
CH···OS	0.0107	0.0380	−0.0071	0.0083	0.0012	−2.23		2.7663
NH···O(w)	0.0221	0.0848	−0.0166	0.0189	0.0023	−5.21		2.0362
CH$_{\mathrm{pheny}}$···O(w)	0.0073	0.0247	−0.0045	0.0053	0.0008	−1.41	−11.77	2.6400
OH(w)···NO	0.0228	0.0824	−0.0164	0.0185	0.0021	−5.15		2.0729
m-a1wb								
CH···OS	0.0106	0.0379	−0.0071	0.0083	0.0012	−2.23		2.7712
NH···O(w)	0.2100	0.0815	−0.0155	0.0179	0.0024	−4.86		2.0490
CH$_{\mathrm{pheny}}$ ···O(w)	0.0086	0.0291	−0.0052	0.0063	0.0011	−1.63	−12.51	2.4873
OH(w)···OS	0.0234	0.0952	−0.0192	0.0215	0.0023	−6.02		2.0135
m-a1wc								
CH···OS[b]	0.0118	0.0444	−0.0082	0.0097	0.0015	−2.57		3.1670
NH···O(w)	0.0199	0.0712	−0.0141	0.0160	0.0019	−4.42		2.1248
OH(w)···CH$_{\mathrm{phenyl}}$	0.0071	0.0226	−0.0038	0.0047	0.0009	−1.19	−10.25	2.9380
OH(w)···NO	0.0211	0.0761	−0.0148	0.0169	0.0021	−4.64		2.1186
m-a3wa								
NH···O(w)	0.0229	0.0907	−0.0174	0.0201	0.0027	−5.46	−12.55	1.9957
OH(w)···OS	0.0265	0.1070	−0.0226	0.0247	0.0021	−7.09		1.9432
m-a1wf								
OH(w)···NO	0.0145	0.0516	−0.0085	0.0107	0.0022	−2.67	−4.18	2.2504
O(w)··· CH$_{\mathrm{phenyl}}$[c]	0.0077	0.0289	−0.0048	0.0060	0.0012	−1.51		3.4614
m-a1wg								
$_{\mathrm{methyl}}$CH···O(w)	0.0062	0.0212	−0.0039	0.0046	0.0007	−1.22		2.6930
OH(w)···ON	0.0128	0.0492	−0.0089	0.0106	0.0017	−2.79	−6.58	2.2666
OH(w)···NH_2	0.0141	0.0466	−0.0082	0.0099	0.0017	−2.57		2.3155
m-a1wd								
CH···OS	0.0104	0.0373	−0.0069	0.0081	0.0012	−2.16		2.9082
OH(w)···ON	0.0135	0.0489	−0.0100	0.0111	0.0011	−3.14	−4.65	2.3450
OH(w)···CH$_{\mathrm{phenyl}}$	0.0103	0.0315	−0.0048	0.0064	0.0016	−1.51		2.5026
m-a1wi								
CH···OS	0.0122	0.0437	−0.0084	0.0096	0.0012	−2.64		2.6409
CH$_{\mathrm{phenyl}}$···O(W)	0.0114	0.0362	−0.0066	0.0078	0.0012	−2.07		2.3866
OH(w)···OS	0.0218	0.0874	−0.0173	0.0196	0.0023	−5.43	−8.06	2.0202
OH(w)···CH[c]	0.0034	0.0121	−0.0018	0.0024	0.0006	−0.56		3.9494
m-i3wa								
CH···OS	0.0143	0.0528	−0.0100	0.0116	0.0016	−3.14		2.5768
NH···O(w)	0.0238	0.0970	−0.0186	0.0214	0.0028	−5.84	−12.37	1.9933
OH(w)···NS	0.0272	0.0915	−0.0208	0.0218	0.0010	−6.53		1.9968
m-i3wb								
CH···OS	0.0160	0.0603	−0.0113	0.0132	0.0019	−3.55		2.4501
NH···O(w)	0.0246	0.0992	−0.0193	0.0221	0.0028	−6.06	−13.15	1.9873
OH(w)···NS	0.0291	0.0947	−0.0226	0.0231	0.0005	−7.09		1.9708
m-i3wc								
CH···OS	0.0176	0.0687	−0.0127	0.0149	0.0022	−3.98		2.3777
CH$_{\mathrm{phenyl}}$···O(w)	0.0101	0.0300	−0.0058	0.0066	0.0008	−1.82		2.4699
OH(w)···OS	0.0142	0.0508	−0.0105	0.0116	0.0011	−3.29	−9.19	2.3500
OH(w)···NS	0.0193	0.0666	−0.0130	0.0148	0.0018	−4.08		2.1680

[b] bond path goes actually to the C atom; [c] bond path O↔C

Table S15: Summary of the QTAIM results regarding the non-covalent interactions in the isomers of the amido and imido tautomers of **sulfisoxazole–H_2O**. Atomic units are used except for the energy of the hydrogen bonds (kcal/mol). The geometries were optimized and the wave functions were derived at the **M05-2X/6-311++G(d,p)** level of theory

