ELECTRONIC SUPPLEMENTARY INFORMATION

Unscrambling –COOH and –NH groups micro-solvation in neat Dimethyl-Sulfoxide: Insights from ^{1}H-NMR Spectroscopy and Computational Studies

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^{1}H-NMR δ shifting examples of acids DMSO interaction

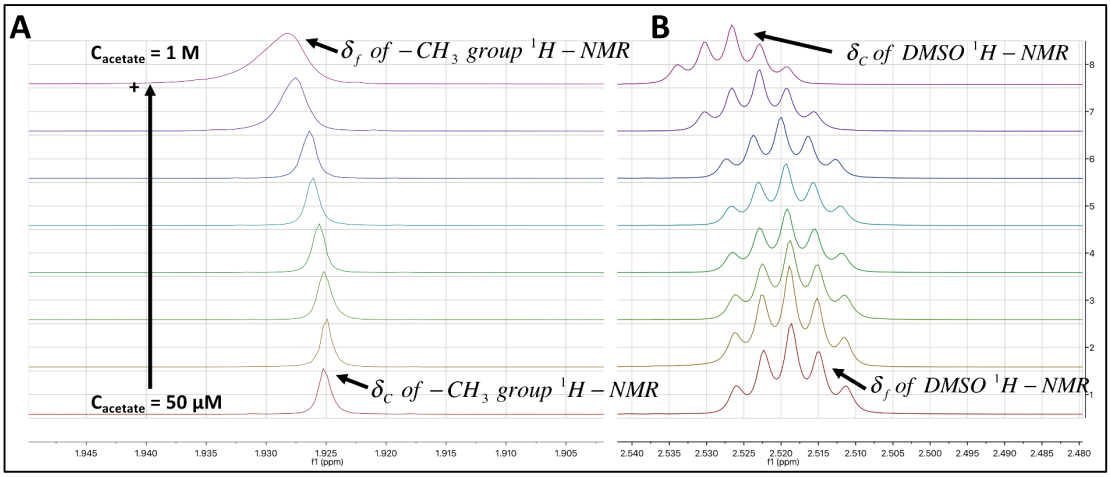

Figure S1. A) The ^{1}H-NMR chemical shifts of $-CH_3$ group of acetic acid in its various concentrations. **B)** The ^{1}H-NMR chemical shifts of DMSO protons in the various concentrations (the same as in the Figure S1A) of acetic acid. All spectra are scaled to the same intensity.

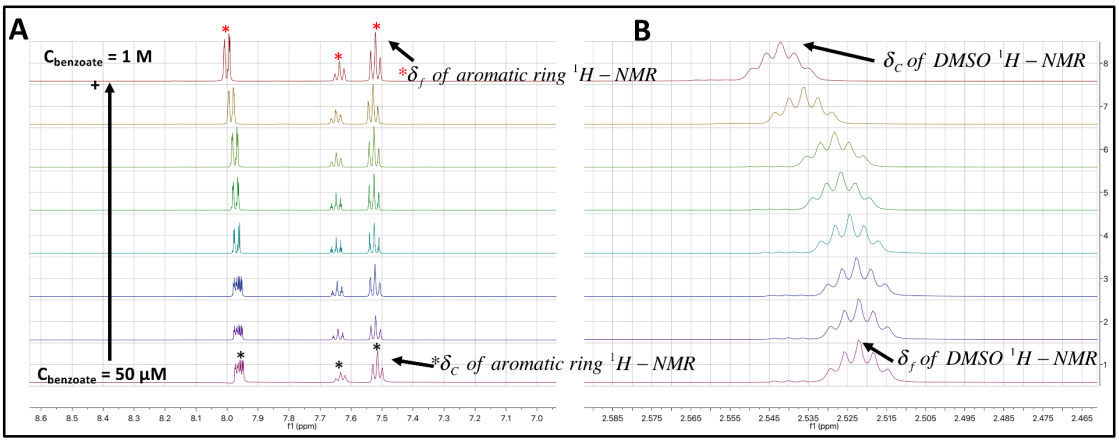

Figure S2. A) The ^{1}H-NMR chemical shifts of the aromatic protons of benzoic acid in its various concentrations. **B)** The ^{1}H-NMR chemical shifts of DMSO protons in the various concentrations (the same as in the Figure S2A) of benzoic acid. All spectra are scaled to the same intensity.

Table S1. The ^{1}H-NMR chemical shifts differences $|\Delta\delta|$ of DMSO protons from the acetic and benzoic acid titration in neat DMSO for various temperatures.

T (K)	$\|\Delta\delta\|$ (in ppm) of ^{1}H-NMR DMSO from 50 μM to 1 M acid concentration	
	Acetic acid	Benzoic acid
298	0.012	0.020
303	0.011	0.018
308	0.010	0.016
313	0.010	0.015
320	0.008	0.013

^{13}C-NMR results for benzoic acid

The following equations were employed in order to calculate the K_1 and K_2 association constants of benzoic acid – DMSO complex and benzoic acid – benzoic acid complex, respectively:

$$\delta_{0,s} = \delta_c + (\delta_m - \delta_c)\frac{C_m + K_2 C_m^2}{C_0}, \qquad \text{(S1)}$$

Equation (S1) could be simplified into:

$$\delta_{0,s} \cong \delta_c + (\delta_m - \delta_c)\frac{C_m}{C_0}, \qquad \text{(S2)}$$

because the expected K_2 as well as the calculated C_m values are much less than unity.

Table S2. Calculated association constants (K_1, K_2) of benzoic acid interactions in DMSO by ^{13}C NMR data (± SE, standard error).

T (K)	K_1	K_2
	Benzoic acid–DMSO	Benzoic acid dimer
298	0.792 ± 0.095	0.017 ± 0.005
303	0.765 ± 0.095	0.016 ± 0.005
308	0.741 ± 0.115	0.015 ± 0.007
313	0.732 ± 0.088	0.014 ± 0.005
320	0.731 ± 0.098	0.014± 0.005

^{13}C-NMR δ shifting example of benzoic acid DMSO interaction

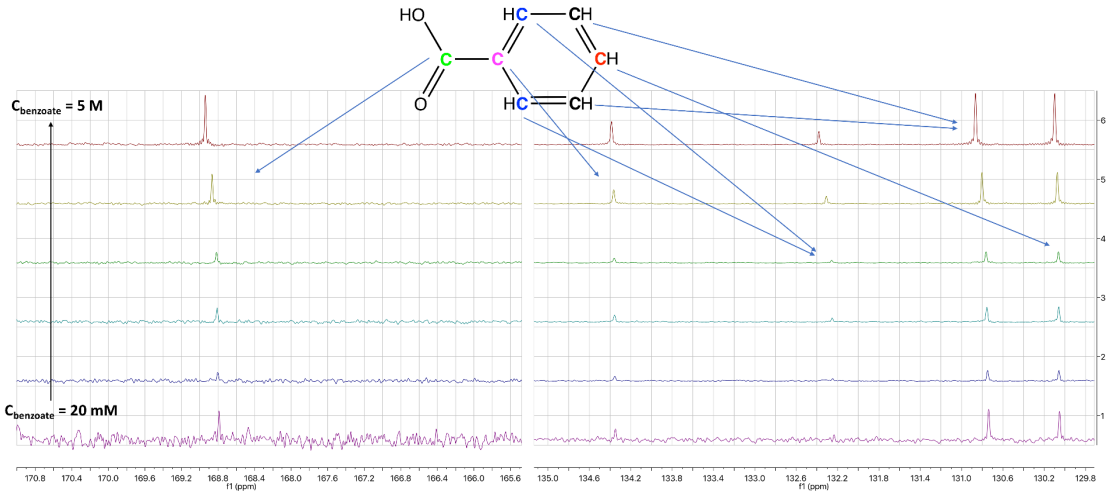

Figure S3. The ^{13}C-NMR chemical shifts evolution of benzoic acid in its various concentrations at 298 K.

