Supporting Information

Inspecting the structural characteristics of chiral drug penicillamine under different pH conditions by Raman Optical Activity spectroscopy and DFT calculations

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solvation model (SMD) and explicit water molecules in H_2O.

- **Figure S11.** The theoretical Raman and ROA spectra of D- and L-penicillamine with different solvation models in H_2O.
- **Table S1.** Dihedral angles of theoretical six conformations of L-penicillamine
- **Table S2.**△G and Boltzmann distributions of theoretical conformations of penicillamine under different pH conditions
- **Table S3.** Assignment of vibrational modes of penicillamine in H_2O

Part one: The atomic coordinates of the optimized structural models of D-penicillamine (pH<1.9):

P_N^I:

C	-0.51615	-0.38198	-0.53597
C	-1.60216	0.63424	-0.0601
C	0.86216	-0.3434	0.17935
O	-2.754	0.15036	0.14647
O	-1.27585	1.84484	0.03687
N	-1.14942	-1.75002	-0.43048
H	-2.16826	-1.56696	-0.38399
H	-0.91547	-2.34649	-1.22699
C	0.71879	-0.29447	1.70545
H	0.20787	0.61786	2.03434
H	1.70817	-0.32863	2.17654
H	0.14548	-1.16052	2.0725
C	1.72501	-1.5424	-0.24929
H	1.76096	-1.64528	-1.34151
H	2.75003	-1.41706	0.1225
H	1.34253	-2.47791	0.18054
S	1.8008	1.16325	-0.43206
H	-0.36641	-0.21251	-1.6078
H	0.77195	2.02953	-0.22897
H	-0.89087	-2.24737	0.42574
H	-3.86047	0.89352	0.

P_N^{II}:

C	0.53625	0.47597	-0.49478
C	1.52021	-0.63228	-0.05014
C	-0.87679	0.35739	0.15879
O	2.80699	-0.24332	-0.04902
O	1.18534	-1.75705	0.23568
H	2.78847	0.71739	-0.26272
N	1.21064	1.77737	-0.3351
H	0.86308	2.46786	-0.99238
H	1.09177	2.15585	0.60191
C	-0.7984	0.35492	1.69238
H	-0.24406	-0.5141	2.06183
H	-1.80728	0.32389	2.12136
H	-0.31058	1.27103	2.06555
C	-1.76001	1.51307	-0.33345
H	-1.81013	1.54369	-1.43024
H	-2.78074	1.40445	0.05414

H	-1.37857	2.47917	0.02681
S	-1.63096	-1.26654	-0.43573
H	0.40745	0.31805	-1.57589
H	-2.86474	-0.75573	-0.68308
H	2.30926	2.0845	-0.29551

P_C^I:

C	-1.79239	0.16123	-0.10701
O	-2.02176	1.31972	0.15381
O	-2.79813	-0.73826	-0.29268
H	-3.63171	-0.25613	-0.1661
C	-0.42703	-0.49776	-0.33464
C	0.78055	0.40692	0.05524
H	-0.37633	-0.63232	-1.43393
N	-0.39724	-1.77996	0.38017
H	-1.26328	-2.2889	0.23036
H	0.35782	-2.34871	0.00573
C	0.86903	1.63716	-0.86091
H	0.92904	1.34637	-1.91945
H	1.76502	2.22157	-0.61821
H	-0.0125	2.2721	-0.72333
C	0.77069	0.80482	1.53451
H	1.69412	1.33944	1.78674
H	0.68548	-0.07933	2.17714
H	-0.08128	1.46635	1.73644
S	2.18981	-0.45831	-0.2815
H	2.19217	-1.23045	0.8336
H	-0.28543	-1.63025	1.40038

P_C^{II}:

C	-1.80058	0.15734	-0.20694
O	-2.24033	1.22389	-0.587
O	-2.48536	-0.71562	0.54749
C	-0.40091	-0.33824	-0.572
C	0.75105	0.43273	0.15958
H	-0.29187	-0.18641	-1.65071
N	-0.32199	-1.82029	-0.35611
H	-0.41191	-2.0831	0.63114
H	-1.06495	-2.30377	-0.87222
C	0.86284	1.84734	-0.42466
H	1.0643	1.82368	-1.50379
H	1.67727	2.38498	0.07462
H	-0.06795	2.40225	-0.26182
C	0.56348	0.47695	1.67877