Interaction	$\rho(\boldsymbol{r}_{\mathrm{BCP}})$	$\nabla^2\rho(\boldsymbol{r}_{\mathrm{BCP}})$	$V(\boldsymbol{r}_{\mathrm{BCP}})$	$G(\boldsymbol{r}_{\mathrm{BCP}})$	$H(\boldsymbol{r}_{\mathrm{BCP}})$	E_{HB}	$\sum_i E_{\mathrm{HB}}^{\mathrm{inter,i}}$	*BPL* (Å)
i-a1wb								
$_{methyl}$CH···OS	0.0083	0.0316	−0.0056	0.0068	0.0012	−1.76		3.0489
NH···O(w)	0.0214	0.0834	−0.0159	0.0184	0.0025	−4.99		2.0371
CH$_{phenyl}$···O(w)	0.0070	0.0234	−0.0043	0.0051	0.0008	−1.35	−12.52	2.6039
OH(w)···OS	0.0239	0.0973	−0.0197	0.0220	0.0023	−6.18		2.0009
i-a1wc								
$_{methyl}$CH···OS[b]	0.0074	0.0292	−0.0051	0.0062	0.0011	−1.60		3.3817
CH$_{phenyl}$···O(w)[b]	0.0063	0.0250	−0.0041	0.0052	0.0011	−1.29		3.4196
NH$_{anilinic}$···O(w)	0.0153	0.0552	−0.0104	0.0121	0.0017	−3.26	−9.19	2.2469
OH(w)···NO	0.0221	0.0775	−0.0148	0.0171	0.0023	−4.64		2.0598
i-a1wa								
$_{methyl}$CH···OS[b]	0.0084	0.0327	−0.0058	0.0070	0.0012	−1.82		3.4081
NH···O(w)	0.0219	0.0861	−0.0166	0.0191	0.0025	−5.21		2.0328
CH$_{phenyl}$···O(w)	0.0055	0.0201	−0.0032	0.0041	0.0009	−1.00	−9.94	3.1100
OH(w)···ON	0.0158	0.0650	−0.0119	0.0141	0.0022	−3.73		2.2051
i-a1wd								
$_{methyl}$CH···OS	0.0072	0.0271	−0.0047	0.0058	0.0011	−1.47		3.1559
CH$_{phenyl}$···O(w)[b,f]	0.0062	0.0211	−0.0036	0.0044	0.0008	−1.13		3.3050
OH(w)···NH_2	0.0137	0.0450	−0.0084	0.0098	0.0014	−2.64	−7.69	2.3506
OH(w)···NO	0.0196	0.0708	−0.0125	0.0151	0.0026	−3.92		2.1131
i-a1wf								
$_{methyl}$CH···OS[b]	0.0081	0.0340	−0.0058	0.0072	0.0014	−1.82		3.0809
NH···O(w)	0.0195	0.0694	−0.0137	0.0155	0.0018	−4.30		2.1387
OH(w)···CH$_{phenyl}$	0.0081	0.0254	−0.0044	0.0054	0.0010	−1.38	−9.48	2.8050
OH(w)···ON	0.0161	0.0684	−0.0121	0.0141	0.0020	−3.80		2.1998
i-a2wa								
$_{methyl}$CH···CS	0.0059	0.0188	−0.0032	0.0040	0.0008	−1.00		3.3799
$_{methyl}$CH···CH$_{phenyl}$	0.0059	0.0168	−0.0029	0.0035	0.0006	−0.91		3.3833
CH$_{phenyl}$···O(w)	0.0118	0.0403	−0.0070	0.0085	0.0015	−2.20		2.3427
OH(w)···OS	0.0201	0.0846	−0.0158	0.0185	0.0027	−4.96	−9.45	2.0355
OH(w)···NO	0.0118	0.0398	−0.0073	0.0086	0.0013	−2.29		2.4214
i-a2wb								
$_{methyl}$CH···CS	0.0064	0.0194	−0.0033	0.0041	0.0008	−1.04		3.1684
$_{methyl}$CH···CH$_{phenyl}$	0.0056	0.0165	−0.0028	0.0035	0.0007	−0.88		3.1221
NH···O(w)	0.0255	0.0968	−0.0200	0.0221	0.0021	−6.28	−11.74	1.9617
OH(w)···OS	0.0217	0.0852	−0.0174	0.0194	0.0020	−5.46		2.0598
i-i1wa								
NH···O(w)	0.0191	0.0756	−0.0141	0.0165	0.0024	−4.42		2.1286
OH(w)···OS	0.0229	0.0950	−0.0183	0.0210	0.0027	−5.74	−13.80	1.9562
OH(w)···ON[c]	0.0139	0.0626	−0.0116	0.0136	0.0020	−3.64		2.7284
i-i1wb								
CH$_{phenyl}$···O(w)	0.0060	0.0189	−0.0035	0.0041	0.0006	−1.10		2.7738
OH(w)···OS	0.0179	0.0658	−0.0134	0.0149	0.0015	−4.20	−8.34	2.1571
OH(w)···NS	0.0151	0.0479	−0.0097	0.0108	0.0011	−3.04		2.3503
i-i2wa								
$_{methyl}$CH···OS[d]	0.0118	0.0388	−0.0076	0.0087	0.0011	−2.38		2.5060
$_{methyl}$CH···OS[e]	0.0120	0.0397	−0.0078	0.0089	0.0011	−2.45		2.5103
OH(w)···CS[f]	0.0070	0.0228	−0.0041	0.0049	0.0008	−1.29	−5.59	3.5700
OH(w)···NS	0.0205	0.0724	−0.0137	0.0159	0.0022	−4.30		2.1095
i-i2wb								
$_{methyl}$CH···OS[d]	0.0121	0.0400	−0.0079	0.0089	0.0010	−2.48		2.4917
$_{methyl}$CH···OS[e]	0.0120	0.0396	−0.0078	0.0089	0.0011	−2.45		2.5093
CH$_{phenyl}$···O(w)	0.0057	0.0227	−0.0034	0.0046	0.0012	−1.07	−5.74	3.1715
OH(w)···NS	0.0217	0.0757	−0.0149	0.0169	0.0020	−4.67		2.0891

Table S15 (*continued*): Summary of the QTAIM results regarding the non-covalent interactions in the isomers of the amido and imido tautomers of **sulfisoxazole–H_2O**. Atomic units are used except for the energy of the hydrogen bonds (kcal/mol). The geometries were optimized and the wave functions were derived at the **M05-2X/6-311++G(d,p)** level of theory

i-i2wc								
$_{\mathrm{methyl}}$CH···OS	0.0150	0.0560	−0.0106	0.0123	0.0017	−3.33		2.4718
$_{\mathrm{methyl}}$CH···CH$_{\mathrm{phenyl}}$	0.0077	0.0222	−0.0037	0.0047	0.0010	−1.16		2.8466
CH$_{\mathrm{phenyl}}$···O(w)	0.0109	0.0327	−0.0063	0.0072	0.0009	−1.98		2.4308
OH(w)···OS	0.0148	0.0528	−0.0109	0.0121	0.0012	−3.42	−9.42	2.3085
OH(w)···NS	0.0187	0.0644	−0.0128	0.0144	0.0016	−4.02		2.1982
i-i2wd								
$_{\mathrm{methyl}}$CH···OS	0.0151	0.0556	−0.0105	0.0122	0.0017	−3.29		2.4458
$_{\mathrm{methyl}}$CH···CH$_{\mathrm{phenyl}}$	0.0079	0.0227	−0.0038	0.0047	0.0009	−1.19		2.8670
CH$_{\mathrm{phenyl}}$···O(w)	0.0108	0.0321	−0.0062	0.0071	0.0009	−1.95		2.4399
OH(w)···OS	0.0150	0.0539	−0.0111	0.0123	0.0012	−3.48	−9.35	2.2908
OH(w)···NS	0.0184	0.0634	−0.0125	0.0142	0.0017	−3.92		2.2080
i-i2we								
$_{\mathrm{methyl}}$CH···OS[b]	0.0154	0.0662	−0.0121	0.0143	0.0022	−3.80		2.9283
OH(w)···CH$_{\mathrm{phenyl}}$	0.0078	0.0238	−0.0040	0.0050	0.0010	−1.26	−3.99	2.7506
OH(w)···ON[c]	0.0113	0.0453	−0.0087	0.0100	0.0013	−2.73		2.9888

[b] bond path goes to the C atom; [c] bond path connects O atoms; [d, e] same/opposite side as heterocycle H atom from NH group, resp.; [f] bond path goes to the O atom

Table S16: Summary of the QTAIM results regarding the non-covalent interactions in the isomers of the amido and imido tautomers of **sulfamethoxazole–H_2O**. Atomic units are used except for the energy of the hydrogen bonds (kcal/mol). The geometries were optimized and the wave functions were derived at the **B3LYP/6-311++G(d,p)** level of theory