^{1}H-NMR δ shifting examples of ethyl acetamidocyanoacetate – DMSO interaction

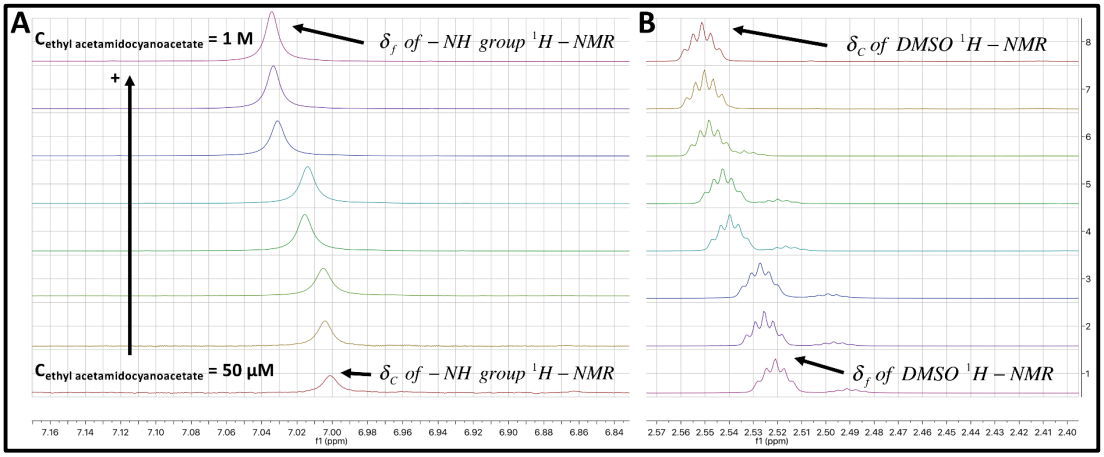

Figure S4. **A)** The ^{1}H-NMR chemical shifts of –NH proton of the ethyl acetamidocyanoacetate in its various concentrations. **B)** The ^{1}H-NMR chemical shifts of DMSO protons in the various concentrations of ethyl acetamidocyanoacetate. All spectra are scaled to the same intensity.

Table S3. The ^{1}H-NMR chemical shifts differences |Δδ| of DMSO and –NH protons from the ethyl acetamidocyanoacetate titration in neat DMSO for various temperatures.

T (K)	|Δδ| (in ppm) of ^{1}H-NMR DMSO from 50 µM to 1 M model peptide concentration	|Δδ| (in ppm) of ^{1}H-NMR –NH group from 50 µM to 1 M model peptide concentration
298	0.030	0.036
303	0.029	0.035
308	0.029	0.035
313	0.028	0.034
320	0.028	0.034

In this section, the fully optimized structure coordinates of all systems studied along with their electronic (E_{elec}), zero-point (ZPE) and Gibbs free energies at 298.15 K and 1 atm (G_{298}) are provided.

The acetic acid dimer without DMSO molecule (X3LYP/cc-pVTZ)

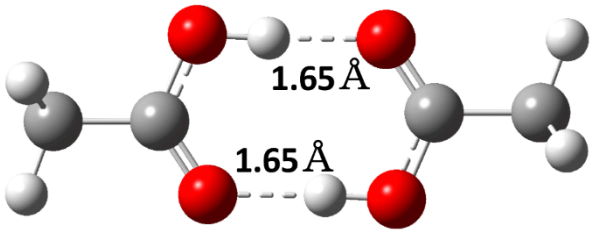

Figure S5. . Fully optimized structure of the acetic acid dimer at the X3LYP/cc-pVTZ level of theory, applying the IEF-PCM model for bulk DMSO solvent, without any DMSO molecule.

Acetic acid Dimer (Fig. S5)

(Charge = 0)
16 Atoms
E_{elec} = -458.21468633 Hartrees
ZPE = 0.124401 Hartrees
G_{298} = -458.128490 Hartrees

	X	Y	Z
C	3.42256700	0.06024000	0.00099500
H	3.78656200	-0.46697300	0.88257700
H	3.79760900	1.07786300	-0.00432100
H	3.78751200	-0.47723200	-0.87385400
C	1.92655700	0.05826100	0.00100500
O	1.39743800	-1.14985800	-0.00114100
H	0.39728400	-1.09730400	0.00128000
O	1.25282500	1.08339100	0.00366900
C	-1.92633500	-0.05822600	-0.00169500
O	-1.25214900	-1.08310000	-0.00329900
O	-1.39841600	1.15044000	-0.00619600
H	-0.39826000	1.10051600	-0.00955400
C	-3.42232800	-0.06129300	0.00567200
H	-3.78247600	0.46830700	0.88748500
H	-3.79199600	0.47321700	-0.86906400
H	-3.79659200	-1.07927500	0.00533100

The less probable [(2 x Acetic acid) – DMSO] complexes (MP2/cc-pVTZ)

A **B**

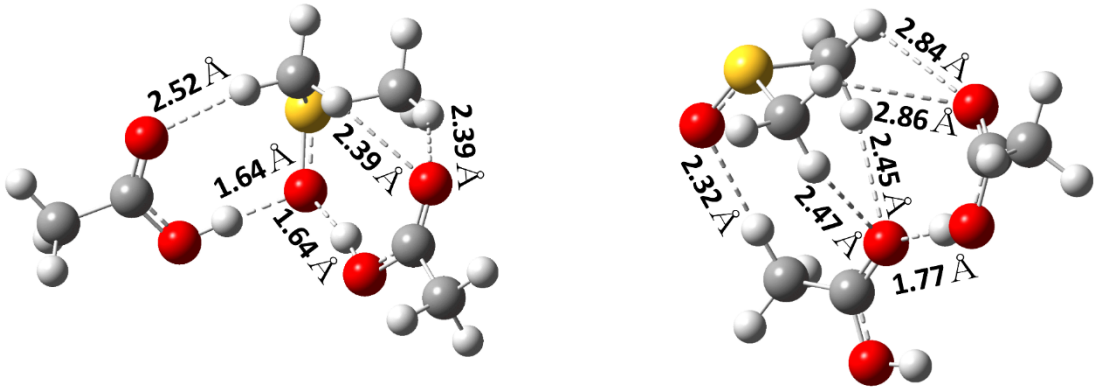

Figure S6. Two fully optimized structures of two acetic acid molecules interaction with one DMSO molecule, optimized at the MP2/cc-pVTZ level of theory, applying the IEF-PCM model for bulk DMSO solvent. Both structures are less abundant in the solution compared to the one reported in the main article (Fig. 5C), according to our extensive MD results analysis.

