RAMAN, SERS AND UV AND CIRCULAR DICHROISM OF N-ACETYL-L-CYSTEINE IN AQUEOUS SOLUTIONS.

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Table S1- Free energies (energies in Hartrees), differences in free energies for conformers of N-acetyl cysteine.

Conformers	G	S	ΔG[b]	% population[c]
		kJ/mol		
1-NAC	-874.688003	0.4923	0.00	29.08
2-NAC	-874.687759	0.4695	0.64	22.45
3-NAC	-874.687581	0.4466	1.11	18.59
4-NAC	-874.687478	0.4724	1.38	16.67

[a]B3LYP/6-311++G(d,p),IEFPCM(water);[b]$\Delta G = G_{NAC-i} - G_{NAC-1}$;[c]The population was calculated according to a Boltzmann distribution: $\%pop_i = \frac{e^{-\Delta G_i/RT}}{\sum_{k=1}^{n} e^{-\Delta G_k/RT}} \times 100\%$

Table S2. Experimental and calculated bond distances and angles for *NAC*.

		1-NAC	*2-NAC*	*3-NAC*	*4-NAC*
		(-)gauche, anti, (-)gauche	*(+)gauche, anti, syn*	*(+)gauche, anti, (+)gauche*	*anti,, anti, (+)gauche*
Distances/Å	Neutron[a]		Calculated[b]		
N-H		1.0097	1.0089	1.010	1.010
N-C_α	1.452	1.446	1.447	1.466	1.457
C_α-C_β	1.532	1.536	1.538	1.527	1.536
C_β-S	1.808	1.849	1.842	1.838	1.838
S-H	1.338	1.348	1.348	1.348	1.349
C_α-C(3)	1.522	1.536	1.530	1.548	1.531
C=O(1)	1.247	1.230	1.231	1.243	1.229
C=O(2)	1.213	1.206	1.209	1.209	1.209
C-O(3)	1.315	1.344	1.340	1.334	1.340
O(3)-H		0.971	0.971	0.996	0.972
C(1)-C(2)	1.498	1.512	1.512	1.505	1.513
N-C(2)	1.337	1.363	1.362	1.351	1.364
H(N)…S	2.747	3.335	3.131	3.292	4.538
N-H…O(3)[c]	2.365		2.630		
N-H…O(2)[c]		2.988	3.910	3.86	2.831
Angles/º					
N-C_α-C_β	112.6	111.9	113.4	111.0	110.8
N-C_α-C(3)	112.3	111.3	113.6	111.3	108.1
C_β -S-H	96.9	95.9	97.4	98.0	97.0
O(17)-C(3)-O(3)	124.8	123.8	123.5	121.5	123.8
C_α -C(3)-O(3)	115.1	110.9	113.6	114.7	112.4
C(2)-N-C_α	120.8	122.6	122.8	123.2	123.3
O(1)-C(2)-N	120.6	122.2	122.3	120.9	122.5
Dihedralangles/°					
S-C_β-C_α-N	61.8	-59.0	62.6	59.9	-179.6
C_β-C_α-N-C(2)	178.6	176.8	178.8	178.5	-179.2
C_α-N-C(2)-C(1)	163.8	-91.7	-123.3	-149.9	-124.6
N-C_α-$C_{(3)}$-$O_{(3)}$	1.1	172.1	9.7	60.2	111.9

[a] ref [14]; [b]B3LYP/6-311++G(d,p), IEFPCM(water); [c]ref [36]

Table S3- Selected bands observed in the Raman spectra of N-acetyl-Lcysteine in aqueous solution at 1.7-6.14 pH and SERS spectra.