H	1.41951	0.97778	2.144
H	0.46693	-0.52055	2.1256
H	-0.339	1.05373	1.92475
S	2.38469	-0.40536	-0.27214
H	2.404	-1.2999	0.75333
H	0.58368	-2.1642	-0.70067
H	-3.39086	-0.37959	0.69032

P_H^I:

C	-1.68484	-0.01165	-0.04591
O	-2.08617	-1.02495	0.49638
O	-2.25779	1.18796	0.07395
H	-3.00009	1.12459	0.70361
C	-0.40526	-0.25353	-0.8419
C	0.90766	0.34094	-0.23105
H	-0.71029	0.2429	-1.75832
N	-0.30583	-1.71673	-1.15025
H	-1.25671	-1.97848	-1.43473
H	0.2975	-1.80902	-1.97402
C	2.01391	0.35545	-1.29441
H	2.92533	0.79103	-0.8697
H	1.69219	0.97602	-2.14226
H	2.26689	-0.6429	-1.67357
C	0.66676	1.76876	0.28035
H	1.61583	2.24901	0.5438
H	0.20277	2.34062	-0.53357
H	0.00594	1.81042	1.15434
S	1.4581	-0.65449	1.26484
H	2.1655	-1.60102	0.59249
H	0.00519	-2.3936	-0.44143

P_H^{II}:

C	-1.68499	0.19849	-0.00803
O	-2.29473	1.24537	0.04738
O	-2.08083	-0.9041	0.6741
H	-2.86793	-0.64991	1.18324
C	-0.43092	-0.02826	-0.86061
C	0.88816	0.4199	-0.14094
H	-0.55405	0.66929	-1.7012
N	-0.2998	-1.37376	-1.41218
H	-1.02109	-1.54884	-2.10644
H	-0.41854	-2.06687	-0.67691
C	2.00011	0.53868	-1.19206
H	2.95357	0.78336	-0.70942

H	1.75394	1.34394	-1.90144
H	2.1122	-0.39316	-1.75692
C	0.71552	1.7566	0.59415
H	1.6851	2.09451	0.97946
H	0.32718	2.51816	-0.09527
H	0.01697	1.68677	1.43653
S	1.39738	-0.81742	1.17369
H	1.83038	-1.78481	0.32781
H	0.55902	-1.35968	-1.82496

The atomic coordinates of the optimized structural models of D-penicillamine (1.9≤pH<7.9):

P_N^I:

C	0.38581	0.45763	-0.30424
C	1.69955	-0.53333	-0.05903
C	-0.86566	0.34263	0.17509
O	2.79436	-0.06344	0.36992
O	1.40376	-1.75121	-0.16319
N	0.77515	1.90485	-0.52012
H	1.8004	1.83592	-0.39121
H	0.54107	2.33484	-1.41751
C	-1.20287	0.93344	2.03449
H	-0.48467	0.22103	2.45668
H	-2.20569	0.66937	2.39016
H	-0.96601	1.93569	2.42535
C	-2.14253	1.17189	-0.33211
H	-2.76871	0.82993	-1.16625
H	-2.77946	1.29523	0.55321
H	-1.74007	2.16419	-0.57656
S	-1.58039	-1.45433	-0.1996
H	0.02705	0.0181	-1.24088
H	-0.41036	-2.1024	-0.44798
H	0.41776	2.50706	0.22639

P_N^{II}:

C	0.53949	0.38002	-0.536
C	1.58807	-0.66773	-0.06129
C	-0.84476	0.36243	0.16717
O	2.75574	-0.22482	0.15942
O	1.20711	-1.85998	0.01801
N	1.19852	1.73246	-0.41294
H	0.97665	2.34546	-1.20055
H	0.94989	2.22031	0.45228
C	-0.71771	0.39144	1.69499
H	-0.1632	-0.47588	2.07104
H	-1.71423	0.39283	2.15259
H	-0.20124	1.3049	2.02914
C	-1.69718	1.53869	-0.33308
H	-1.76528	1.55024	-1.42828
H	-2.71092	1.47367	0.08098
H	-1.27673	2.49741	0.00201
S	-1.69155	-1.23974	-0.3674
H	0.39476	0.22119	-1.61038

H	-2.93811	-0.70134	-0.42121
H	2.21332	1.52905	-0.36865

P_C^I:

C	-1.87275	0.10801	-0.16381
O	-2.33087	1.13105	-0.73538
O	-2.45248	-0.60507	0.70379
C	-0.43782	-0.33681	-0.57653
C	0.69738	0.38921	0.20326
H	-0.30681	-0.16141	-1.64747
N	-0.37362	-1.82319	-0.37139
H	-0.79689	-2.05338	0.53648
H	-0.92448	-2.30258	-1.08967
C	0.6787	1.88576	-0.13197
H	0.75466	2.06147	-1.21309
H	1.51808	2.38641	0.36464
H	-0.25333	2.34052	0.22292
C	0.62274	0.16708	1.71692
H	1.46214	0.67075	2.21021
H	0.65823	-0.89607	1.9893
H	-0.30962	0.59194	2.11187
S	2.36309	-0.24789	-0.4373
H	2.55377	-1.21663	0.49619
H	0.58749	-2.1797	-0.41932

P_C^{II}:

C	-1.87028	0.10724	-0.17554
O	-2.32019	1.12004	-0.76938
O	-2.45849	-0.59203	0.69761
C	-0.4318	-0.34897	-0.5646
C	0.69535	0.39602	0.20839
H	-0.2977	-0.20047	-1.63998
N	-0.36209	-1.82823	-0.31034
H	-0.90444	-2.03144	0.54077
H	-0.79223	-2.3473	-1.08091
C	0.64475	1.89842	-0.08729
H	0.65942	2.09778	-1.16593
H	1.51149	2.39067	0.36934
H	-0.26449	2.34287	0.3366
C	0.65174	0.13728	1.7183
H	1.48311	0.65681	2.21004
H	0.72155	-0.92795	1.97138
H	-0.28491	0.53065	2.13488
S	2.15869	-0.04397	-0.60388

H	2.97075	0.84738	0.01748
H	0.60989	-2.14688	-0.20803

P_H^I:

C	1.70245	-0.35154	-0.09306
O	2.55613	0.34388	0.53633
O	1.77657	-1.57856	-0.34469
C	0.48078	0.43099	-0.66378
C	-0.94065	-0.09716	-0.3394
H	0.59025	0.43675	-1.7556
N	0.65425	1.86178	-0.22553
H	1.64095	1.92478	0.08726
H	0.45649	2.52929	-0.97443
C	-2.00451	0.88005	-0.86185
H	-3.00537	0.47099	-0.68204
H	-1.87365	1.01106	-1.94595
H	-1.95843	1.86907	-0.38947
C	-1.17405	-1.475	-0.97488
H	-2.22681	-1.75657	-0.85135
H	-0.95288	-1.42354	-2.04991
H	-0.54346	-2.25189	-0.53488
S	-1.14161	-0.33245	1.52111
H	-1.5572	0.92666	1.82107
H	0.07048	2.10363	0.58092

P_H^{II}:

C	-1.68499	0.19849	-0.00803
O	-2.29473	1.24537	0.04738
O	-2.08083	-0.9041	0.6741
C	-0.43092	-0.02826	-0.86061
C	0.88816	0.4199	-0.14094
H	-0.55405	0.66929	-1.7012
N	-0.2998	-1.37376	-1.41218
H	-1.02109	-1.54884	-2.10644
H	-0.41854	-2.06687	-0.67691
C	2.00011	0.53868	-1.19206
H	2.95357	0.78336	-0.70942
H	1.75394	1.34394	-1.90144
H	2.1122	-0.39316	-1.75692
C	0.76155	1.96498	0.09806
H	1.58041	2.45103	0.6421
H	0.53164	2.56069	-0.79544
H	-0.12848	1.97333	0.73853
S	1.37024	-0.75145	1.1036

H	2.75122	-0.90885	0.58936
H	0.57023	-1.76047	-1.78069

The atomic coordinates of the optimized structural models of D-penicillamine (7.9≤pH<10.7):

P_N^I:

C	-0.51615	-0.38198	-0.53597
C	-1.60216	0.63424	-0.0601
C	0.86216	-0.3434	0.17935
O	-2.754	0.15036	0.14647
O	-1.27585	1.84484	0.03687
N	-1.14942	-1.75002	-0.43048
H	-0.91547	-2.34649	-1.22699
C	0.71879	-0.29447	1.70545
H	0.20787	0.61786	2.03434
H	1.70817	-0.32863	2.17654
H	0.14548	-1.16052	2.0725
C	1.72501	-1.5424	-0.24929
H	1.76096	-1.64528	-1.34151
H	2.75003	-1.41706	0.1225
H	1.34253	-2.47791	0.18054
S	1.8008	1.16325	-0.43206
H	-0.36641	-0.21251	-1.6078
H	0.77195	2.02953	-0.22897
H	-0.89087	-2.24737	0.42574

P_N^{II}:

C	0.45461	0.21943	-0.58959
C	1.50319	-0.82832	-0.11487
C	-0.92964	0.20184	0.11358
O	2.67086	-0.38542	0.10583
O	1.12223	-2.02057	-0.03558
N	1.11364	1.57186	-0.46652
H	0.89178	2.18486	-1.25413
H	0.86501	2.05971	0.39869
C	-0.80259	0.23085	1.6414
H	-0.24808	-0.63647	2.01746
H	-1.79911	0.23224	2.09901
H	-0.28612	1.14431	1.97556
C	-1.78206	1.3781	-0.38666
H	-1.85016	1.38964	-1.48186
H	-2.7958	1.31307	0.0274
H	-1.36161	2.33682	-0.05158
S	-1.69155	-1.23974	-0.3674
H	0.30988	0.06059	-1.66396
H	-2.93811	-0.70134	-0.42121

P_C^I:

C	-1.70574	0.04413	-0.22804
O	-2.16385	1.06717	-0.7996
O	-2.28547	-0.66895	0.63956
C	-0.2708	-0.40069	-0.64075
C	0.86439	0.32533	0.13903
H	-0.1398	-0.22529	-1.71169
N	-0.20661	-1.88707	-0.43562
H	-0.62988	-2.11726	0.47226
H	-0.75746	-2.36646	-1.15389
C	0.84571	1.82188	-0.19619
H	0.92167	1.99759	-1.27732
H	1.68509	2.32253	0.30041
H	-0.08632	2.27664	0.1587
C	0.78975	0.1032	1.65269
H	1.62915	0.60687	2.14598
H	0.82524	-0.95995	1.92508
H	-0.14261	0.52806	2.04764
S	2.36309	-0.24789	-0.4373
H	2.55377	-1.21663	0.49619

P_C^{II}:

C	-1.87038	0.10701	-0.17543
O	-2.32063	1.11966	-0.76929
O	-2.45829	-0.59229	0.69789
C	-0.43185	-0.34885	-0.56468
C	0.69529	0.39612	0.20839
H	-0.29781	-0.20002	-1.64003
N	-0.36176	-1.82814	-0.31094
H	-0.90282	-2.03185	0.54083
H	-0.79289	-2.34701	-1.0811
C	0.64465	1.8985	-0.08742
H	0.65991	2.09781	-1.16607
H	1.51102	2.39093	0.36969
H	-0.26496	2.3428	0.33584
C	0.65153	0.13745	1.7183
H	1.48288	0.65691	2.21013
H	0.72116	-0.92779	1.97142
H	-0.28514	0.53092	2.13474
S	2.3245	-0.28539	-0.49938
H	2.99444	-0.3631	0.67758

P_H^I:

C	1.70245	-0.35154	-0.09306
O	2.55613	0.34388	0.53633
O	1.77657	-1.57856	-0.34469
C	0.48078	0.43099	-0.66378
C	-0.94065	-0.09716	-0.3394
H	0.59025	0.43675	-1.7556
N	0.65425	1.86178	-0.22553
H	0.45649	2.52929	-0.97443
C	-2.00451	0.88005	-0.86185
H	-3.00537	0.47099	-0.68204
H	-1.87365	1.01106	-1.94595
H	-1.95843	1.86907	-0.38947
C	-1.17405	-1.475	-0.97488
H	-2.22681	-1.75657	-0.85135
H	-0.95288	-1.42354	-2.04991
H	-0.54346	-2.25189	-0.53488
S	-1.14161	-0.33245	1.52111
H	-1.5572	0.92666	1.82107
H	0.07048	2.10363	0.58092

P_H^{II}:

C	1.7255	0.23036	0.08294
O	2.23189	1.24511	0.65307
O	2.10065	-0.2242	-1.03868
C	0.48397	-0.46947	0.69616
C	-0.90107	0.14702	0.32668
H	0.58281	-0.2775	1.77829
N	0.96161	-2.0091	0.84479
H	0.27278	-2.62787	1.26418
C	-2.02014	-0.6649	0.99626
H	-2.99852	-0.22331	0.76659
H	-1.88696	-0.64745	2.08933
H	-2.03154	-1.70755	0.6612
C	-1.02061	1.61294	0.75843
H	-2.03883	1.97684	0.56604
H	-0.8318	1.69732	1.83891
H	-0.31298	2.26137	0.23393
S	-1.10032	0.05027	-1.58329
H	-2.45033	0.17287	-1.51283
H	0.91431	-2.1503	-0.16145

The atomic coordinates of the optimized structural models of D-penicillamine (pH ≥ 10.7):

P_N^I:

C	-0.51615	-0.38198	-0.53597
C	-1.60216	0.63424	-0.0601
C	0.86216	-0.3434	0.17935
O	-2.754	0.15036	0.14647
O	-1.27585	1.84484	0.03687
N	-1.14942	-1.75002	-0.43048
H	-0.91547	-2.34649	-1.22699
C	0.71879	-0.29447	1.70545
H	0.20787	0.61786	2.03434
H	1.70817	-0.32863	2.17654
H	0.14548	-1.16052	2.0725
C	1.72501	-1.5424	-0.24929
H	1.76096	-1.64528	-1.34151
H	2.75003	-1.41706	0.1225
H	1.34253	-2.47791	0.18054
S	1.8008	1.16325	-0.43206
H	-0.36641	-0.21251	-1.6078
H	-0.89087	-2.24737	0.42574

P_N^{II}:

C	0.53625	0.47597	-0.49478
C	1.52021	-0.63228	-0.05014
C	-0.87679	0.35739	0.15879
O	2.80699	-0.24332	-0.04902
O	1.18534	-1.75705	0.23568
N	1.21064	1.77737	-0.3351
H	0.86308	2.46786	-0.99238
H	1.09177	2.15585	0.60191
C	-0.7984	0.35492	1.69238
H	-0.24406	-0.5141	2.06183
H	-1.80728	0.32389	2.12136
H	-0.31058	1.27103	2.06555
C	-1.76001	1.51307	-0.33345
H	-1.81013	1.54369	-1.43024
H	-2.78074	1.40445	0.05414
H	-1.37857	2.47917	0.02681
S	-1.63096	-1.26654	-0.43573
H	0.40745	0.31805	-1.57589

P_C^I:

C	-1.62538	0.05869	-0.14692
O	-1.85475	1.21718	0.1139
O	-2.63112	-0.8408	-0.33259
C	-0.26002	-0.60029	-0.37455
C	0.94756	0.30438	0.01534
H	-0.20932	-0.73486	-1.47383
N	-0.23023	-1.8825	0.34027
H	-1.09627	-2.39143	0.19045
H	0.52483	-2.45124	-0.03417
C	1.03603	1.53463	-0.90081
H	1.09605	1.24383	-1.95936
H	1.93203	2.11903	-0.65812
H	0.15451	2.16956	-0.76324
C	0.9377	0.70228	1.49461
H	1.86113	1.2369	1.74683
H	0.85248	-0.18187	2.13724
H	0.08573	1.36381	1.69653
S	2.35682	-0.56085	-0.32141

P_C^{II}:

C	-1.87038	0.10701	-0.17543
O	-2.32063	1.11966	-0.76929
O	-2.45829	-0.59229	0.69789
C	-0.43185	-0.34885	-0.56468
C	0.69529	0.39612	0.20839
H	-0.29781	-0.20002	-1.64003
N	-0.36176	-1.82814	-0.31094
H	-0.90282	-2.03185	0.54083
H	-0.79289	-2.34701	-1.0811
C	0.64465	1.8985	-0.08742
H	0.65991	2.09781	-1.16607
H	1.51102	2.39093	0.36969
H	-0.26496	2.3428	0.33584
C	0.65153	0.13745	1.7183
H	1.48288	0.65691	2.21013
H	0.72116	-0.92779	1.97142
H	-0.28514	0.53092	2.13474
S	2.3245	-0.28539	-0.49938

P_H^I:

C	1.64939	-0.11206	-0.08085
O	2.44386	0.49895	0.59985
O	1.83627	-1.41046	-0.41124

C	0.40132	0.50554	-0.71458
C	-0.95571	-0.1663	-0.29932
H	0.50176	0.32462	-1.80093
N	0.39594	1.93408	-0.39996
H	1.29025	2.20566	-0.00047
H	0.21716	2.50214	-1.22029
C	-2.10492	0.64583	-0.91714
H	-3.06738	0.19961	-0.64093
H	-2.02555	0.63914	-2.01684
H	-2.09289	1.68424	-0.57102
C	-1.07452	-1.6287	-0.75257
H	-2.08665	-1.99736	-0.54199
H	-0.90946	-1.69776	-1.8378
H	-0.35544	-2.28509	-0.25606
S	-1.11011	-0.17191	1.56379

P_H^{II}:

C	-1.68499	0.19849	-0.00803
O	-2.29473	1.24537	0.04738
O	-2.08083	-0.9041	0.6741
C	-0.43092	-0.02826	-0.86061
C	0.88816	0.4199	-0.14094
H	-0.55405	0.66929	-1.7012
N	-0.2998	-1.37376	-1.41218
H	-1.02109	-1.54884	-2.10644
H	-0.41854	-2.06687	-0.67691
C	2.00011	0.53868	-1.19206
H	2.95357	0.78336	-0.70942
H	1.75394	1.34394	-1.90144
H	2.1122	-0.39316	-1.75692
C	0.71552	1.7566	0.59415
H	1.6851	2.09451	0.97946
H	0.32718	2.51816	-0.09527
H	0.01697	1.68677	1.43653
S	1.39738	-0.81742	1.17369

The D-Pen and L-Pen mentioned there represent D-penicillamine and L-penicillamine.