[(2 x Acetic acid) – DMSO] (Fig. S6 A)

(Charge = 0)
26 Atoms
E_{elec} = -1009.89634839 Hartrees
ZPE = 0.207425 Hartrees
G_{298} = -1009.738784 Hartrees

	X	Y	Z
S	0.05073100	-0.01601000	-0.08502200
O	0.06134800	-0.00001900	1.46057500
C	1.78141100	-0.06120800	-0.53033100
H	1.85438100	0.02320900	-1.61229100
H	2.28442500	0.76053100	-0.02719200
H	2.16643700	-1.02297500	-0.20449900
C	-0.29957500	1.66598200	-0.57638800
H	0.41435900	2.32246500	-0.08534400
H	-0.21734500	1.72463400	-1.65965600
H	-1.31969900	1.86394700	-0.26283500
H	0.78919800	1.13916700	2.40284600
O	1.13105100	1.73999000	3.12386600
H	-1.38494300	-0.43742600	2.08693200
O	-2.25632900	-0.67513300	2.51775400
C	1.97087500	2.62784500	2.59566100
C	-3.23678300	-0.27971400	1.70602300
C	-4.59498800	-0.55794100	2.27661800
H	-4.70748400	-0.02718100	3.21936600
H	-5.36275900	-0.24323700	1.58009000
H	-4.69194900	-1.62103100	2.48430900
C	2.52917800	3.56317200	3.62560900
H	3.19789400	4.27540500	3.15751400
H	1.71460800	4.08564200	4.12185100
H	3.06288400	2.99228400	4.38208300
O	2.24798100	2.66719800	1.40704800
O	-3.03804000	0.24694300	0.62300400

[(2 x Acetic acid) – DMSO] (Fig. S6 B)

(Charge = 0)

26 Atoms

E_{elec} = -1009.87834818 Hartrees

ZPE = 0.207134 Hartrees

G_{298} = -1009.723095 Hartrees

	X	Y	Z
C	0.07592700	0.16205500	0.03382400
C	0.09490300	0.10927800	1.52409200
O	1.28751400	-0.23391400	2.02297300
H	1.21871000	-0.20550600	2.99070400
O	-0.86397000	0.37163100	2.23381000
H	-0.93218900	-0.03344900	-0.32223700
H	0.37130900	1.16638300	-0.26869200
H	0.78772700	-0.54164000	-0.38494300
C	-3.64084400	-0.27183200	6.21697800
C	-3.04702300	0.22207300	4.93312700
O	-1.82986400	-0.29773600	4.71676500
H	-1.49516900	0.03652800	3.85492400
O	-3.58785500	0.99308800	4.16372700
H	-4.59796100	0.20535600	6.38932100
H	-3.76924400	-1.35079600	6.16201200
H	-2.96260000	-0.06239000	7.04054500
C	-3.89865700	-1.20392200	1.53085500
S	-4.23660200	-0.23188600	0.06005000
C	-3.86942800	1.36936200	0.78231800
O	-3.11490200	-0.53052400	-0.91606100
H	-4.01898600	-2.24824100	1.25581100
H	-2.87976300	-0.99772500	1.84913700
H	-4.61139300	-0.93194700	2.30627100
H	-3.96043600	2.10236700	-0.01484100
H	-4.59008700	1.57450900	1.57056900
H	-2.85870200	1.34207800	1.18215100

Depiction, geometrical details and energetics of the fully optimized molecules and complexes

B3LYP/cc-pVTZ

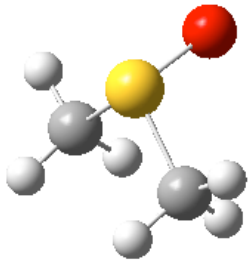

Figure S7. Fully optimized structure of DMSO at the B3LYP/cc-pVTZ level of theory, applying the IEF-PCM model for bulk DMSO solvent.

DMSO (Fig. S7)

(Charge = 0)
10 Atoms
E_{elec} = -553.31404029 Hartrees
ZPE = 0.078943 Hartrees
G_{298} = -553.263364 Hartrees

	X	Y	Z
S	0.00026700	0.21864600	-0.44665700
O	0.00164800	1.49355800	0.38124200
C	1.36512500	-0.79842000	0.18962400
H	1.33371000	-1.77619900	-0.28735900
H	2.28762700	-0.28633700	-0.07213200
H	1.26639100	-0.88297800	1.27034200
C	-1.36681000	-0.79579300	0.18957500
H	-2.28790600	-0.27725900	-0.06419800
H	-1.34301200	-1.77027900	-0.29453600
H	-1.26414800	-0.88847700	1.26926200

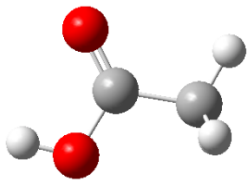

Figure S8. Fully optimized structure of acetic acid at the B3LYP/cc-pVTZ level of theory, applying the IEF-PCM model for bulk DMSO solvent.

Acetic acid (Fig. S8)

(Charge = 0)

8 Atoms

E_{elec} = -229.19037739 Hartrees

ZPE = 0.061125 Hartrees

G_{298} = -229.157093 Hartrees

	X	Y	Z
C	1.39014700	-0.12296200	-0.00022000
H	1.66853700	-0.68565900	0.89087500
H	1.92201700	0.82231700	-0.02123500
H	1.66530600	-0.72536700	-0.86577000
C	-0.08835800	0.12158500	-0.00063300
O	-0.78971800	-1.02973600	-0.00012800
H	-1.73401200	-0.80759200	0.00158700
O	-0.62685400	1.20530700	0.00008500

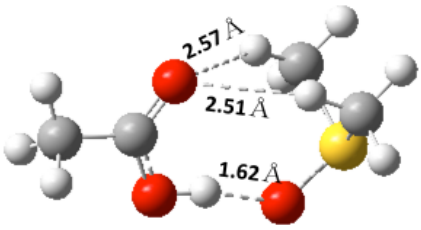

Figure S9. Fully optimized structure of the acetic acid plus one DMSO molecule complex at the B3LYP/cc-pVTZ level of theory, applying the IEF-PCM model for bulk DMSO solvent.

Acetic acid–DMSO complex (Fig. S9)

(Charge = 0)

18 Atoms

E_{elec} = -782.51792940 Hartrees

ZPE = 0.141186 Hartrees

G_{298} = -782.415843 Hartrees

	X	Y	Z
S	2.09459500	0.34923200	-0.00665400
O	0.95806700	1.37518000	-0.11819900
C	1.78348700	-0.88905700	-1.29286600
H	2.51034300	-1.69085600	-1.17796300
H	0.76416700	-1.25425500	-1.19132900
H	1.92898600	-0.38956200	-2.24735300
C	1.71627300	-0.67193500	1.44245600
H	0.71933100	-1.09063800	1.32747700
H	2.47060800	-1.45299000	1.51436200
H	1.77359500	-0.01944300	2.31001600
H	-0.63027900	1.06941900	-0.09415400
O	-1.63741900	1.09041600	-0.05900400
C	-2.14876600	-0.13462700	-0.01576600
C	-3.65134300	-0.13190700	0.05047200
H	-4.02775300	-1.14899000	0.08655900
H	-3.97950200	0.41539700	0.93432400
H	-4.05776000	0.38311000	-0.82015800
O	-1.46854300	-1.14606500	-0.02793300

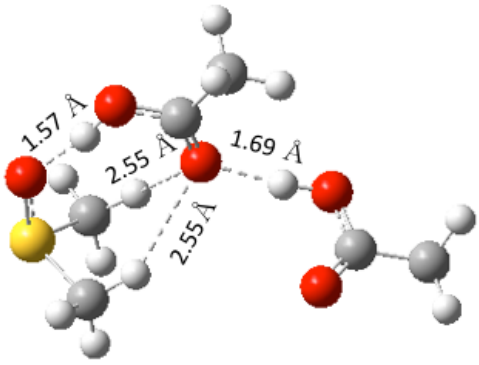

Figure S10. Fully optimized structure of the acetic acid dimer plus one DMSO molecule complex at the B3LYP/cc-pVTZ level of theory, applying the IEF-PCM model for bulk DMSO solvent.