	Normal Raman						*SERS*	
Solid	*Water solution (1M)*						*Water solution (25μM)*	
	pH							*Approximate description of modes*
	1.76	*2.5*	*3.01*	*4.01*	*5.10*	*6.14*		
2548 (100)	2582 (69)	2582 (77)	2581 (78)		2580(77)	2581(79)		ν S-H
1718 (20)	1722 (13)	1721 (10)	1721 sh	-	-	-		ν C= O(OH)
1590 (15)	1645 (23)	1645(23)	1642(24)	1642(23)br	1643 (23) 1632(26)	1642 (51) 1632(26)	1649	ν C= O(NH)
-	-	-	1558 sh	1559 sh	1556 sh	1559 sh	1555	ν_a COO^-
1521 sh								δ NH
1520 sh	1447 sh	1440 sh	1440 sh	1440 sh	1438 sh	1440 sh		δ_a CH_3
1430 (2)	1429 (10)	1429 (10)	1427 (11)	1427 (15)	1428 (20)	1426 (19)	1415	δ CH_2
1414 (8)	1419 sh							δ_a CH_3
-	-	1396 sh	1395 sh	1394 (25)	1395 (25)	1395 (27)	1377	ν_s COO^-
1373 (9)	1379 (11)	1381 (11)	1381 (13)	1381(21)	1380 (21)	1383 sh		δ_s CH_3
1334 (4)	1326 sh	1327 sh	1328 (15)	1329 (23)	1330(22)	1330 (24)	1316	δ $C_\alpha H$
1313 (1)	1314 (12)	1312 (13) br	1301 (13)	1297 (18)	1296 (16)	1297 (17)	1282	υN-C(O)
1277 (4)	1280 sh	1280 sh	1280 sh	1280 sh	1280 sh	1282 sh		tw CH_2
1260 sh	1261 (3)	1248 (2)	1248 (2)	1248 (2)	1250 (1)	1250 sh	1234	wag CH_2
1200 (6)	1200 (1)	1200 (2)	1200(2)	1200(2)	1200(2)	1201 (6)	1179	δ $C_\alpha H$
1128 (5)	1133 (5)	1134 (4)	1134(4)	1129 (4)	1128 (5)	1129 (6)		υN-Cα
	1061 sh	1064 sh	1064 sh	1064 sh		1070 (4)		ρ CH_3
1043 (11)	1044 (5)	1042 (2)	1041(2)	1039 (4)	1040 (4)	1041 (7)	1044	υC_β-Cα
	1025(2)	1025(2)	1025(2)	1025(2)	1025(2)	1025(2)		υC(O)-CH_3

989 (11)	986 (16)	983 (13)	983 (15)	983(25)	982 (22)	984 (23)	996	υCα-CO_2^-
	967 (12)	966 (10)	967 (10)	968(18)	969 sh	967 sh	948	
901 (6)	895 (3)	897 (4)	897 (4)	894(2)	895(2)	897 (2)	881	υCα-C(O)
				820 (8)	825 (9)	821 (9)	838	δ CO_2^-
795 (13)	793 (9)	772 (2)	772 (2)	779(4)	780 (7)	780 (7)	795	δ C-S-H
695 (25)	685 (26)	680 (21)	679 (45)	685(40)	686 (31)	684 (34)		υ C-S
676 (9)	658 (14)	654 (2)	653 (1.2)	656(13)	653 sh	653 sh		πCH_3–C=O out-of- plane
649 (5)	649 sh	647 (2)					735 650	π C=O_{acid} in-of- plane
575 (7)	584 sh	600 (2)	535 (0.5)				539	π C=O_{acid} of- plane
373 (15)	389 (6)	385(5)	388 (0.5)	387 (12)	386 (1)	386 (10)		ρ N-H out-of- plane

Table S4- Free energies (energies in Hartrees), differences in free energies for three conformers of *NACdep*$^-$

Conformers	G[a]	S	ΔG[b]	% population[c]
		kJ/mol		
1-NACdep$^-$	-874.244533	0.4548	0.00	75.51
2-NACdep$^-$	-874.242897	0.4530	1.03	13.34
3-NACdep$^-$	-874.242703	0.4541	1.15	10.86
4-NACdep$^-$	-874.238252	0.4601	3.94	0.10
5-NACdep$^-$	-874.238899	0.4590	3.54	0.19

[a]B3LYP/6-311++G(d,p),IEFPCM(water);[b]$\Delta G = G_{NACdep-i} - G_{NACdep-1}$;[c] The population was calculated according to a Boltzmann distribution: $\%pop_i = \frac{e^{-\Delta G_i/RT}}{\sum_{k=1}^{n} e^{-\Delta G_k/RT}} \times 100\%$

Table S5. Calculated bond distances and angles for *NACdep*$^-$

Distances/	*1-NACdep*$^-$	*2-NACdep*$^-$	*3-NACdep*$^-$

Å			
	(+)gauche, anti, syn	*(-)gauche, anti, (-)gauche*	*Anti, anti, syn*
N-C_α	1.456	1.456	1.457
C_α-C_β	1.536	1.535	1.541
C_β-S	1.842	1.854	1.853
S-H	1.348	1.349	1.350
C_α-C(3)	1.568	1.569	1.560
C=O(1)	1.234	1.236	1.238
C=O(2)	1.256	1.253	1.258
C=O(3)	1.254	1.256	1.253
C(1)-C(2)	1.517	1.516	1.516
N-C2	1.356	1.353	1.349
H(S)…N	2.831	-	-
N-H…O(2)	2.25	2.16	2.10
Angles/º			
N-C_α-C_β	112.1	112.8	109.6
N-C_α-C(3)	110.1	109.5	108.8
C_β -S-H	97.0	96.0	95.6
O(2)-C(3)-O(3)	127.9	127.9	127.7
C_α -C(3)-O(3)	116.7	115.5	116.9
C(2)-N-C_α	124.6	124.6	124.6
O(1)-C(2)-N	124.4	123.1	122.7
Dihedralangles/°			
S-C_β-C_α-N	65.0	-65.5	-170.0
C_α-N-C(5)-C(1)	169.7	171.0	175.5
C_β-C_α-N-C(2)	115.6	104.5	80.1
N-C_α-C(3)-O(3)	162.9	135.3	