Interaction	$\rho(\boldsymbol{r}_{\mathrm{BCP}})$	$\nabla^2\rho(\boldsymbol{r}_{\mathrm{BCP}})$	$V(\boldsymbol{r}_{\mathrm{BCP}})$	$G(\boldsymbol{r}_{\mathrm{BCP}})$	$H(\boldsymbol{r}_{\mathrm{BCP}})$	E_{HB}	$\sum_i E_{\mathrm{HB}}^{\mathrm{inter,i}}$	*BPL* (Å)
m-a1wa								
CH···OS	0.0104	0.0375	−0.0067	0.0081	0.0014	−2.10		2.6876
NH···O(w)	0.0237	0.0838	−0.0170	0.0190	0.0020	−5.33	−10.48	2.0097
OH(w)···NO	0.0239	0.0806	−0.0164	0.0183	0.0019	−5.15		2.0588
m-a1wb								
CH···OS	0.0094	0.0334	−0.0060	0.0072	0.0012	−1.88		2.7701
NH···O(w)	0.0206	0.0739	−0.0142	0.0163	0.0021	−4.46		2.0684
CH$_{\mathrm{pheny}}$···O(w)	0.0060	0.0203	−0.0036	0.0043	0.0007	-1.13	−10.99	2.6529
OH(w)···OS	0.0225	0.0865	−0.0172	0.0194	0.0022	−5.40		2.0275
m-a1wc								0
CH···OS	0.0109	0.0395	−0.0071	0.0085	0.0014	−2.23		2.6771
NH···O(w)	0.0222	0.0804	−0.0158	0.0179	0.0021	-4.96	−10.33	2.0299
OH(w)···NO	0.0245	0.0830	−0.0171	0.0189	0.0018	−5.37		2.0450
m-a3wa								
$_{\mathrm{phenyl}}$CH···ON	0.0066	0.0225	−0.0034	0.0045	0.0011	−1.07		3.1485
NH···O(w)	0.0245	0.0887	−0.0178	0.0200	0.0022	−5.58	−11.60	1.9788
OH(w)···OS	0.0246	0.0924	−0.0192	0.0212	0.0020	−6.02		1.9850
m-a1wh								
CH···OS	0.0095	0.0346	−0.0061	0.0074	0.0013	−1.91		2.8044
$_{\mathrm{methyl}}$CH···O(w)	0.0058	0.0208	−0.0036	0.0044	0.0008	−1.13	−5.02	2.6909
OH(w)···ON	0.0178	0.0705	−0.0124	0.0150	0.0026	−3.89		2.0903
m-a1wd								
CH···OS	0.0090	0.0333	−0.0058	0.0071	0.0013	−1.82		3.0113
OH(w)···ON	0.0110	0.0381	−0.0072	0.0084	0.0012	−2.26	−2.98	2.3630
OH(w)··· CH$_{\mathrm{phenyl}}$	0.0055	0.0147	−0.0023	0.0030	0.0007	−0.72		2.8704
m-a1wi								
CH···OS	0.0095	0.0335	−0.0061	0.0072	0.0011	−1.91		2.7257
CH$_{\mathrm{phenyl}}$···O(W)	0.0116	0.0397	−0.0068	0.0084	0.0016	−2.13	−7.50	2.3444
OH(w)···OS	0.0226	0.0896	−0.0171	0.0198	0.0027	−5.37		1.9791
m-i3wa								
CH···OS	0.0132	0.0476	−0.0087	0.0103	0.0016	−2.73		2.5395
NH···O(w)	0.0247	0.0918	−0.0182	0.0206	0.0024	−5.71	−11.67	1.9926
OH(w)···NS	0.0269	0.0837	−0.0190	0.0199	0.0009	−5.96		2.0115

Table S17: Summary of the QTAIM results regarding the non-covalent interactions in the isomers of the amido and imido tautomers of **sulfamethoxazole–H_2O**. Atomic units are used except for the energy of the hydrogen bonds (kcal/mol). The geometries were optimized and the wave functions were derived at the **M06-2X/6-311++G(d,p)** level of theory

Interaction	$\rho(\boldsymbol{r}_{\mathrm{BCP}})$	$\nabla^2\rho(\boldsymbol{r}_{\mathrm{BCP}})$	$V(\boldsymbol{r}_{\mathrm{BCP}})$	$G(\boldsymbol{r}_{\mathrm{BCP}})$	$H(\boldsymbol{r}_{\mathrm{BCP}})$	E_{HB}	$\sum_i E_{\mathrm{HB}}^{\mathrm{inter,i}}$	*BPL* (Å)
m-a1wa								
CH···OS	0.0107	0.0379	−0.0071	0.0083	0.0012	−2.23		2.7557
NH···O(w)	0.0227	0.0889	−0.0175	0.0198	0.0023	−5.49		2.0212
CH$_{pheny}$···O(w)	0.0083	0.0280	−0.0051	0.0060	0.0009	−1.60	−12.36	2.5840
OH(w)···NO	0.0229	0.0845	−0.0168	0.0189	0.0021	−5.27		2.0669
m-a1wb								
CH···OS	0.0108	0.0386	−0.0072	0.0084	0.0012	−2.26		2.7409
NH···O(w)	0.0215	0.0848	−0.0162	0.0184	0.0022	−5.08		2.0363
CH$_{pheny}$···O(w)	0.0095	0.0328	−0.0059	0.0070	0.0011	−1.85	−12.92	2.4418
OH(w)···OS	0.0230	0.0957	−0.0191	0.0215	0.0024	−5.99		2.0193
m-a1wc								
CH···OS[b]	0.0117	0.0444	−0.0082	0.0097	0.0015	−2.57		3.1686
NH···O(w)	0.0199	0.0723	−0.0143	0.0162	0.0019	−4.49		2.1262
OH(w)···CH$_{phenyl}$	0.0078	0.0251	−0.0043	0.0053	0.0010	−1.35	−10.58	2.9034
OH(w)···NO	0.0211	0.0778	−0.0151	0.0173	0.0022	−4.74		2.1148
m-a3wa								
$_{phenyl}$CH···ON[b]	0.0085	0.0292	−0.0047	0.0060	0.0013	−1.47		3.1833
NH···O(w)	0.0235	0.0947	−0.0184	0.0210	0.0026	−5.77	−12.74	1.9812
OH(w)···OS	0.0259	0.1072	−0.0222	0.0245	0.0023	−6.97		1.9495
m-a1wf								
$_{anilinic}$NH···O(w)[c]	0.0084	0.0305	−0.0058	0.0067	0.0009	−1.82		3.2331
OH(w)···NO	0.0154	0.0554	−0.0093	0.0116	0.0023	−2.92	−6.53	2.2249
O(w)··· CH$_{phenyl}$[b]	0.0089	0.0349	−0.0057	0.0072	0.0015	−1.79		3.2408
m-a1we								
$_{anilinic}$NH···O(w)[c]	0.0077	0.0289	−0.0054	0.0063	0.0009	−1.69		3.2179
OH(w)···NO	0.0120	0.0417	−0.0071	0.0088	0.0017	−2.23	−5.68	2.3602
O(w)··· CH$_{phenyl}$[b]	0.0090	0.0338	−0.0056	0.0070	0.0014	−1.76		3.1504
m-a1wg								
$_{methyl}$CH···O(w)	0.0078	0.0273	−0.0049	0.0059	0.0010	−1.54		2.5730
OH(w)···ON	0.0144	0.0564	−0.0104	0.0122	0.0018	−3.26	−7.53	2.2225
OH(w)···NH_2	0.0144	0.0488	−0.0087	0.0104	0.0017	−2.73		2.3032
m-a1wd								
CH···OS	0.0106	0.0380	−0.0071	0.0083	0.0012	−2.23		2.8150
OH(w)···ON	0.0139	0.0510	−0.0105	0.0116	0.0011	−3.29	−4.92	2.3749
OH(w)··· CH$_{phenyl}$	0.0105	0.0336	−0.0052	0.0068	0.0016	−1.63		2.5226
m-a1wi								
CH···OS	0.0125	0.0448	−0.0086	0.0099	0.0013	−2.70		2.6284
CH$_{phenyl}$···O(W)	0.0119	0.0383	−0.0071	0.0083	0.0012	−2.23		2.3693
OH(w)···OS	0.0217	0.0873	−0.0173	0.0196	0.0023	−5.43	−9.77	2.0264
OH(w)···CH	0.0049	0.0165	−0.0026	0.0034	0.0008	−0.82		3.1100
OH(w)···NS[d]	0.0064	0.0209	−0.0041	0.0047	0.0006	−1.29		3.3643
m-i3wa								
CH···OS	0.0148	0.0558	−0.0104	0.0122	0.0018	−3.26		2.5233
NH···O(w)	0.0244	0.1010	−0.0195	0.0224	0.0029	−6.12	−12.55	1.9768
OH(w)···NS	0.0267	0.0925	−0.0205	0.0218	0.0013	−6.43		2.0016
m-i3wb								
CH···OS	0.0155	0.0588	−0.0109	0.0128	0.0019	−3.42		2.4615
NH···O(w)	0.0253	0.1033	−0.0203	0.0230	0.0027	−6.37	−13.40	1.9710
OH(w)···NS	0.0286	0.0959	−0.0224	0.0232	0.0008	−7.03		1.9742
m-i3wc								
CH···OS	0.0167	0.0655	−0.0120	0.0142	0.0022	−3.77		2.3982
CH$_{phenyl}$···O(w)	0.0107	0.0326	−0.0063	0.0072	0.0009	−1.98		2.4392
OH(w)···OS	0.0140	0.0505	−0.0105	0.0116	0.0009	−3.29	−9.66	2.3863
OH(w)···NS	0.0201	0.0717	−0.0140	0.0159	0.0019	−4.39		2.1380