Acetic acid dimer–DMSO complex (Fig. S10)

(Charge = 0)

26 Atoms

E_{elec} = -1011.71691855 Hartrees

ZPE = 0.203806 Hartrees

G_{298} = -1011.565232 Hartrees

	X	Y	Z
C	-0.94405600	3.05380300	-0.07504700
H	-1.94971300	2.71430300	0.15032700
H	-0.91467000	3.48644700	-1.07494400
H	-0.65329100	3.83547000	0.62661600
C	0.03320200	1.91840400	0.00789600
O	1.27464200	2.27400600	-0.24121700
H	1.91443700	1.48614600	-0.18711100
O	-0.27860800	0.76235400	0.28142300
C	-3.36755900	-0.79526000	-0.13364800
O	-2.85436000	-1.03835600	-1.20690900
O	-2.75788000	-0.09359500	0.82573400
H	-1.84945700	0.19210500	0.53458400
C	-4.74171500	-1.24678700	0.27605300
H	-4.67557500	-1.86046500	1.17456600
H	-5.35785200	-0.38097600	0.51904700
H	-5.20376900	-1.81459700	-0.52512300
S	3.09006300	-1.04459300	-0.03765700
O	3.13069200	0.48415500	-0.18656000
C	2.22068400	-1.37773700	1.51711100
H	2.04574400	-2.44973500	1.58730200
H	2.87924500	-1.05660900	2.31989300
H	1.28729800	-0.82010400	1.52699100
C	1.82116900	-1.63346200	-1.19009600
H	2.17808700	-1.40086000	-2.19005900
H	1.73126300	-2.71165500	-1.07117600
H	0.88100700	-1.12826400	-0.98176200

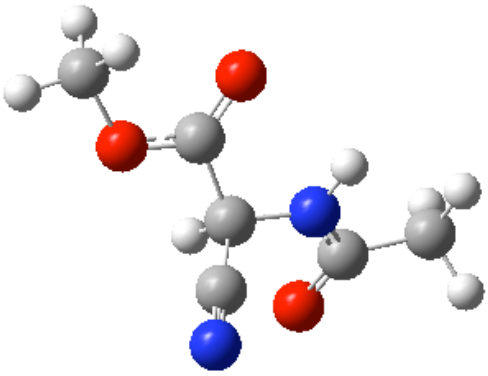

Figure S11. Fully optimized structure of the ethyl acetamidocyanoacetate molecule at the B3LYP/cc-pVTZ level of theory, applying the IEF-PCM model for bulk DMSO solvent.

Ethyl acetamidocyanoacetate (Fig. S11)

(Charge = 0)

19 Atoms

E_{elec} = -568.86373173 Hartrees

ZPE = 0.142982 Hartrees

G_{298} = -568.761262 Hartrees

	X	Y	Z
N	1.10789300	-0.34112400	-0.34937500
C	-0.04363500	0.32148400	0.20156200
H	0.08621500	0.42185000	1.28214700
H	0.94660700	-0.99553200	-1.09836500
C	2.33546600	-0.22562300	0.22773300
C	3.42975900	-1.06209600	-0.38285100
H	3.76355000	-1.78760400	0.35886200
H	3.11836900	-1.59040000	-1.28084400
H	4.27401300	-0.41608500	-0.61863100
O	2.52355000	0.51493800	1.18591500
C	-0.21463100	1.68529900	-0.33163000
N	-0.32174200	2.74912000	-0.75326900
C	-1.31145600	-0.52081100	-0.04233300
O	-1.29344100	-1.58523100	-0.60454000
O	-2.37224800	0.08528900	0.45917500
C	-3.64592400	-0.59473300	0.31104200
H	-3.62083800	-1.54013400	0.84641800
H	-4.37820300	0.07527200	0.74529900
H	-3.85314500	-0.76442500	-0.74191400

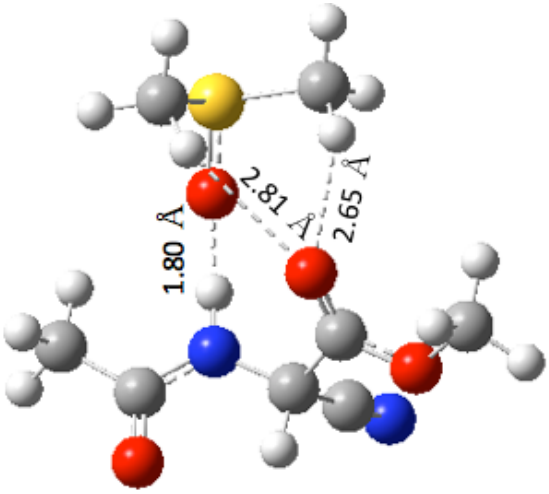

Figure S12. Fully optimized structure of the ethyl acetamidocyanoacetate plus one DMSO molecule complex at the B3LYP/cc-pVTZ level of theory, applying the IEF-PCM model for bulk DMSO solvent.

Ethyl acetamidocyanoacetate–DMSO complex (Fig. S12)

(Charge = 0)

29 Atoms

E_{elec} = -1122.18591953 Hartrees

ZPE = 0.223506 Hartrees

G_{298} = -1122.013790 Hartrees

	X	Y	Z
N	0.46470500	1.29520800	0.14378200
C	1.65467800	0.50399200	0.27376900
H	2.47885700	1.09531900	-0.13820000
H	-0.43408800	0.89464400	0.43606600
C	0.51833800	2.52744300	-0.42908100
C	-0.80093900	3.25005300	-0.53379800
H	-1.02851100	3.41052300	-1.58776400
H	-1.61693000	2.70632100	-0.06487000
H	-0.69917700	4.22867300	-0.06638900
O	1.56780900	3.02143300	-0.83362900
C	1.97200200	0.22703700	1.68219800
N	2.19350900	0.02729900	2.79269500
C	1.59976100	-0.80364400	-0.54839700
O	0.70832800	-1.07436500	-1.31061400
O	2.67293900	-1.54224500	-0.30977000
C	2.78820300	-2.78901600	-1.04149900
H	2.82302000	-2.58768000	-2.10889300
H	3.71624100	-3.23386800	-0.70247000
H	1.94483600	-3.43398200	-0.80945400
S	-3.03574700	-0.66476300	0.48067200
O	-2.00003800	0.28679700	1.08501000
C	-2.26146200	-2.30558500	0.45377900
H	-2.09219400	-2.58829400	1.48955600
H	-2.95213800	-3.00489100	-0.01353300
H	-1.32445500	-2.25279400	-0.09604400
C	-3.02693200	-0.35987100	-1.30818800
H	-2.00396100	-0.42315100	-1.67344300
H	-3.66312600	-1.10159900	-1.78709300
H	-3.43811600	0.63402000	-1.46423600

X3LYP/cc-pVTZ

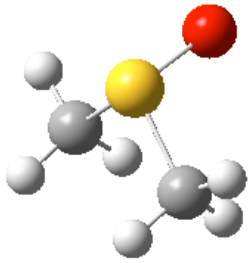

Figure S13. Fully optimized structure of DMSO at the X3LYP/cc-pVTZ level of theory, applying the IEF-PCM model for bulk DMSO solvent.