[a] ref [5]; [ba]B3LYP/6-311++G(d,p), IEFPCM(water);

Table S6- Free energies (energies in Hartrees), differences in free energies for conformers of *NACdepp*$^{-2}$

Conformers	G	S	ΔG[b]	% population[c]
		kJ/mol		
1-NACdepp^{-2}	-873.777673	0.4370	0	42.0
2-NACdepp^{-2}	-873.777589	0.4387	0.66	38.0
3-NACdepp^{-2}	-873.777195	0.4461	0.30	13.3
4-NACdepp^{-2}	-874.238252	0.4447	2.62	0.30

[a]B3LYP/6-311++G(d,p),IEFPCM(water);[b]$\Delta G = G_{NACdepp-i} - G_{NACdepp-1}$;[c]The population was calculated according to a Boltzmann distribution: $\%pop_i = \frac{e^{-\Delta G_i/RT}}{\sum_{k=1}^{n} e^{-\Delta G_k/RT}} \times 100\%$

Table S7. Calculated bond distances and angles for *NACdepp*$^{-2}$

Distances/Å	*1-NACdepp*$^{-2}$	*2-NACdepp*$^{-2}$	*3-NACdepp*$^{-2}$
	(+)gauche, anti, syn	*(+)gauche, syn, anti*	*(-)gauche, anti, syn*
N-C_α	1.452	1.458	1.459
C_α-C_β	1.543	1.545	1.545
C_β-S	1.858	1.856	1.854
C_α-C(3)	1.565	1.557	1.561
C=O(1)	1.240	1.240	1.239
C=O(2)	1.261	1.260	1.260
C=O(3)	1.255	1.256	1.258
C(1)-C(2)	1.518	1.518	1.516
N-C(2)	1.344	1.343	1.348
(S)…H-N	2.580	-	-
N-H…O(17)		2.120	2.370
Angles/º			
N-C_α-C_β	109.0	113.6	112.1
N-C_α-C(3)	114.2	109.0	109.8
C_α -C_β -S	115.0	116.9	116.4
O(2)-C-O(3)	126.7	126.9	127.9
C_α -C(3)-O(3)	118.9	117.4	115.5
C(2)-N-C_α	125.4	125.5	125.9
O(1)-C(2)-N	123.4	123.4	123.9

Dihedralangles/°			
S-C_β-C_α-N	53.6	61.8	-66.8
C_α-N-C(2)-C(1)	176.7	176.5	173.2
C_β-C_α-N-C(2)	150.0	79.4	120.3
N-C_α-C(3)-O(3)	173.1	171.6	153.9

[a] ref [5]; [ba]B3LYP/6-311++G(d,p), IEFPCM(water);

Table S8- Selected bands observed in the Raman spectra of N-acetyl-L cysteine in aqueous solution at 6.93-12 pH.