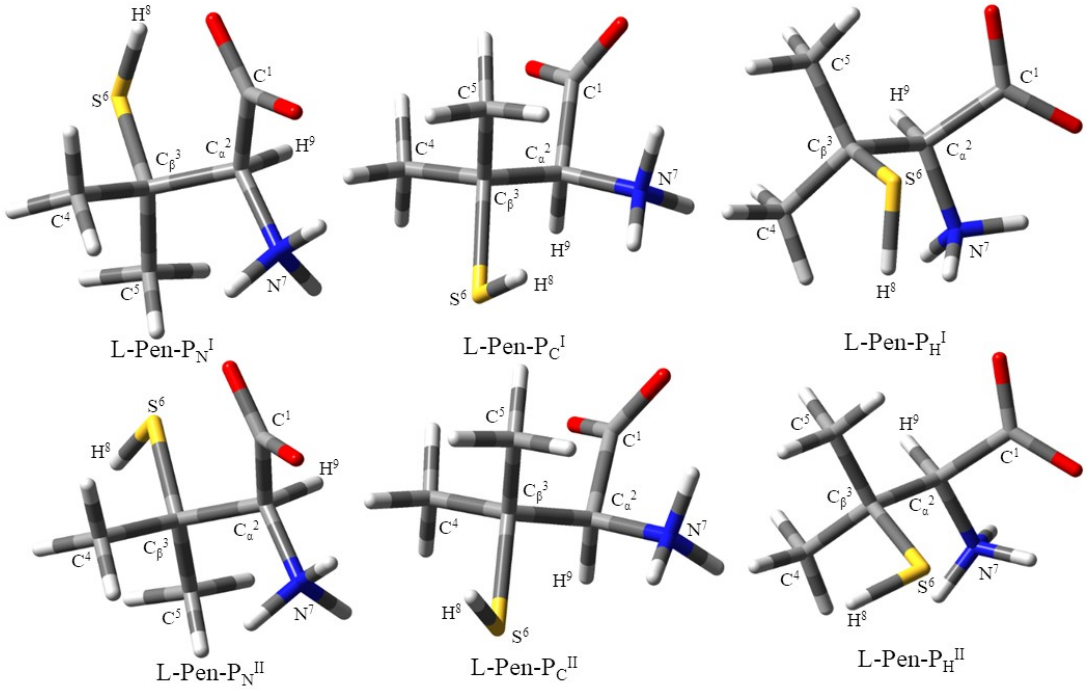
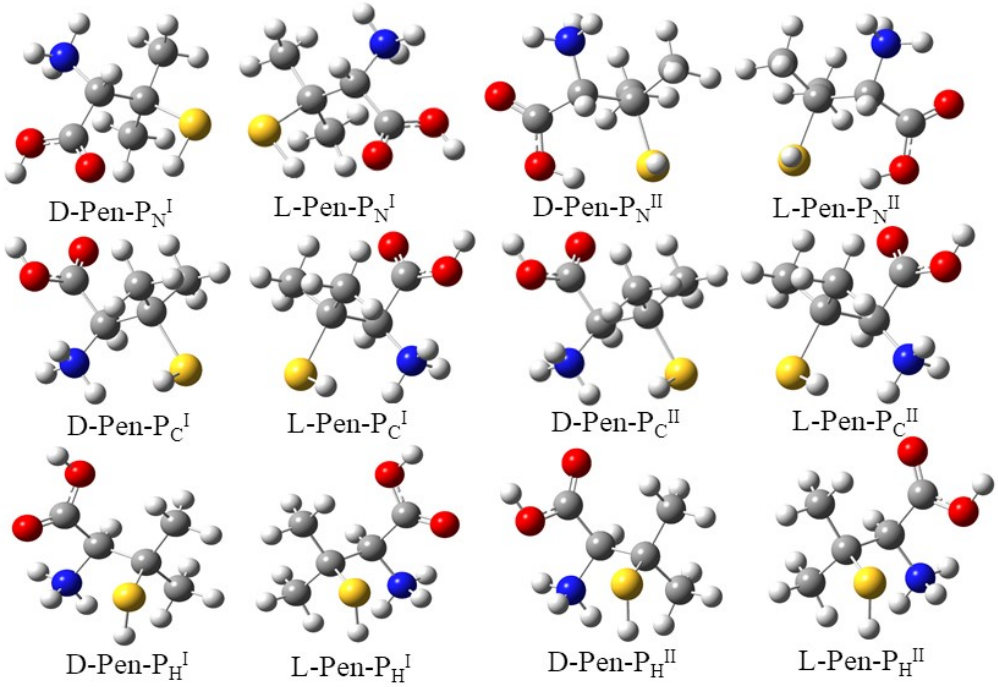
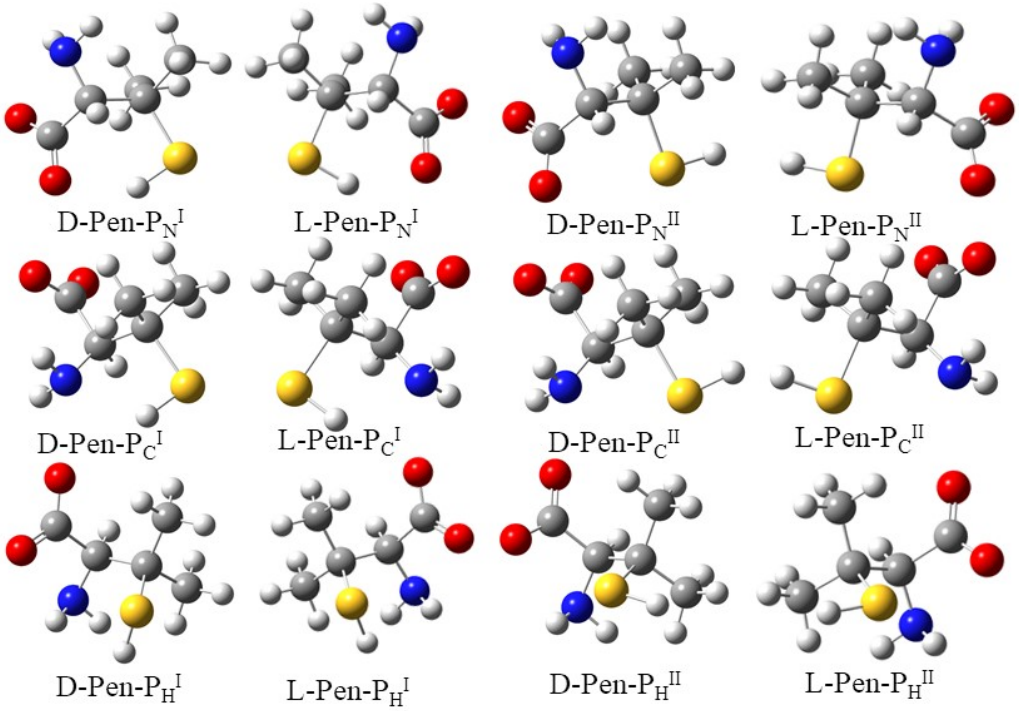