DMSO (Fig. S13)

(Charge = 0)
10 Atoms
E_{elec} = -553.19473228 Hartrees
ZPE = 0.079073 Hartrees
G_{298} = -553.143910 Hartrees

	X	Y	Z
S	0.00027200	0.21819300	-0.44674500
O	0.00180200	1.49139900	0.38108300
C	1.36273200	-0.79718800	0.18957600
H	1.33073500	-1.77573900	-0.28536000
H	2.28568500	-0.28652500	-0.07252500
H	1.26329500	-0.87943600	1.27029200
C	-1.36455700	-0.79433200	0.18955000
H	-2.28602600	-0.27697700	-0.06439100
H	-1.34046800	-1.76952000	-0.29273400
H	-1.26104000	-0.88495700	1.26920900

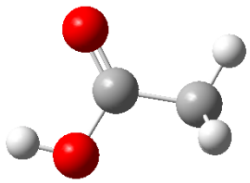

Figure S14. Fully optimized structure of acetic acid at the X3LYP/cc-pVTZ level of theory, applying the IEF-PCM model for bulk DMSO solvent.

Acetic acid (Fig. S14)

(Charge = 0)

8 Atoms

E_{elec} = -229.09794303 Hartrees

ZPE = 0.061245 Hartrees

G_{298} = -229.064474 Hartrees

	X	Y	Z
C	1.38912900	-0.12283300	-0.00019200
H	1.66693400	-0.68546800	0.89088500
H	1.92038000	0.82255900	-0.02116300
H	1.66364100	-0.72505100	-0.86572200
C	-0.08822900	0.12118000	-0.00050500
O	-0.78909500	-1.02858800	-0.00017000
H	-1.73294100	-0.80635000	0.00170300
O	-0.62633200	1.20411700	-0.00002000

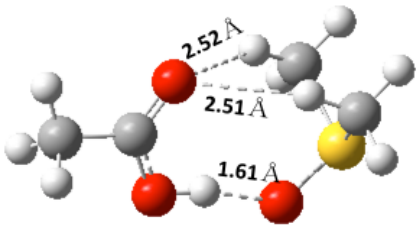

Figure S15. Fully optimized structure of the acetic acid plus one DMSO molecule complex at the X3LYP/cc-pVTZ level of theory, applying the IEF-PCM model for bulk DMSO solvent.

Acetic acid–DMSO complex (Fig. S15)

(Charge = 0)
18 Atoms
E_{elec} = -782.30753861 Hartrees
ZPE = 0.141629 Hartrees
G_{298} = -782.204346 Hartrees

	X	Y	Z
S	2.08956800	0.34492900	-0.00021100
O	0.95909800	1.38117000	-0.04583500
C	1.75397100	-0.82182200	-1.34259600
H	2.48921600	-1.62242900	-1.29221700
H	0.74117700	-1.20158500	-1.23186600
H	1.86979900	-0.27031000	-2.27192200
C	1.71711100	-0.74412500	1.39687100
H	0.71030100	-1.13695900	1.27760900
H	2.45747200	-1.54136200	1.41506500
H	1.80135300	-0.13959200	2.29613200
H	-0.62255900	1.07698600	-0.02847200
O	-1.63066800	1.09436000	-0.01763700
C	-2.13800200	-0.13101400	-0.00606200
C	-3.64061600	-0.13705900	0.01320000
H	-4.01197300	-1.15657100	0.02198900
H	-3.99901200	0.39560700	0.89403800
H	-4.02183800	0.38880800	-0.86204000
O	-1.45365500	-1.13894800	-0.00945600

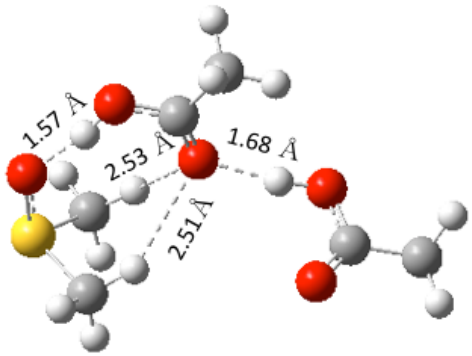

Figure S16. Fully optimized structure of the acetic acid dimer plus one DMSO molecule complex at the X3LYP/cc-pVTZ level of theory, applying the IEF-PCM model for bulk DMSO solvent.

Acetic acid dimer–DMSO complex (Fig. S16)

(Charge = 0)

26 Atoms

E_{elec} = -1011.41507383 Hartrees

ZPE = 0.204150 Hartrees

G_{298} = -1011.263340 Hartrees

	X	Y	Z
C	-0.88787400	3.10578400	-0.10276300
H	-1.90365200	2.78208000	0.09895300
H	-0.83000600	3.54984100	-1.09602100
H	-0.59657100	3.87271300	0.61464200
C	0.06566200	1.95282200	-0.01325800
O	1.31291600	2.27890500	-0.26623700
H	1.93401700	1.47570000	-0.20813100
O	-0.26999300	0.80588600	0.26813800
C	-3.29612400	-0.81501100	-0.11585100
O	-2.68625000	-1.22135200	-1.08321600
O	-2.77901100	0.04208400	0.76635000
H	-1.84620900	0.28686200	0.51801900
C	-4.70397200	-1.20847900	0.23022000
H	-4.72627200	-1.66383500	1.22022400
H	-5.33632500	-0.32153100	0.26630500
H	-5.08941600	-1.90639300	-0.50567600
S	3.01349500	-1.08759800	-0.02737200
O	3.10707500	0.43595800	-0.19850800
C	2.14747500	-1.36498400	1.53727100
H	2.00114000	-2.43643100	1.65927500
H	2.79540700	-0.98842300	2.32415300
H	1.20079700	-0.83095800	1.51827500
C	1.71585600	-1.64892200	-1.15757200
H	2.06961200	-1.44353600	-2.16439400
H	1.59339600	-2.72176200	-1.02134300
H	0.79412800	-1.11187500	-0.94681000

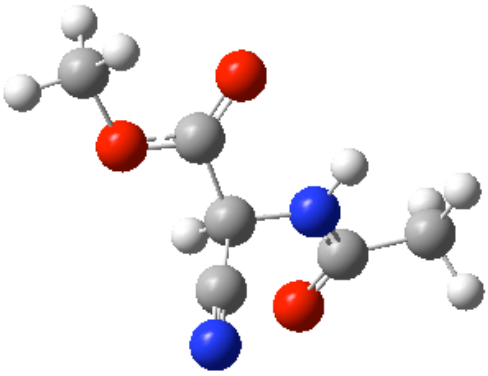

Figure S17. Fully optimized structure of the ethyl acetamidocyanoacetate molecule at the X3LYP/cc-pVTZ level of theory, applying the IEF-PCM model for bulk DMSO solvent.