pH	*Approximate description of modes*

6.93	*8.63*	*9.06*	*9.50*	*10.05*	*10.50*	*10.75*	*10.82*	*11.04*	*11.30*	*12.00*	
2582 (70)	2580 (70)	2581 (66)	2581 (56)	2581(35)	2581(17)	2580(11)	2580 (10)	2580 (5)	2580 (4)	-	ν S-H
1637 (26)	1631(29)	1628 (27)	1635 (30)	1645 sh 1632(35)	1645 sh 1632(39)	1633 (38)	1633(41)	1630 (38)	1630 (39)	1630 (23)	ν C= O(NH)
1556 sh	1554 sh	1554 sh	1556 sh	1558 sh	1558sh	1558(11)	1558 (15)	1558 (13)	1558 (13)	1553 (18)	ν_a CO_2^-
-											δ NH
1443 sh	1440 sh	1440 sh	1440 sh	1438 sh	1438 sh	1435 sh	-	-			δ_a CH_3
1429 (19)	1428(20)	1428 (20)	1430 (19)	1433 (27)	1435(25)	1435(20)	1434 (28)	1436 (26)	1436 (28)	1435 (26)	δ CH_2
	1397 sh										δ_a CH_3
1394 (26)	1393 (27)	1394 (26)	1394 (26)	1395 (27)	1395 (24)	1401(15)	1397 (21)	1397(21)	1396(21)	1398 (26)	ν_s CO_2^-
1380 (21)	1381 (23)	1381 (24)	1381(23)	1381 (27)	1380(24)	1380 (19)	1379 (23)	1379(22)	1380(23)	1381 (26)	δ_s CH_3
1329 (21)	1331 (25)	1330 (26)	1329 (25)	1331(30)	1331 (30)	1332 (31)	1331 (30)	1330(29)	1332 (30)	1332 ((30)	δ $C_\alpha H$
1296 (15)	1296 (19) br	1296(22)br	1296 (21)br	1292 (27)	1289 (29)br	1289 (31) 1285 sh	1289 (30)br	1289 (29)br	1287 (30) br	1288 (30)br	υN-C(O)
1244 (3)	1244 (3)	1244 (3)	1244 (3)	1244 (3)	1244 (3)	1236 (8)	1244 (3)	1241 (3)	1244 (3)	1244 (3)	tw CH_2
											wag CH_2
1203 (1)	1200 (2)	1200(2)	1200(2)	1190(8)	1189 (9)	1187 (11)	1186 (12)	1188 (12)	1188 (12)	1188 (11)	δ $C_\alpha H$
1132 (1)	1125 (4)	1120(5)	1122 (4)	1116 (6)	1113 (8)	1112 (11)	1113 (10)	1113(12)	1113 (10)	1113 (11)	υN-Cα
1062 (2)	1062 (2)	1062 (2)	1062 (2)	1062 (2)	1062 (2)	1062 (2)	1062 (2)	1062 (2)	1062 (2)	1062 (2)	ρ CH_3
1044 (2)	1040 (2)	1040(6)	1038 (6)	1036 (8)	1037 (10)	1040 (11)	1039 ((9)	1038(7)	1039 (8)	1039 (10)	υ□C_β-Cα
983 (20)	982 (21)	982 (23)	983(19)	980 (15)	976sh	980 sh	976 sh	977 sh	975 sh	976 sh	υC(O)-CH_3
966 (16)	966 (16)	970 (21)	968(16)	969 (18)	964 (23)	963 (20)	963 (24)	963(19)	963 (23)	963 (16)	υCα-CO_2^-
940 (5)	935 (6)	935 (8)	935 (10)	934 (18)	935 (21)	933 (23)	936 (32)	934 (30)	935 (32)	935 (26)	
897(6)	897(6)	897(6)	897(6)	897(6)	897(6)	897 (11)	-			-	υCα-C(O)
821	823 (9)	823 (9)	822 (9)	822 (9)	821 (12)	836 (5)	836 (10)	835 (10)	835 (32)	836	δ CO_2^-

(9)						821(4)				(7)	
783 (2)	783 (2)	784 (4)	□□□□□□	784 (9)	780 (7)	795 (1)	795 (1)	790 sh	790 sh	-	δ C-S-H
686 (32)	686 (36)	684 (35)	□□□□□□□	686 (47)	686 (47)	686 (50)	686(51)	686 (52)	686 (50)	685 (51)	υ C-S
653 (11)	651 (13)	651 (13)	□□□□□□□	653 (18)	652(14)	655 (14)	650 (18)	650(19)	651 (15)	652 (18)	πCH_3-C=O out-of- plane
											π C=O_{acid} in-of- plane
544 (2)	541 (1)	542 (6)	543 (7)	542 (8)	544 (10)	545 (8)	542 (11)	545 (11)	544 (10)	545 (11)	π C=O_{acid} of-plane
389 (2)	387(2)	385 (8)	□□□□□□□□	386 (8)	386 (10)	390 (10)	389 (9)	389 (9)	389 (9)	389 (9)	ΠN-H out-of- plane

Table S9- pK' values of the -SH group in *NAC*

pH	pK’
6.94	8.90
8.63	9.15
9.06	9.32
9.50	9,56
10.05	9,73
10.50	9,72
10.75	9,77
10.82	9,77
11.04	9,77
11.30	9,78

Table S10- C=O_{amide} , C(O)-N, C_{α}-N, C-S and N-H electron occupancy of the Natural Bond Orbitals and NPA charges at the B3LYP / 6-311++G(d,p) level of theory.