[b] bond path goes to the C atom; [c] bond path goes to the N atom; [d] bond path connects O and N

Table S18: Summary of the QTAIM results regarding the non-covalent interactions in the isomers of the amido and imido tautomers of **sulfisoxazole–H_2O**. Atomic units are used except for the energy of the hydrogen bonds (kcal/mol). The geometries were optimized and the wave functions were derived at the **B3LYP/6-311++G(d,p)** level of theory

Interaction	$\rho(\boldsymbol{r}_{\mathrm{BCP}})$	$\nabla^2\rho(\boldsymbol{r}_{\mathrm{BCP}})$	$V(\boldsymbol{r}_{\mathrm{BCP}})$	$G(\boldsymbol{r}_{\mathrm{BCP}})$	$H(\boldsymbol{r}_{\mathrm{BCP}})$	E_{HB}	$\sum_i E_{\mathrm{HB}}^{\mathrm{inter,i}}$	*BPL* (Å)
i-a1wb								
$_{\mathrm{methyl}}$CH⋯OS	0.0066	0.0235	−0.0041	0.0050	0.0009	−1.29		2.8681
NH⋯O(w)	0.0215	0.0774	−0.0150	0.0172	0.0022	−4.71		2.0461
CH$_{\mathrm{phenyl}}$⋯O(w)	0.0047	0.0162	−0.0028	0.0034	0.0006	−0.88	−11.17	2.7827
OH(w)⋯OS	0.0231	0.0885	−0.0178	0.0199	0.0021	−5.58		2.0128
i-a1we								
$_{\mathrm{methyl}}$CH⋯OS	0.0065	0.0238	−0.0041	0.0050	0.0009	−1.29		2.9271
$_{\mathrm{methyl}}$CH⋯O(w)	0.0047	0.0171	−0.0028	0.0035	0.0007	−0.88	−6.46	2.8737
OH(w)⋯NO	0.0260	0.0851	−0.0178	0.0196	0.0018	−5.58		2.0037
i-a1wc								
$_{\mathrm{methyl}}$CH⋯OS	0.0051	0.0191	−0.0031	0.0039	0.0008	−0.97		3.0938
$_{\mathrm{anilinic}}$NH…O(w)	0.0106	0.0350	−0.0066	0.0077	0.0011	−2.07	−5.99	2.4435
OH(w)⋯NO	0.0208	0.0676	−0.0125	0.0147	0.0022	−3.92		2.0993
i-a1wa								
$_{\mathrm{methyl}}$CH⋯OS	0.0075	0.0270	−0.0047	0.0057	0.0010	−1.47		2.8294
NH⋯O(w)	0.0227	0.0828	−0.0164	0.0185	0.0021	−5.15		2.0204
CH$_{\mathrm{phenyl}}$⋯O(w)	0.0019	0.0076	−0.0009	0.0014	0.0005	−0.28	−8.60	3.7423
OH(w)⋯ON	0.0143	0.0551	−0.0101	0.0119	0.0018	−3.17		2.2606
i-a1wf								
$_{\mathrm{methyl}}$CH⋯OS	0.0069	0.0255	−0.0044	0.0054	0.0010	−1.38		2.9321
NH⋯O(w)	0.0219	0.0832	−0.0159	0.0184	0.0025	−4.99	−8.03	2.0221
OH(w)⋯ON	0.0138	0.0541	−0.0097	0.0116	0.0019	−3.04		2.2820
i-a2wa								
CH$_{\mathrm{phenyl}}$⋯O(w)	0.0091	0.0288	−0.0051	0.0062	0.0011	−1.60		2.4779
OH(w)⋯OS	0.0196	0.0785	−0.0144	0.0170	0.0026	−4.52	−5.78	2.0437
OH(w)⋯NO	0.0072	0.0228	−0.0040	0.0049	0.0009	−1.26		2.6573
i-a2wb								
$_{\mathrm{methyl}}$CH⋯CS	0.0042	0.0120	−0.0020	0.0025	0.0005	−0.63		3.1543
NH⋯O(w)	0.0266	0.0918	−0.0197	0.0213	0.0016	−6.18	−11.42	1.9536
OH(w)⋯OS	0.0219	0.0824	−0.0167	0.0186	0.0019	−5.24		2.0484
i-i1wa								
NH⋯O(w)	0.0170	0.0624	−0.0115	0.0136	0.0021	−3.61		2.1808
OH(w)⋯OS	0.0206	0.0796	−0.0147	0.0173	0.0026	−4.61	−11.29	2.0110
OH(w)⋯ON[c]	0.0122	0.0536	−0.0098	0.0116	0.0018	−3.07		2.7872
i-i2wb								
$_{\mathrm{methyl}}$CH⋯OS[d]	0.0101	0.0318	−0.0062	0.0071	0.0009	−1.95		2.5659
$_{\mathrm{methyl}}$CH⋯OS[e]	0.0101	0.0325	−0.0062	0.0072	0.0010	−1.95		2.5911
OH(w)⋯NS	0.0211	0.0684	−0.0132	0.0151	0.0019	−4.14	−4.14	2.1050
i-i2wc								
$_{\mathrm{methyl}}$CH⋯HC$_{\mathrm{methyl}}$	0.0090	0.0343	−0.0051	0.0068	0.0017	−1.60		2.5138
$_{\mathrm{methyl}}$CH⋯OS	0.0140	0.0511	−0.0093	0.0110	0.0017	−2.92		2.4492
$_{\mathrm{methyl}}$CH⋯CH$_{\mathrm{phenyl}}$	0.0047	0.0138	−0.0022	0.0028	0.0006	−0.69		2.9948
CH$_{\mathrm{phenyl}}$⋯O(w)	0.0092	0.0254	−0.0050	0.0057	0.0007	−1.57		2.5251
OH(w)⋯OS	0.0098	0.0334	−0.0067	0.0075	0.0008	−2.10	−7.72	2.5870
OH(w)⋯NS	0.0201	0.0653	−0.0129	0.0146	0.0017	−4.05		2.1518
i-i2wd								
$_{\mathrm{methyl}}$CH⋯OS	0.0148	0.0537	−0.0098	0.0116	0.0018	−3.07		2.3848
$_{\mathrm{methyl}}$CH⋯CH$_{\mathrm{phenyl}}$	0.0044	0.0132	−0.0020	0.0027	0.0007	−0.63		3.0310
CH$_{\mathrm{phenyl}}$⋯O(w)	0.0089	0.0247	−0.0049	0.0055	0.0006	−1.54		2.5385
OH(w)⋯OS	0.0111	0.0376	−0.0076	0.0085	0.0009	−2.38	−7.65	2.4732
OH(w)⋯NS	0.0189	0.0613	−0.0119	0.0136	0.0017	−3.73		2.1856

[c] bond path connects O atoms; [d, e] same/opposite side as heterocycle H atom from NH group, resp.