Ethyl acetamidocyanoacetate (Fig. S17)

(Charge = 0)

19 Atoms

E_{elec} = -568.8328456 Hartrees

ZPE = 0.142670 Hartrees

G_{298} = -568.761849 Hartrees

	X	Y	Z
N	1.09594300	-0.38932000	-0.30986300
C	-0.04591100	0.30531100	0.22296500
H	0.06894300	0.41863600	1.30434900
H	0.91290700	-1.10707600	-0.99311300
C	2.33711800	-0.22846400	0.22379600
C	3.42451200	-1.08295100	-0.37521900
H	3.94142100	-1.60405800	0.42894700
H	3.05347200	-1.80798700	-1.09640400
H	4.14612100	-0.43077100	-0.86732500
O	2.54508500	0.57695900	1.12427700
C	-0.18593300	1.66382100	-0.33192200
N	-0.27213400	2.72264300	-0.77033500
C	-1.32421400	-0.52032900	-0.02448000
O	-1.31223500	-1.60033400	-0.55681800
O	-2.38432400	0.11594500	0.43831900
C	-3.66586300	-0.54831100	0.28204500
H	-3.66843600	-1.47639100	0.84736200
H	-4.39616400	0.14711800	0.67799000
H	-3.85139500	-0.74774400	-0.76976500

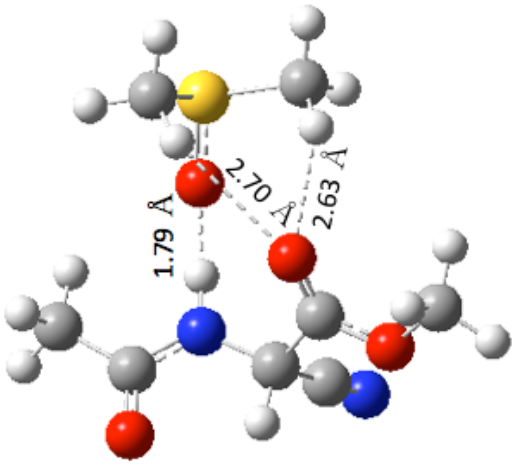

Figure S18. Fully optimized structure of the ethyl acetamidocyanoacetate plus one DMSO molecule complex at the X3LYP/cc-pVTZ level of theory, applying the IEF-PCM model for bulk DMSO solvent.

Ethyl acetamidocyanoacetate–DMSO complex (Fig. S18)

(Charge = 0)

29 Atoms

E_{elec} = -1121.83355675 Hartrees

ZPE = 0.223941 Hartrees

G_{298} = -1121.661164 Hartrees

	X	Y	Z
N	0.46447400	1.30092300	0.15371700
C	1.64459600	0.49675100	0.27829800
H	2.47511600	1.08022700	-0.13165500
H	-0.43843300	0.91119400	0.44829300
C	0.52963200	2.52983700	-0.42189200
C	-0.78230100	3.26317700	-0.52726400
H	-1.01637400	3.40955300	-1.58167000
H	-1.59975100	2.73345100	-0.04512700
H	-0.66804800	4.24751500	-0.07585500
O	1.58225300	3.01188300	-0.83002200
C	1.95961600	0.20637500	1.68391800
N	2.17912600	-0.00805900	2.79110000
C	1.57314100	-0.80541200	-0.54767300
O	0.67422000	-1.06595200	-1.30359300
O	2.63872200	-1.55494400	-0.31897900
C	2.73416200	-2.80008600	-1.05227800
H	2.76390000	-2.59762300	-2.11944900
H	3.65867100	-3.25702600	-0.72047400
H	1.88465100	-3.43518600	-0.81609300
S	-3.01690100	-0.64869700	0.46605900
O	-1.98822700	0.29557200	1.09036500
C	-2.25819500	-2.29373000	0.47161700
H	-2.11156600	-2.56678600	1.51311500
H	-2.94570300	-2.99145100	-0.00238000
H	-1.31051500	-2.25419400	-0.06035600
C	-2.95496300	-0.35614700	-1.32100200
H	-1.92072900	-0.42233000	-1.65216800
H	-3.57504700	-1.10172400	-1.81426000
H	-3.36082000	0.63643300	-1.49710200

MP2/cc-pVTZ

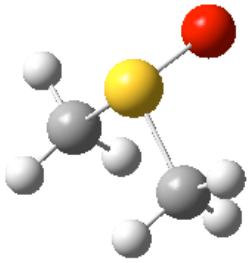

Figure S19. Fully optimized structure of DMSO at the MP2/cc-pVTZ level of theory, applying the IEF-PCM model for bulk DMSO solvent.

DMSO (Fig. S19)

(Charge = 0)

10 Atoms

E_{elec} = -553.19473228 Hartrees

ZPE = 0.080325 Hartrees

G_{298} = -553.142456 Hartrees

	X	Y	Z
S	0.00027200	0.21819300	-0.44674500
O	0.00180200	1.49139900	0.38108300
C	1.36273200	-0.79718800	0.18957600
H	1.33073500	-1.77573900	-0.28536000
H	2.28568500	-0.28652500	-0.07252500
H	1.26329500	-0.87943600	1.27029200
C	-1.36455700	-0.79433200	0.18955000
H	-2.28602600	-0.27697700	-0.06439100
H	-1.34046800	-1.76952000	-0.29273400
H	-1.26104000	-0.88495700	1.26920900

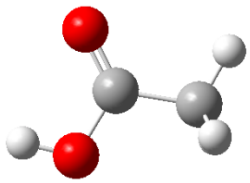

Figure S20. Fully optimized structure of acetic acid at the MP2/cc-pVTZ level of theory, applying the IEF-PCM model for bulk DMSO solvent.

Acetic acid (Fig. S20)

(Charge = 0)

8 Atoms

E_{elec} = -228.77002240 Hartrees

ZPE = 0.062049 Hartrees

G_{298} = -228.735004 Hartrees

	X	Y	Z
C	-1.38184400	-0.11224300	-0.00003900
H	-1.65560100	-0.69282600	-0.87347000
H	-1.90250000	0.83339100	-0.00380500
H	-1.65613600	-0.68581400	0.87789600
C	0.08766600	0.11997000	-0.00010000
O	0.77284500	-1.03585800	-0.00001000
H	1.71366200	-0.80560400	0.00015100
O	0.63536000	1.19892000	0.00001800

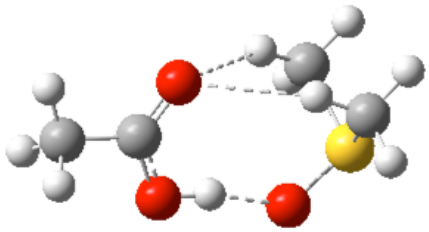

Figure S21. Fully optimized structure of the acetic acid plus one DMSO molecule complex at the MP2/cc-pVTZ level of theory, applying the IEF-PCM model for bulk DMSO solvent. (For the H-bonds distances see Fig. 5B)