C=O_{amide}	σ	π	σ*	π*	q(O)	q(C)
1-NAC	1.993	1.992	0.043	0.247	-0.637	0.687

1-NACdep^{-}	1.992	1.991	0.059	0.287	-0.674	0.665
1-NACdepp^{-2}	1.993	1.993	0.023	0.377	-0.719	0.657

C(O)-N	σ	σ*	q(C)	q(N)
1-NAC	1.991	0.075	0.687	-0.638
1-NACdep^{-}	1.990	0.070	0.665	-0.641
1-NACdepp^{-2}	1.990	0.064	0.657	-0.612

C_{α}-N	σ	σ*	q(C)	q(N)
1-NAC	1.986	0.029	-0.135	-0.638
1-NACdep^{-}	1.985	0.035	-0.138	-0.641
1-NACdepp^{-2}	1.985	0.037	-0.143	-0.612

N-H	σ	σ*	q(N)	q(N)
1-NAC	1.985	0.018	-0.638	0.200
1-NACdep^{-}	1.979	0.028	-0.641	0.408
1-NACdepp^{-2}	1.982	0.043	-0.612	0.410

C-S	σ	σ*	q(C)	q(S)
1-NAC	1.985	0.015	-0.484	-0.028
1-NACdep^{-}	1.988	0.027	-0.473	-0.084
1-NACdepp^{-2}	1.984	0.016	-0.492	-0.750

Figure S1. The pH metric titration curve of NAC

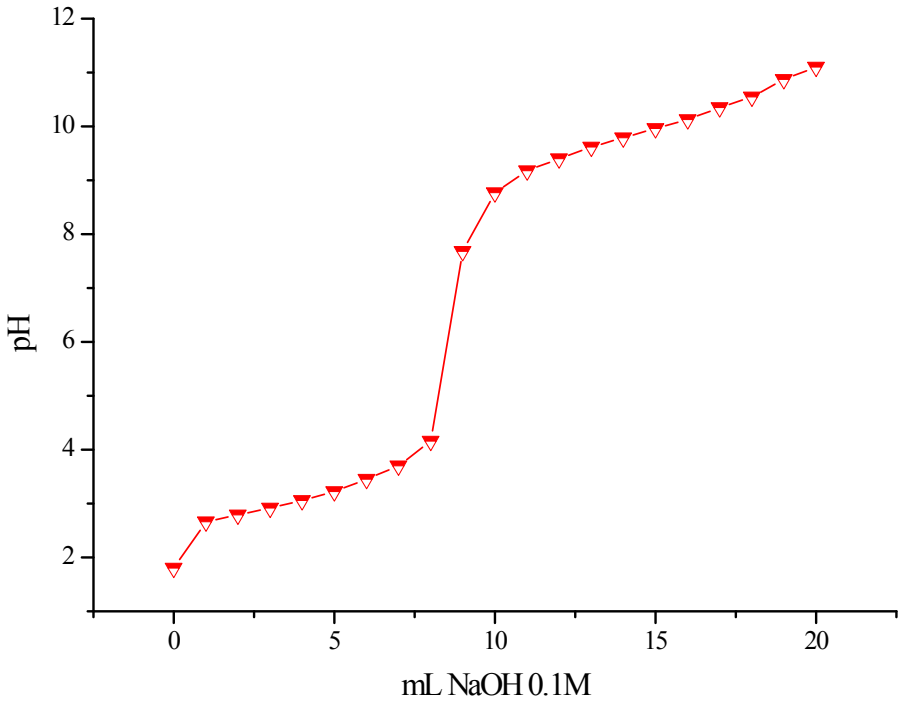


Figure S2. Raman spectra of *NAC* in the solid state and in water solution at different concentrations.