Table S19: Summary of the QTAIM results regarding the non-covalent interactions in the isomers of the amido and imido tautomers of **sulfisoxazole–H_2O**. Atomic units are used except for the energy of the hydrogen bonds (kcal/mol). The geometries were optimized and the wave functions were derived at the **M06-2X/6-311++G(d,p)** level of theory

Interaction	$\rho(\boldsymbol{r}_{\text{BCP}})$	$\nabla^2\rho(\boldsymbol{r}_{\text{BCP}})$	$V(\boldsymbol{r}_{\text{BCP}})$	$G(\boldsymbol{r}_{\text{BCP}})$	$H(\boldsymbol{r}_{\text{BCP}})$	E_{HB}	$\sum_i E_{\text{HB}}^{\text{inter,i}}$	*BPL* (Å)
i-a1wb								
$_{\text{methyl}}$CH···OS[b]	0.0088	0.0341	−0.0061	0.0073	0.0012	−1.91		3.3495
NH···O(w)	0.0219	0.0869	−0.0167	0.0192	0.0025	−5.24		2.0239
CH$_{\text{phenyl}}$···O(w)	0.0079	0.0266	−0.0049	0.0058	0.0009	−1.54	−12.90	2.5493
OH(w)···OS	0.0234	0.0976	−0.0195	0.0220	0.0025	−6.12		2.0087
i-a1wc								
$_{\text{methyl}}$CH···OS[b]	0.0079	0.0309	−0.0054	0.0066	0.0012	−1.69		3.2960
CH$_{\text{phenyl}}$···O(w)[b]	0.0076	0.0295	−0.0050	0.0062	0.0012	−1.57		3.4683
NH$_{\text{anilinic}}$···O(w)	0.0167	0.0620	−0.0117	0.0136	0.0019	−3.67	−10.45	2.1987
OH(w)···NO	0.0237	0.0836	−0.0166	0.0187	0.0021	−5.21		2.0278
i-a1wa								
$_{\text{methyl}}$CH···OS[b]	0.0088	0.0347	−0.0062	0.0074	0.0012	−1.95		3.2718
NH···O(w)	0.0226	0.0904	−0.0176	0.0201	0.0025	−5.52		2.0191
CH$_{\text{phenyl}}$···O(w)	0.0066	0.0238	−0.0040	0.0050	0.0010	−1.26	−10.70	3.2129
OH(w)···ON	0.0163	0.0680	−0.0125	0.0147	0.0022	−3.92		2.1869
i-a1wd								
$_{\text{methyl}}$CH···OS[a]	0.0075	0.0289	−0.0051	0.0062	0.0011	−1.60		3.3961
CH$_{\text{phenyl}}$···O(w)[b,f]	0.0074	0.0244	−0.0044	0.0053	0.0009	−1.38		3.2597
OH(w)···NH_2	0.0144	0.0487	−0.0092	0.0107	0.0015	−2.89	−8.66	2.3327
OH(w)···NO	0.0209	0.0765	−0.0140	0.0166	0.0026	−4.39		2.0815
i-a1wf								
$_{\text{methyl}}$CH···OS[b]	0.0088	0.0367	−0.0064	0.0078	0.0014	−2.01		3.0411
NH···O(w)	0.0196	0.0713	−0.0140	0.0159	0.0019	−4.39		2.1348
OH(w)···CH$_{\text{phenyl}}$	0.0083	0.0266	−0.0046	0.0056	0.0010	−1.44	−9.88	2.8737
OH(w)···ON	0.0168	0.0692	−0.0129	0.0151	0.0022	−4.05		2.1735
i-a2wa								
$_{\text{methyl}}$CH···CS	0.0064	0.0198	−0.0034	0.0042	0.0008	−1.07		3.1942
$_{\text{methyl}}$CH···CH$_{\text{phenyl}}$	0.0065	0.0185	−0.0031	0.0039	0.0008	−0.97		3.5200
CH$_{\text{phenyl}}$···O(w)	0.0131	0.0473	−0.0082	0.0100	0.0018	−2.57		2.2855
OH(w)···OS	0.0208	0.0890	−0.0168	0.0195	0.0027	−5.27	−10.35	2.0187
OH(w)···NO	0.0124	0.0434	−0.0080	0.0094	0.0014	−2.51		2.4001
i-a2wb								
$_{\text{methyl}}$CH···CS[b]	0.0065	0.0212	−0.0035	0.0044	0.0009	−1.10		3.8181
$_{\text{methyl}}$CH···CH$_{\text{phenyl}}$	0.0063	0.0184	−0.0032	0.0039	0.0007	−1.00		3.1998
NH···O(w)	0.0258	0.0993	−0.0206	0.0227	0.0021	−6.46	−11.76	1.9571
OH(w)···OS	0.0211	0.0832	−0.0169	0.0188	0.0019	−5.30		2.0768
i-i1wa								
NH···O(w)	0.0194	0.0783	−0.0146	0.0171	0.0025	−4.58		2.1211
OH(w)···OS	0.0236	0.0990	−0.0193	0.0220	0.0027	−6.06	−14.47	1.9414
OH(w)···ON[c]	0.0145	0.0667	−0.0122	0.0144	0.0022	−3.83		2.6997
i-i2wa								
$_{\text{methyl}}$CH···OS[d]	0.0118	0.0390	−0.0076	0.0087	0.0011	−2.38		2.4915
$_{\text{methyl}}$CH···OS[e]	0.0120	0.0405	−0.0079	0.0090	0.0011	−2.48		2.5121
OH(w)···CS[f]	0.0074	0.0244	−0.0044	0.0053	0.0009	−1.38	−5.80	3.5344
OH(w)···NS	0.0207	0.0743	−0.0141	0.0163	0.0022	−4.42		2.1019
i-i2wb								
$_{\text{methyl}}$CH···OS[d]	0.0120	0.0401	−0.0078	0.0089	0.0011	−2.45		2.4833
$_{\text{methyl}}$CH···OS[e]	0.0121	0.0408	−0.0080	0.0091	0.0011	−2.51		2.4971
CH$_{\text{phenyl}}$···O(w)	0.0073	0.0279	−0.0045	0.0058	0.0013	−1.41	−6.40	2.9096
OH(w)···NS	0.0225	0.0795	−0.0159	0.0179	0.0020	−4.99		2.0708
i-i2wc								
$_{\text{methyl}}$CH···OS	0.0149	0.0566	−0.0105	0.0123	0.0017	−3.29		2.4774
$_{\text{methyl}}$CH···CH$_{\text{phenyl}}$	0.0081	0.0241	−0.0040	0.0050	0.0010	−1.26		2.7460
CH$_{\text{phenyl}}$···O(w)	0.0116	0.0357	−0.0069	0.0079	0.0010	−2.16		2.3993
OH(w)···OS	0.0150	0.0545	−0.0112	0.0124	0.0012	−3.51	−9.81	2.2958
OH(w)···NS	0.0189	0.0666	−0.0132	0.0149	0.0017	−4.14		2.1870

Table S19 (*continued*): Summary of the QTAIM results regarding the non-covalent interactions in the isomers of the amido and imido tautomers of **sulfisoxazole–H_2O**. Atomic units are used except for the energy of the hydrogen bonds (kcal/mol). The geometries were optimized and the wave functions were derived at the **M06-2X/6-311++G(d,p)** level of theory

i-i2wd								
$_{methyl}$CH···OS	0.0150	0.0563	−0.0105	0.0123	0.0017	−3.29		2.4513
$_{methyl}$CH···CH$_{phenyl}$	0.0082	0.0244	−0.0040	0.0051	0.0011	−1.26		2.7615
CH$_{phenyl}$···O(w)	0.0115	0.0353	−0.0068	0.0078	0.0010	−2.13		2.4052
OH(w)···OS	0.0153	0.0558	−0.0115	0.0127	0.0012	−3.61	−9.79	2.2761
OH(w)···NS	0.0186	0.0653	−0.0129	0.0146	0.0017	−4.05		2.1988
i-i2we								
$_{methyl}$CH···CH$_{phenyl}$[g]	0.0055	0.0167	−0.0029	0.0035	0.0006	−0.91		2.3577
$_{methyl}$CH···OS[b]	0.0149	0.0649	−0.0118	0.0140	0.0022	−3.70		2.8731
OH(w)···CH$_{phenyl}$	0.0078	0.0236	−0.0038	0.0049	0.0011	−1.19	−4.33	2.9960
OH(w)···ON[c]	0.0126	0.0514	−0.0100	0.0114	0.0014	−3.14		2.8315