Acetic acid–DMSO complex (Fig. S21)

(Charge = 0)

18 Atoms

E_{elec} = -781.17261217 Hartrees

ZPE = 0.142389 Hartrees

G_{298} = -781.067960 Hartrees

	X	Y	Z
S	2.06911300	0.33450500	0.00375600
O	0.95990600	1.38306900	-0.11952400
C	1.74045800	-0.87720600	-1.27173400
H	2.44510400	-1.69740700	-1.15554300
H	0.71223500	-1.21324300	-1.16417800
H	1.89792800	-0.38367700	-2.22644800
C	1.63124300	-0.68284500	1.41007200
H	0.62363000	-1.06235200	1.26011700
H	2.35632100	-1.49031300	1.48751300
H	1.68745000	-0.04750500	2.28944500
H	-0.59916100	1.07913300	-0.07095000
O	-1.60753300	1.10661900	-0.03953800
C	-2.09878300	-0.12753200	-0.01633200
C	-3.59726900	-0.14506400	0.03028800
H	-3.95817400	-1.16651600	0.04309000
H	-3.93794700	0.38148900	0.91893800
H	-3.99360800	0.37976800	-0.83597100
O	-1.40155900	-1.13163500	-0.03092300

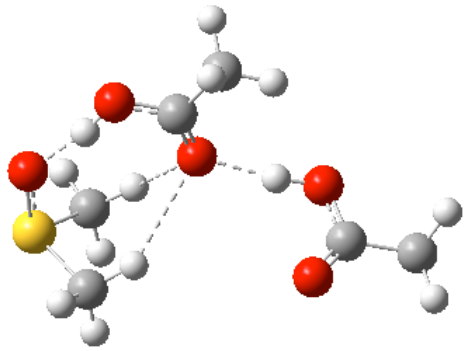

Figure S22. Fully optimized structure of the acetic acid dimer plus one DMSO molecule complex at the MP2/cc-pVTZ level of theory, applying the IEF-PCM model for bulk DMSO solvent (For the H-bonds distances see Fig. 5C).

Acetic acid dimer–DMSO complex (Fig. S22)

(Charge = 0)

26 Atoms

E_{elec} = -1010.09686690 Hartrees

ZPE = 0.207249 Hartrees

G_{298} = -1009.9387659 Hartrees

	X	Y	Z
C	-1.32987900	2.69151500	-0.13636600
H	-2.06361900	2.65609400	0.66145300
H	-1.77491200	2.27579400	-1.03960200
H	-1.02961000	3.71453300	-0.33828100
C	-0.14412900	1.84877100	0.21205400
O	0.95135900	2.17982200	-0.43418600
H	1.69201000	1.50884200	-0.23055900
O	-0.19105000	0.90815200	1.00687400
C	-2.79290600	-0.78060400	-0.12825300
O	-2.10638800	-0.48877700	-1.09231200
O	-2.50033300	-0.40600000	1.12132900
H	-1.65597200	0.11876900	1.09648300
C	-4.05304700	-1.58982600	-0.19259900
H	-3.94941300	-2.47444000	0.43160000
H	-4.88059300	-1.00441700	0.20178000
H	-4.25705800	-1.87860500	-1.21660700
S	2.80689300	-0.93264600	-0.21441400
O	2.92110700	0.59139600	-0.10997400
C	2.13163500	-1.48531000	1.34965700
H	1.93453200	-2.55280000	1.27882100
H	2.88850200	-1.29619300	2.10555500
H	1.22676700	-0.91795200	1.54963400
C	1.36515500	-1.26708000	-1.22470500
H	1.57376400	-0.87134800	-2.21496200
H	1.23732500	-2.34623900	-1.27748100
H	0.48946600	-0.79126200	-0.78977700

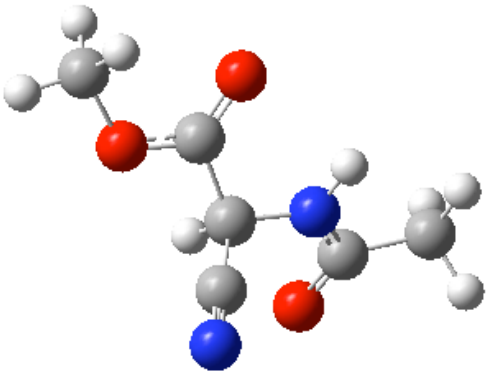

Figure S23. Fully optimized structure of the ethyl acetamidocyanoacetate molecule at the MP2/cc-pVTZ level of theory, applying the IEF-PCM model for bulk DMSO solvent.

Ethyl acetamidocyanoacetate (Fig. S23)

(Charge = 0)

19 Atoms

E_{elec} = -567.80523380 Hartrees

ZPE = 0.147322 Hartrees

G_{298} = -567.735612 Hartrees

	X	Y	Z
N	1.05032800	-0.53181600	-0.18300100
C	-0.04942600	0.24098200	0.29995800
H	0.02790500	0.38194300	1.37641600
H	0.83828500	-1.31678600	-0.77503000
C	2.31045300	-0.22841300	0.19782900
C	3.38682000	-1.11574900	-0.33804500
H	3.97513300	-1.48414700	0.49389400
H	2.99860600	-1.95132300	-0.90584300
H	4.03762400	-0.52344400	-0.97164300
O	2.53314100	0.72741900	0.93410900
C	-0.09384800	1.57025100	-0.30854500
N	-0.11758000	2.62483100	-0.80452500
C	-1.34355800	-0.50543400	0.01555900
O	-1.37772600	-1.60091000	-0.48864300
O	-2.38013500	0.20693700	0.40966000
C	-3.66139800	-0.42059000	0.19850200
H	-3.71199500	-1.34358500	0.76022700
H	-4.38876800	0.28993600	0.55771900
H	-3.80251400	-0.61755100	-0.85561900

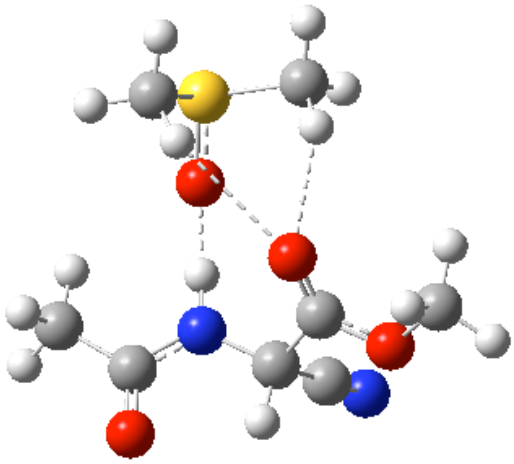

Figure S24. Fully optimized structure of the ethyl acetamidocyanoacetate plus one DMSO molecule complex at the MP2/cc-pVTZ level of theory, applying the IEF-PCM model for bulk DMSO solvent. (For the H-bonds distances see Fig. 6B)

Ethyl acetamidocyanoacetate–DMSO complex (Fig. S24)

(Charge = 0)