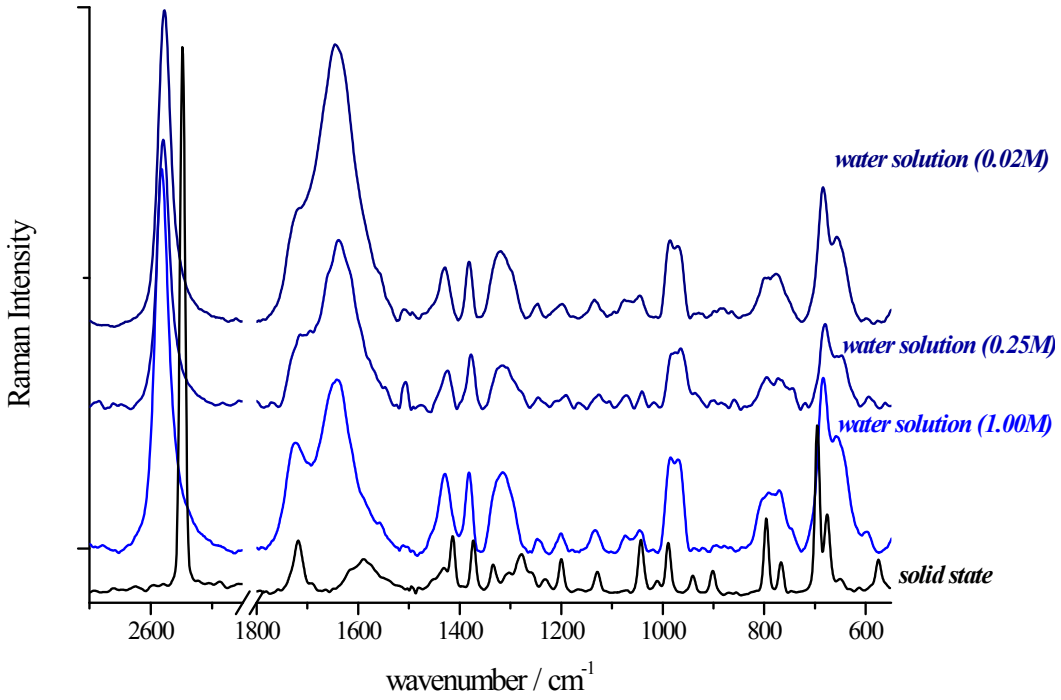


Figure S3. Fractional ionization α_{SH} *vs* concentration

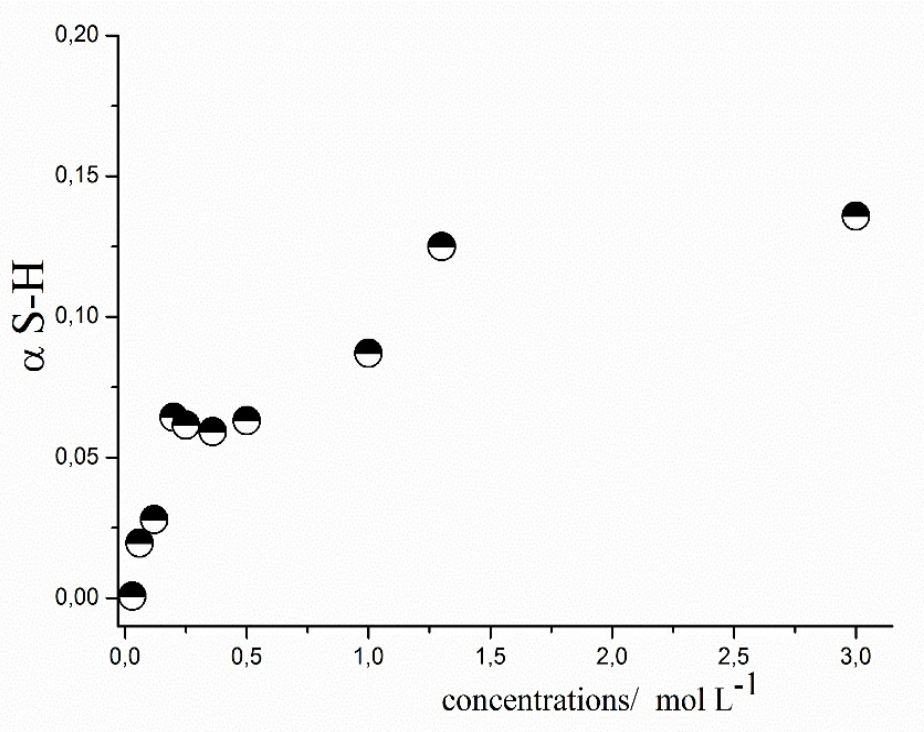
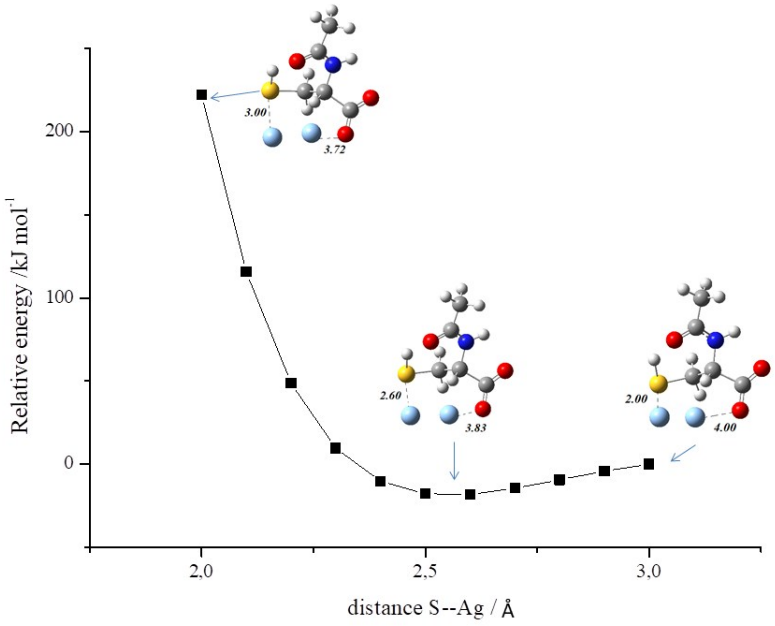