[b] bond path goes to the C atom; [c] bond path connects O atoms; [d, e] same/opposite side as heterocycle H atom from NH group, resp.; [f] bond path goes to the O atom; [g] bond path connects the two H atoms

Table S20: Summary of the QTAIM results regarding the non-covalent interactions in the two isomers of the amido tautomers of **sulfamethoxazole–H_2O** studied further with IQA analysis. Atomic units are except unless for the energy of the hydrogen bonds (kcal/mol). The geometries were optimized and the wave functions were derived using **6-311++G(3df,3pd)** as basis set

Interaction	$\rho(\boldsymbol{r}_{\mathrm{BCP}})$	$\nabla^2\rho(\boldsymbol{r}_{\mathrm{BCP}})$	$V(\boldsymbol{r}_{\mathrm{BCP}})$	$G(\boldsymbol{r}_{\mathrm{BCP}})$	$H(\boldsymbol{r}_{\mathrm{BCP}})$	E_{HB}	$\sum_i E_{\mathrm{HB}}^{\mathrm{inter,i}}$	*BPL* (Å)
M05-2X								
m-a1wa								
CH···OS	0.0113	0.0415	−0.0079	0.0091	0.0012	−2.48		2.8578
NH···O(w)	0.0223	0.0834	−0.0176	0.0192	0.0016	−5.52		2.0488
CH$_{pheny}$···O(w)	0.0047	0.0167	−0.0027	0.0034	0.0013	−0.85	−11.83	2.8988
OH(w)···NO	0.0234	0.0818	−0.0174	0.0189	0.0015	−5.46		2.0669
m-a1wb								
CH···OS	0.0114	0.0416	−0.0079	0.0092	0.0013	−2.48		2.8267
NH···O(w)	0.0209	0.0789	−0.0162	0.0179	0.0017	−5.08		2.0701
CH$_{pheny}$···O(w)	0.0075	0.0277	−0.0047	0.0058	0.0011	−1.47	−12.61	2.5396
OH(w)···OS	0.0230	0.0947	−0.0193	0.0215	0.0022	−6.06		2.0127
M06-2X								
m-a1wa								
CH···OS	0.0112	0.0413	−0.0078	0.0090	0.0012	−2.45		2.8319
NH···O(w)	0.0228	0.0883	−0.0182	0.0201	0.0019	−5.71		2.0338
CH$_{pheny}$···O(w)	0.0053	0.0183	−0.0030	0.0038	0.0008	−0.94	−12.23	2.8629
OH(w)···NO	0.0234	0.0850	−0.0178	0.0195	0.0017	−5.58		2.0601
m-a1wb								
CH···OS	0.0114	0.0422	−0.0079	0.0092	0.0013	−2.48		2.7672
NH···O(w)	0.0214	0.0832	−0.0167	0.0188	0.0021	−5.24		2.0542
CH$_{pheny}$···O(w)	0.0082	0.0298	−0.0051	0.0063	0.0012	−1.60	−12.86	2.5037
OH(w)···OS	0.0227	0.0968	−0.0192	0.0217	0.0025	−6.02		2.0149
B3LYP								
m-a1wa								
CH···OS	0.0108	0.0394	−0.0071	0.0085	0.0014	−2.23		2.6948
NH···O(w)	0.0231	0.0780	−0.0169	0.0182	0.0013	−5.30	−10.98	2.0405
OH(w)···NO	0.0252	0.0800	−0.0181	0.0191	0.0010	−5.68		2.0407
m-a1wb								
CH···OS	0.0100	0.0365	−0.0065	0.0078	0.0013	−2.04		2.7633
NH···O(w)	0.0207	0.0720	−0.0148	0.0164	0.0016	−4.64		2.0802
CH$_{pheny}$···O(w)	0.0043	0.0161	−0.0026	0.0033	0.0007	−0.82	−10.70	2.7952
OH(w)···OS	0.0218	0.0841	−0.0167	0.0189	0.0022	−5.24		2.0354

Table S21: Summary of the QTAIM results regarding the non-covalent interactions in the two isomers of the amido tautomers of **sulfisoxazole–H_2O** studied further with IQA analysis. Atomic units are used except for the energy of the hydrogen bonds (kcal/mol).The wave functions were derived using **6-311++G(3df,3p)** as basis set. All structures were fully optimized at the same level of theory

Interaction	$\rho(\boldsymbol{r}_{\mathrm{BCP}})$	$\nabla^2\rho(\boldsymbol{r}_{\mathrm{BCP}})$	$V(\boldsymbol{r}_{\mathrm{BCP}})$	$G(\boldsymbol{r}_{\mathrm{BCP}})$	$H(\boldsymbol{r}_{\mathrm{BCP}})$	E_{HB}	$\sum_i E_{\mathrm{HB}}^{\mathrm{inter,i}}$	*BPL* (Å)
M05-2X								
i-a1wb								
$_{\mathrm{methyl}}$CH···OS	0.0081	0.0313	−0.0055	0.0067	0.0012	−1.73		3.1396
NH···O(w)	0.0213	0.0807	−0.0167	0.0184	0.0017	−5.24		2.0583
CH_{phenyl}···O(w)	0.0058	0.0211	−0.0036	0.0044	0.0008	−1.13	−12.61	2.6909
OH(w)···OS	0.0236	0.0962	−0.0199	0.0220	0.0021	−6.24		2.0007
i-a1wa								
$_{\mathrm{methyl}}$CH···OS[b]	0.0083	0.0323	−0.0057	0.0069	0.0012	−1.79		3.4132
NH···O(w)	0.0212	0.0808	−0.0164	0.0183	0.0019	−5.15		2.0626
CH_{phenyl}···O(w)	0.0044	0.0165	−0.0024	0.0033	0.0009	−0.75	−9.19	3.3239
OH(w)···ON	0.0144	0.0608	−0.0105	0.0128	0.0023	−3.29		2.2363
M06-2X								
i-a1wb								
$_{\mathrm{methyl}}$CH···OS[b]	0.0086	0.0331	−0.0059	0.0071	0.0012	−1.85		3.3986
NH···O(w)	0.0218	0.0851	−0.0173	0.0193	0.0020	−5.43		2.0423
CH_{phenyl}···O(w)	0.0066	0.0233	−0.0041	0.0050	0.0009	−1.29	−12.90	2.6369
OH(w)···OS	0.0231	0.0980	−0.0197	0.0221	0.0024	−6.18		2.0056
i-a1wa								
$_{\mathrm{methyl}}$CH···OS[b]	0.0087	0.0339	−0.0060	0.0073	0.0013	−1.88		3.3299
NH···O(w)	0.0220	0.0868	−0.0173	0.0195	0.0022	−5.43		2.0438
CH_{phenyl}···O(w)[b]	0.0055	0.0201	−0.0032	0.0041	0.0009	−1.00	−9.94	3.5917
OH(w)···ON	0.0151	0.0647	−0.0112	0.0137	0.0025	−3.51		2.2094
B3LYP								
i-a1wb								
$_{\mathrm{methyl}}$CH···OS	0.0064	0.0236	−0.0039	0.0049	0.0010	−1.22		2.9449
NH···O(w)	0.0212	0.0736	−0.0153	0.0168	0.0015	−4.80		2.0694
CH_{phenyl}···O(w)	0.0033	0.0131	−0.0019	0.0026	0.0007	−0.60	−10.86	2.9401
OH(w)···OS	0.0225	0.0856	−0.0174	0.0194	0.0020	−5.46		2.0194
i-a1wa								0
$_{\mathrm{methyl}}$CH···OS	0.0072	0.0269	−0.0046	0.0056	0.0010	−1.44		2.9230
NH···O(w)	0.0219	0.0763	−0.0159	0.0175	0.0016	−4.99	−7.78	2.0519
OH(w)···ON	0.0132	0.0517	−0.0089	0.0109	0.0020	−2.79		2.2835