29 Atoms

E_{elec} = -1120.34762679 Hartrees

ZPE = 0.227759 Hartrees

G_{298} = -1120.166847 Hartrees

	X	Y	Z
N	0.26299000	1.29845700	0.19249700
C	1.54065000	0.67442500	0.26507200
H	2.25993400	1.36287300	-0.18023600
H	-0.56000500	0.80150200	0.55549100
C	0.13035000	2.48631900	-0.43866000
C	-1.26755200	3.01840900	-0.48416200
H	-1.58557900	3.06648700	-1.52048600
H	-1.95717200	2.40461900	0.08103800
H	-1.26647200	4.02801000	-0.09005900
O	1.08121900	3.08244700	-0.93860700
C	1.93560300	0.42969700	1.64743700
N	2.22219100	0.24337500	2.76218000
C	1.60180600	-0.61279100	-0.54812000
O	0.74259900	-0.95167400	-1.32511900
O	2.72322300	-1.26569300	-0.29929000
C	2.89881400	-2.47891700	-1.05755100
H	2.89774900	-2.25265200	-2.11537300
H	3.85393900	-2.87357300	-0.74886700
H	2.10320500	-3.17470400	-0.82599800
S	-2.80361900	-0.95434200	0.47303100
O	-1.91424800	0.02108200	1.23931100
C	-1.86348600	-2.46607300	0.34378700
H	-1.70995800	-2.82830900	1.35239200
H	-2.44145400	-3.18446100	-0.22678400
H	-0.92018900	-2.24753900	-0.14247700
C	-2.68587200	-0.47746800	-1.24417300
H	-1.63712700	-0.38897400	-1.50583000
H	-3.17813000	-1.23582800	-1.84265100
H	-3.20133100	0.46829500	-1.35352300

Particle based molecule species traced during the MD simulation of the 1M acetic acid in DMSO solution.

Table S4. Molecular species traced during the MD simulation of the 1M acetic acid in DMSO solution. Molecule species spc1 corresponds to DMSO (S), while molecule species 3 corresponds to acetic acid (E). Up to molecule species scp6 a significant number of reversible was observed. Molecules species scp7 and scp8 appeared rarely during the 2ns of the NVE MD simulation. Molecules species scp9 to spc11 not only were traced more rarely but also participate in reactions with low number of occurrences of even observed as non-reversible (Table S4). To this end, the quality of analysis that can be improved further, if needed, either by increasing the observation frequency (i.e. number of configuration dumped during the simulation) and the observation time (i.e. simulation time) or by refining further the criteria adopted for the calculation of H-bonds defining the particle based molecular species.

ID	Molecular species (particle based)	Syntactic type	$\langle n \rangle$ [molecules]	$\langle C \rangle$ [mol/lt]
spc1	S	S	352.370	12.791 ± 0.052
spc2	ES	E-S	22.139	0.805 ± 0.064
spc3	E	E	1.815	0.066 ± 0.047
spc4	E_2S	E-E-S	0.449	0.016 ± 0.023
spc5	E_2S	E-S-E	0.037	$1.34\times10^{-3} \pm 6.92\times10^{-3}$
spc6	E_2 (open)	E-E	0.028	$1.03\times10^{-3} \pm 6.11\times10^{-3}$
spc7	E_3S	E-E-E-S	3.55×10^{-3}	$1.29\times10^{-4} \pm 2.16\times10^{-3}$
spc8	E_2 (closed)	E=E	1.27×10^{-3}	$4.60\times10^{-5} \pm 1.29\times10^{-3}$
spc9	E_3S	S-E$\langle^{E}_{E}$	7.75×10^{-4}	$2.80\times10^{-5} \pm 1.01\times10^{-3}$
spc10	E_3S	E-E-S-E	1.50×10^{-4}	$0.50\times10^{-5} \pm 4.45\times10^{-3}$
spc11	E_3	E-E-E	1.50×10^{-4}	$0.50\times10^{-5} \pm 4.45\times10^{-3}$

Table S5. Reactions traced during the MD simulations of the 1M acetic acid in DMSO solution.

ID	Reaction	Forward	Reverse	K
	Higher occurrence (significant)			
1	S [spc1] + E [spc3] ⇆ ES [spc2]	38716	38715	0.954
2	E [spc3] + ES [spc2] ⇆ E_2S [spc4]	1519	1542	0.308
3	E_2 [spc6] + S [spc1] ⇆ E_2S [spc4]	607	589	1.239
4	E [spc3] + ES [spc2] ⇆ E_2S [spc5]	263	249	0.025
5	E [spc3] + ES [spc2] ⇆ E_2 [spc6] + S [spc1]	67	53	0.249
6	S [spc1] + 2 E [spc3] ⇆ E_2S [spc4]	61	60	0.294
7	2 E [spc3] ⇆ E_2 [spc6]	42	37	0.237
	Low occurrence (insignificant)			
8	E [spc3] + E_2S [spc4] ⇆ E_3S [spc7]	12	12	0.120
9	E_2 [spc6] ⇆ E_2 [spc8]	11	10	0.045
10	2 ES [spc2] ⇆ S [spc1] + E_2S [spc4]	8	8	0.323
11	E [spc3] + E_2S [spc4] ⇆ E_3S [spc9]	8	9	0.026
12	S [spc1] + 2 E [spc3] ⇆ E_2S [spc5]	3	9	0.024
13	S [spc1] + E_3 [spc10] ⇆ E_3S [spc7]	3	3	1.850
14	E_2 [spc6] + ES [spc2] ⇆ E_3S [spc7]	3	3	0.159
15	2 E [spc3] ⇆ E_2 [spc8]	1	2	0.011
16	E [spc3] + E_2S [spc4] ⇆ E_3S [spc11]	1	2	0.005
17	S [spc1] + E_3 [spc10] ⇆ E_3S [spc9]	1	1	0.404
18	E [spc3] + E_2S [spc4] ⇆ E_3S [spc11]	1	2	0.005
19	S [spc1] + E_3 [spc10] ⇆ E_3S [spc9]	1	1	0.404
20	2 E [spc3] + ES [spc2] ⇆ E_3S [spc7]	1	1	0.037
21	E_3S [spc7] ⇆ 2 E [spc3] + ES [spc2]	1	1	27.073
	Non reversible (analysis false)			
22	E [spc3] + ES [spc2] → E [spc3] + ES [spc2]	28		
23	S [spc1] + ES [spc2] → S [spc1] + ES [spc2]	53		
24	S [spc1] + E_2S [spc4] → S [spc1] + E_2S [spc4]	3		
25	E_2S [spc5] → E_2S [spc4]	5		
26	E [spc3] + E_2S [spc5] → E_3S [spc11]	1		
27	E [spc3] + E_2S [spc5] → E_3S [spc9]	1		
28	E_3S [spc11] → 2 E [spc3] + ES [spc2]	1		
29	E_3S [spc9] → E_3S [spc11]	1		
30	S [spc1] + E_2S [spc4] → E [spc3] + S [spc1] + ES [spc2]	1		
31	E_2S [spc4] + ES [spc2] → S [spc1] + E_3S [spc9]	1		
32	E_2 [spc6] + ES [spc2] → S [spc1] + E_3 [spc10]	1		
33	E_3 [spc10] → E_2 [spc6] + E [spc3]	1		
34	S [spc1] + E_2S [spc5] → 2 ES [spc2]	1		