0,20
0,15
0,10
0,05
0,00
α S-H
0,0
0,5
1,0
1,5
2,0
2,5
3,0
concentrations/ mol L-1

Figure S4- Calculated potential curves about the Ag–S bond (up) and Ag-O(down) in 1-NACdep$^-$ using semiempirical (PM6) levels of theory



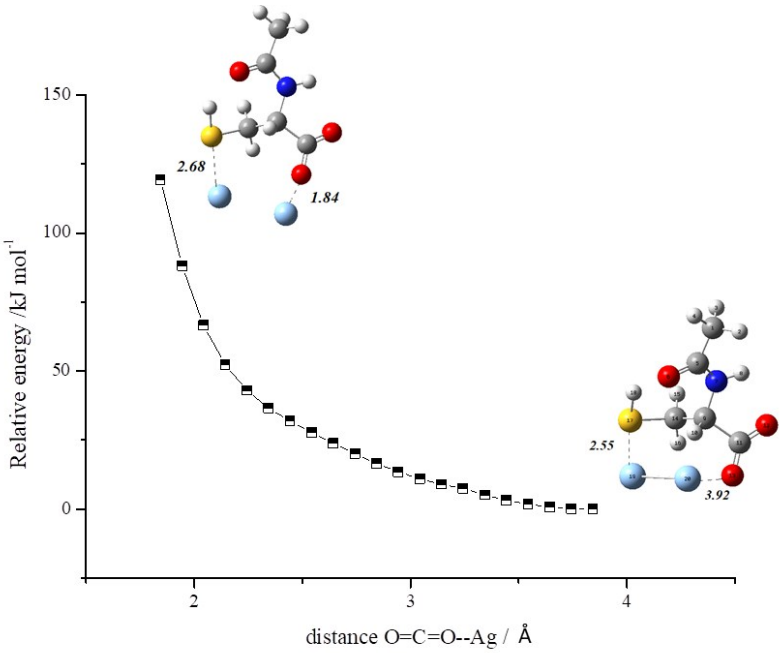
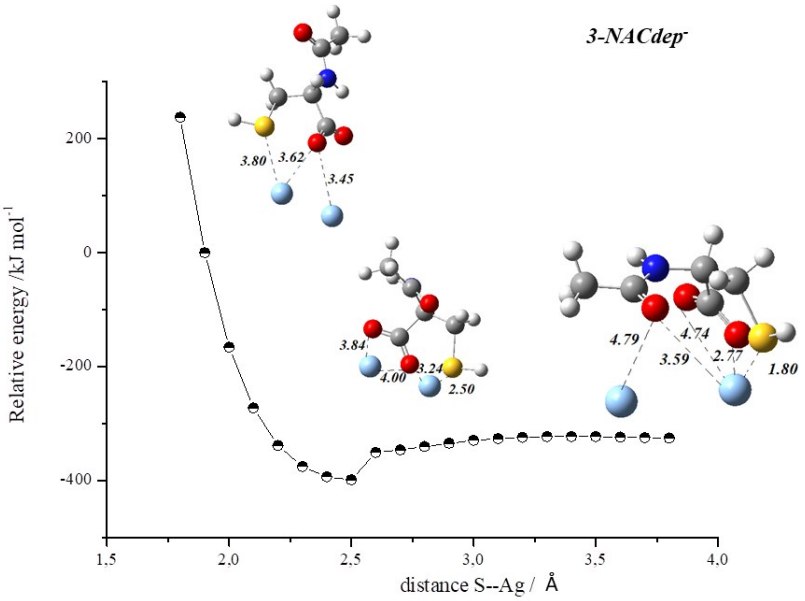


Figure S5- Calculated potential curves about the Ag–S bond (up) and Ag-O(down) in 3-NACdep$^-$ using semiempirical (PM6) levels of theory