[b] bond path goes to C atom

IQF results with B3LYP

Table S22: Summary of the IQF results (kcal/mol) calculated using structures optimized at the B3LYP/6-311++G(3df,3pd) level of theory. The 5-methyl-1,2-oxazole and the 3,4-dimethyl-1,2-oxazole group are abbreviated both with htc

m-a1wa				**i-a1wa**			
Group $\mathcal{G}$	E_{def}			Group $\mathcal{G}$	E_{def}		
SO_2	−1.03			SO_2	−0.77		
NH	4.81			NH	4.83		
htc	5.09			htc	−0.70		
($PhNH_2$)	−0.27			($PhNH_2$)	−0.08		
H_2O	17.88			H_2O	14.06		
Groups $\mathcal{G}\cdots\mathcal{H}$	E_{int}	V_{cl}	V_{xc}	Groups $\mathcal{G}\cdots\mathcal{H}$	E_{int}	V_{cl}	V_{xc}
$SO_2\cdots H_2O$	−3.35	−3.05	−0.31	$SO_2\cdots H_2O$	−2.94	−2.61	−0.33
$NH\cdots H_2O$	−15.43	−0.57	−14.86	$NH\cdots H_2O$	−14.25	−0.29	−13.96
$htc\cdots H_2O$	−25.99	−7.66	−18.33	$htc\cdots H_2O$	−14.40	−5.30	−9.10
$(PhNH_2)\cdots H_2O$	−0.88	−0.38	−0.50	$(PhNH_2)\cdots H_2O$	−1.56	−0.46	−1.10
$SO_2\cdots NH$	3.57	3.86	−0.30	$SO_2\cdots NH$	3.03	3.71	−0.67
$SO_2\cdots(PhNH_2)$	0.23	0.19	0.04	$SO_2\cdots(PhNH_2)$	0.36	−0.09	0.46
$SO_2\cdots htc$	−2.31	−2.30	−0.02	$SO_2\cdots htc$	−2.25	−2.26	0.01
$NH\cdots(PhNH_2)$	0.15	−0.09	0.24	$NH\cdots(PhNH_2)$	0.31	0.07	0.25
$NH\cdots htc$	8.46	10.98	−2.52	$NH\cdots htc$	8.62	10.68	−2.06
$(PhNH_2)\cdots htc$	0.11	0.05	0.04	$(PhNH_2)\cdots htc$	0.07	0.02	0.05
E_{bind}	−8.96			E_{bind}	−5.67		
$\sum E_{HB}$	−10.98			$\sum E_{HB}$	−7.78		
$E_{complex}$	−8.73			$E_{complex}$	−6.42		

m-a1wb				**i-a1wb**			
Group $\mathcal{G}$	E_{def}			Group $\mathcal{G}$	E_{def}		
SO_2	2.39			SO_2	1.70		
NH	6.40			NH	5.41		
htc	−1.60			htc	−2.19		
($PhNH_2$)	1.87			($PhNH_2$)	1.80		
H_2O	17.14			H_2O	17.17		
Groups $\mathcal{G}\cdots\mathcal{H}$	E_{int}	V_{cl}	V_{xc}	Groups $\mathcal{G}\cdots\mathcal{H}$	E_{int}	V_{cl}	V_{xc}
$SO_2\cdots H_2O$	−22.15	−7.55	−14.61	$SO2\cdots H_2O$	−22.51	−7.54	−14.97
$NH\cdots H_2O$	−15.17	−1.81	−13.36	$NH\cdots H_2O$	−15.67	−1.92	−13.75
$htc\cdots H_2O$	−1.33	−0.99	−0.34	$htc\cdots H_2O$	−1.56	−1.28	−0.28
$(PhNH_2)\cdots H_2O$	−3.28	−0.54	−2.74	$(PhNH_2)\cdots H_2O$	−2.25	−0.20	−2.05
$SO_2\cdots NH$	5.53	7.09	−1.57	$SO_2\cdots NH$	7.69	9.44	−1.75
$SO_2\cdots(PhNH_2)$	1.83	1.57	0.25	$SO_2\cdots(PhNH_2)$	1.46	1.24	0.23
$SO_2\cdots htc$	−1.75	−1.75	0.00	$SO_2\cdots htc$	−2.06	−2.06	0.00
$NH\cdots(PhNH_2)$	−1.15	−1.48	0.33	$NH\cdots(PhNH_2)$	−1.01	−1.25	0.24
$NH\cdots htc$	2.70	3.00	−0.30	$NH\cdots htc$	3.46	3.90	−0.44
$(PhNH_2)\cdots htc$	0.61	0.61	0.01	$(PhNH_2)\cdots htc$	0.55	0.54	0.00
E_{bind}	−7.97			E_{bind}	−8.01		
$\sum E_{HB}$	−10.70			$\sum E_{HB}$	−10.86		
$E_{complex}$	−7.87			$E_{complex}$	−7.99		

Cartesian coordinates

Table S23: Coordinates (in Å) of the global minimum of SMX (left) and SIX (right)

(a) **m-a1** M05-2X/6-311++G(3df,3pd)

C	−3.071399	−1.519238	−0.008135
C	−2.055108	−1.548447	0.950862
C	−1.168188	−0.499174	1.063379
C	−1.285851	0.593460	0.216096
C	−2.292375	0.640912	−0.739378
C	−3.178146	−0.407517	−0.850524
H	−1.970453	−2.399594	1.608519
H	−0.394198	−0.510821	1.812574
H	−2.384367	1.507189	−1.374296
H	−3.964724	−0.374156	−1.588278
S	−0.134317	1.903346	0.314927
O	−0.734353	3.086945	−0.215679
O	0.472560	1.868897	1.609142
N	1.070412	1.538975	−0.772030
N	−3.931568	−2.582498	−0.146567
H	−4.010282	−3.212104	0.629281
H	−4.792629	−2.414739	−0.631357
C	1.813342	0.370287	−0.623469
C	3.067497	−1.242600	0.101867
N	2.037587	−0.378230	−1.661270
H	0.784381	1.715861	−1.724514
O	2.844351	−1.396811	−1.208431
C	2.441758	−0.130752	0.548948
C	3.920094	−2.260502	0.758923
H	3.470453	−3.245094	0.666264
H	4.899025	−2.289500	0.289087
H	4.036947	−2.019729	1.808556
H	2.429689	0.290597	1.532732

(b) **i-a1** M05-2X/6-311++G(3df,3pd)

S	−0.139815	1.966220	0.148478
O	1.127832	−0.794774	−1.578047
O	0.553717	1.999677	1.397047
O	−0.715711	3.136968	−0.436586
N	0.983772	1.455260	−0.991198
N	1.801598	−1.943135	−1.227663
N	−4.058421	−2.426929	0.204288
C	−1.337543	0.701066	0.218276
C	1.562622	0.206825	−0.798493
C	2.494190	−0.228521	0.076777
C	2.591696	−1.616211	−0.248856
C	−1.154431	−0.372343	1.079886
C	−2.431271	0.745549	−0.635325
C	3.260198	0.533349	1.100410
C	−2.064893	−1.405838	1.082587
C	−3.344081	−0.285413	−0.627031
C	−3.171979	−1.378977	0.228506
C	3.482407	−2.626557	0.382800
H	0.633692	1.610900	−1.926040
H	−0.307272	−0.381910	1.745730
H	−2.565968	1.595041	−1.285081
H	3.182667	1.597889	0.910956
H	2.869685	0.353230	2.098808
H	4.307022	0.241233	1.084693
H	−1.927004	−2.244768	1.746694
H	−4.199593	−0.255143	−1.283678
H	3.274747	−2.702594	1.446901
H	3.328456	−3.592943	−0.082828
H	4.523760	−2.336997	0.267440
H	−4.060978	−3.049528	0.989319
H	−4.959008	−2.262829	−0.203074

Table S24: Coordinates (in Å) of the two isomers of SMX and SIX presented in more detail in the main text

(a) **m-a1wa** M05-2X/6-311++G(3df,3pd)

C	−3.090071	1.457331	0.205557
C	−2.404938	1.532682	−1.008659
C	−1.494039	0.556947	−1.359506
C	−1.267209	−0.508021	−0.503062
C	−1.936105	−0.597221	0.711932
C	−2.838698	0.380346	1.063331
H	−2.590660	2.362341	−1.673064
H	−0.964219	0.604720	−2.296246
H	−1.742513	−1.424713	1.376207
H	−3.356710	0.321436	2.007911
S	−0.098218	−1.740587	−0.917952
O	−0.622402	−3.027627	−0.587645
O	0.412181	−1.447360	−2.222500
N	1.148945	−1.526151	0.159365
N	−3.967120	2.451715	0.577467
H	−4.335748	3.027548	−0.155742
H	−4.633930	2.222841	1.290275
C	1.783378	−0.293020	0.221106
C	2.811097	1.569079	−0.218391
N	2.065640	0.232928	1.379338
H	0.913497	−1.901805	1.076453
O	2.728145	1.406654	1.107493
C	2.232132	0.524638	−0.851280
C	3.494311	2.792631	−0.697731
H	2.971303	3.677317	−0.345660
H	4.512009	2.826603	−0.319610
H	3.516589	2.799632	−1.780578
H	2.139654	0.335914	−1.900643
O	0.555301	−1.533758	3.028883
H	1.114399	−0.759460	2.870212
H	0.970597	−2.028056	3.734897

(b) **m-a1wb** M05-2X/6-311++G(3df,3pd)

C	−2.977776	−1.759268	−0.292704
C	−2.237141	−1.896376	0.883126
C	−1.363211	−0.904739	1.278930
C	−1.228169	0.237385	0.506407
C	−1.952384	0.389754	−0.670513
C	−2.819294	−0.602854	−1.065726
H	−2.349738	−2.787133	1.481412
H	−0.791408	−1.000749	2.186721
H	−1.831946	1.277648	−1.272172
H	−3.380683	−0.495216	−1.980746
S	−0.108753	1.490122	0.984645
O	−0.734834	2.773678	0.815583
O	0.463706	1.122939	2.242004
N	1.095144	1.477641	−0.144787
N	−3.817706	−2.764504	−0.711796
H	−4.119708	−3.425080	−0.021107
H	−4.520163	−2.521448	−1.384236
C	1.835617	0.315988	−0.347504
C	3.026918	−1.482324	−0.123737
N	2.156246	−0.031490	−1.557586
H	0.822181	1.966048	−0.995969
O	2.923534	−1.166326	−1.419014
C	2.358794	−0.578259	0.626839
C	3.818529	−2.689676	0.208884
H	3.375573	−3.568427	−0.251353
H	4.833814	−2.587139	−0.163371
H	3.845996	−2.826543	1.283081
H	2.258002	−0.526336	1.690954
O	−0.448380	3.281373	−1.901362
H	−0.684016	3.535551	−1.000131
H	−0.157158	4.074246	−2.349930

Table S24 *(continued)*: Coordinates (in Å) of the two isomers of SMX and SIX presented in more detail in the main text

(c) **i-a1wb** M05-2X/6-311++G(3df,3pd)

S	0.156189	1.606981	−0.829241
O	−1.136465	−0.505671	1.607692
O	−0.568470	1.349504	−2.032792
O	0.811499	2.871181	−0.623199
N	−0.926634	1.497313	0.435241
N	−1.870165	−1.669579	1.599223
N	3.845762	−2.860346	0.199640
C	1.294964	0.311492	−0.580138
C	−1.561905	0.271987	0.601079
C	−2.545882	−0.335017	−0.097418
C	−2.686785	−1.577637	0.592390
C	1.148169	−0.874309	−1.284564
C	2.286921	0.448886	0.383124
C	−3.324150	0.162699	−1.264332
C	2.005923	−1.924192	−1.035911
C	3.142518	−0.600204	0.628603
C	3.015568	−1.802400	−0.077372
C	−3.642429	−2.674801	0.282102
H	−0.524435	1.896235	1.282549
H	0.370051	−0.958063	−2.024997
H	2.380421	1.369475	0.936915
H	−3.191006	1.232879	−1.374901
H	−2.989997	−0.302834	−2.188036
H	−4.381268	−0.055069	−1.135011
H	1.898514	−2.849754	−1.579665
H	3.914350	−0.502944	1.376065
H	−3.479136	−3.045717	−0.726370
H	−3.510100	−3.486179	0.988243
H	−4.665941	−2.313521	0.341849
H	3.907207	−3.591699	−0.482385
H	4.702034	−2.663119	0.681037
O	0.815958	3.154802	2.140426
H	0.948405	3.470411	1.237297
H	0.601488	3.918916	2.674133

(d) **i-a1wa** M05-2X/6-311++G(3df,3pd)

C	−3.119547	1.467645	−0.372948
C	−2.060245	1.542417	−1.281387
C	−1.150043	0.511709	−1.379602
C	−1.290490	−0.6063271	−0.570046
C	−2.334359	−0.696572	0.341222
C	−3.243479	0.333409	0.436389
H	−1.957982	2.415312	−1.907250
H	−0.335842	0.557341	−2.083973
H	−2.424496	−1.569797	0.966386
H	−4.057873	0.270786	1.141419
S	−0.087242	−1.870430	−0.619474
O	−0.674144	−3.108868	−0.215555
O	0.647761	−1.742547	−1.839490
N	0.977692	−1.493212	0.620692
N	−4.005429	2.512704	−0.246133
H	−4.059212	3.159572	−1.009915
H	−4.887581	2.312057	0.185459
C	1.551318	−0.230546	0.578567
C	2.584063	1.652364	0.271726
H	0.550409	−1.708566	1.519633
C	2.511473	0.306785	−0.203719
C	3.490280	2.726657	−0.215480
H	3.314270	3.638187	0.343513
H	4.528384	2.427967	−0.094623
H	3.319444	2.913670	−1.272351
C	3.327122	−0.334361	−1.270763
H	3.254142	−1.413505	−1.199125
H	2.974158	−0.051293	−2.259040
H	4.369077	−0.038028	−1.180514
O	1.076775	0.687365	1.444314
N	1.755040	1.873117	1.246922
O	−0.474193	−1.069761	3.153971
H	−0.205383	−0.161689	2.986300
H	−0.282921	−1.241988	4.075625

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