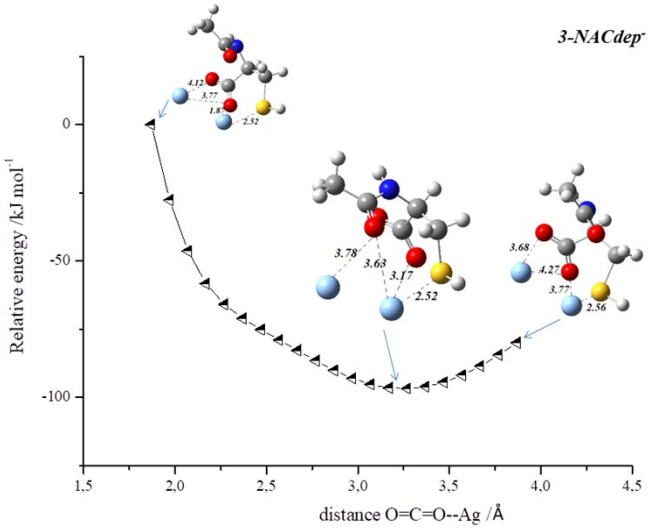


Figure S6

Theoretical UV spectra of NACdepp^{2-} form in wáter solution

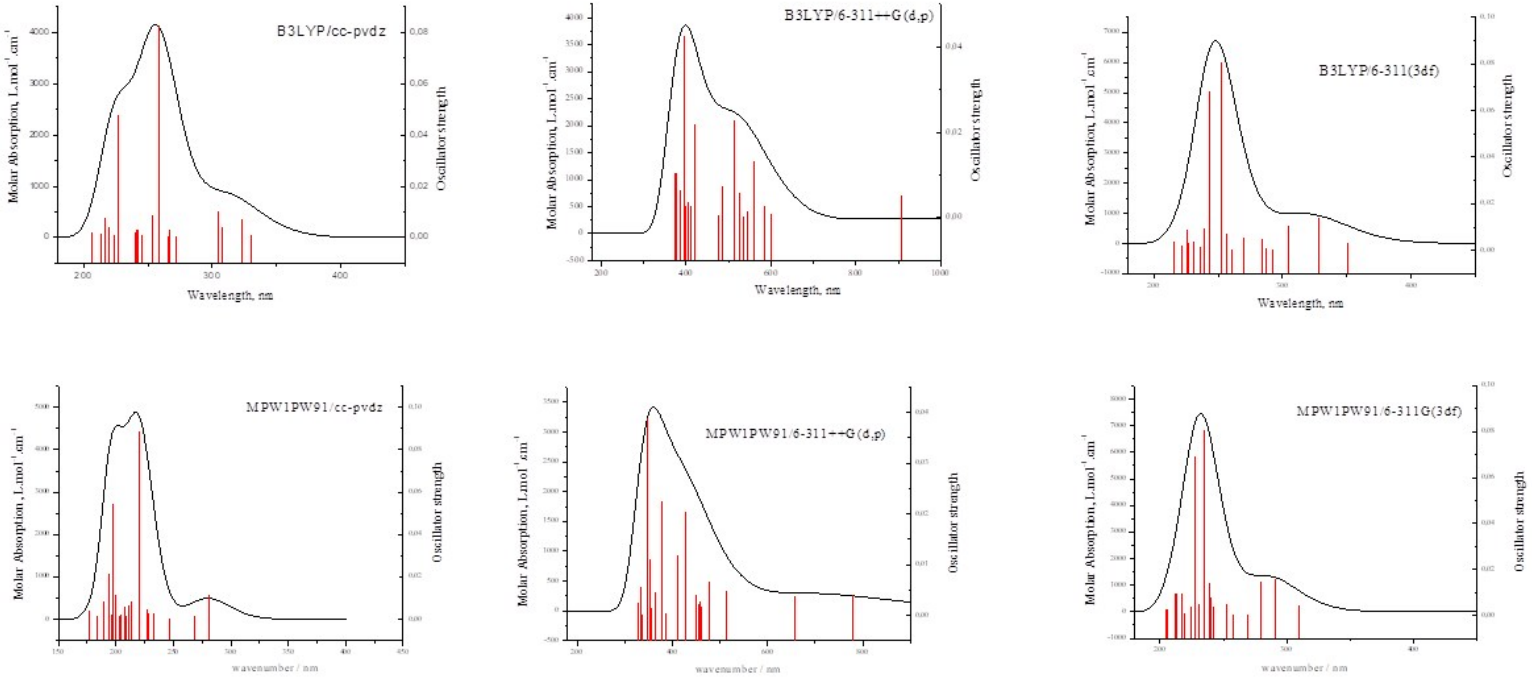


Figure S7- Raman spectra of the *NAC* at different pH value in the 1500-1200 region.