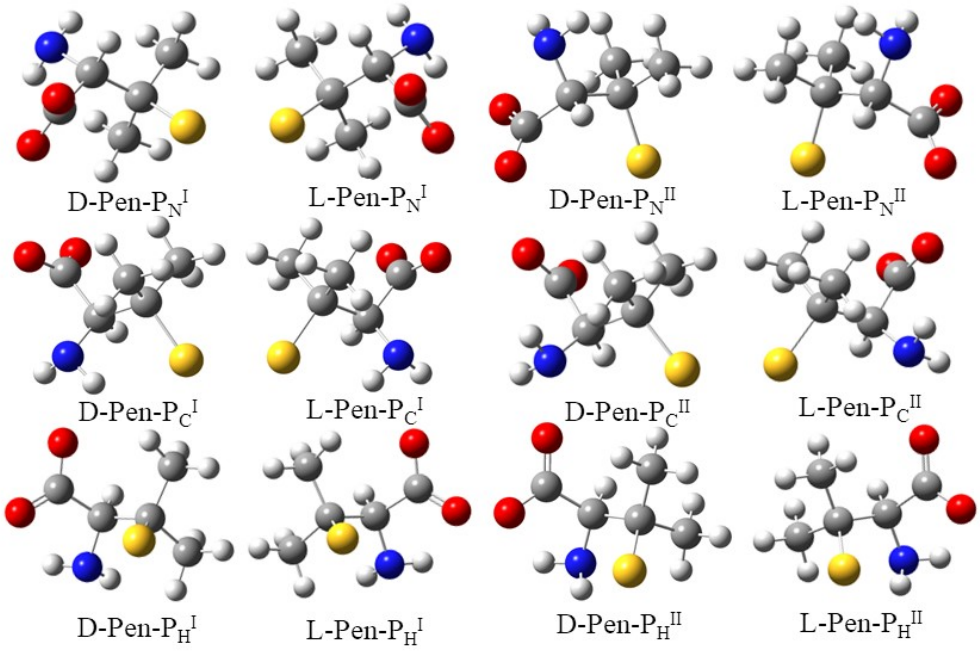
Figure S1. Optimized conformations of L-penicillamine in H_2O
(The implicit SMD model is used for considering the solvent effects. The P_N, P_C and P_H mean the sulfur atom in trans orientations with respect to amino groups, carboxylate and hydrogen, respectively. Because of the different orientations of SH, they are divided into P_N^I, P_N^{II}, P_C^I, P_C^{II}, P_H^I, P_H^{II}. In detail, there are twelve torsion angles are defined: $\Psi_{a1}(C^1\text{- }C^2\text{- }C^3\text{-}C^5)$, $\Psi_{a2}(C^1\text{- }C^2\text{- }C^3\text{-}C^4)$, $\Psi_{a3}(C^1\text{- }C^2\text{- }C^3\text{-}S^6)$; $\Psi_{b1}(N^7\text{- }C^2\text{- }C^3\text{-}C^5)$, $\Psi_{b2}(N^7\text{- }C^2\text{- }C^3\text{-}C^4)$, $\Psi_{b3}(N^7\text{- }C^2\text{- }C^3\text{-}S^6)$; $\Psi_{c1}(H^9\text{- }C^2\text{- }C^3\text{-}C^5)$, $\Psi_{c2}(H^9\text{- }C^2\text{- }C^3\text{-}C^4)$, $\Psi_{c3}(H^9\text{- }C^2\text{- }C^3\text{-}S^6)$; $\Psi_{d1}(H^8\text{- }S^6\text{- }C^3\text{-}C^2)$, $\Psi_{d2}(H^8\text{- }S^6\text{- }C^3\text{ -}C^5)$,$\Psi_{d3}(H^8\text{- }S^6\text{- }C^3\text{-}C^4)$)



pH<1.9 (Cation state)



7.9 ≤ pH < 10.7 (Monovalent anion)



pH ≥ 10.7 (Dianion)

Figure S2. Optimized conformations of D- and L-penicillamine in H_2O under different pH conditions (The structure models remain at the same state in 1.9≤pH<7.9, and the models are shown in Figure 3 in the article)

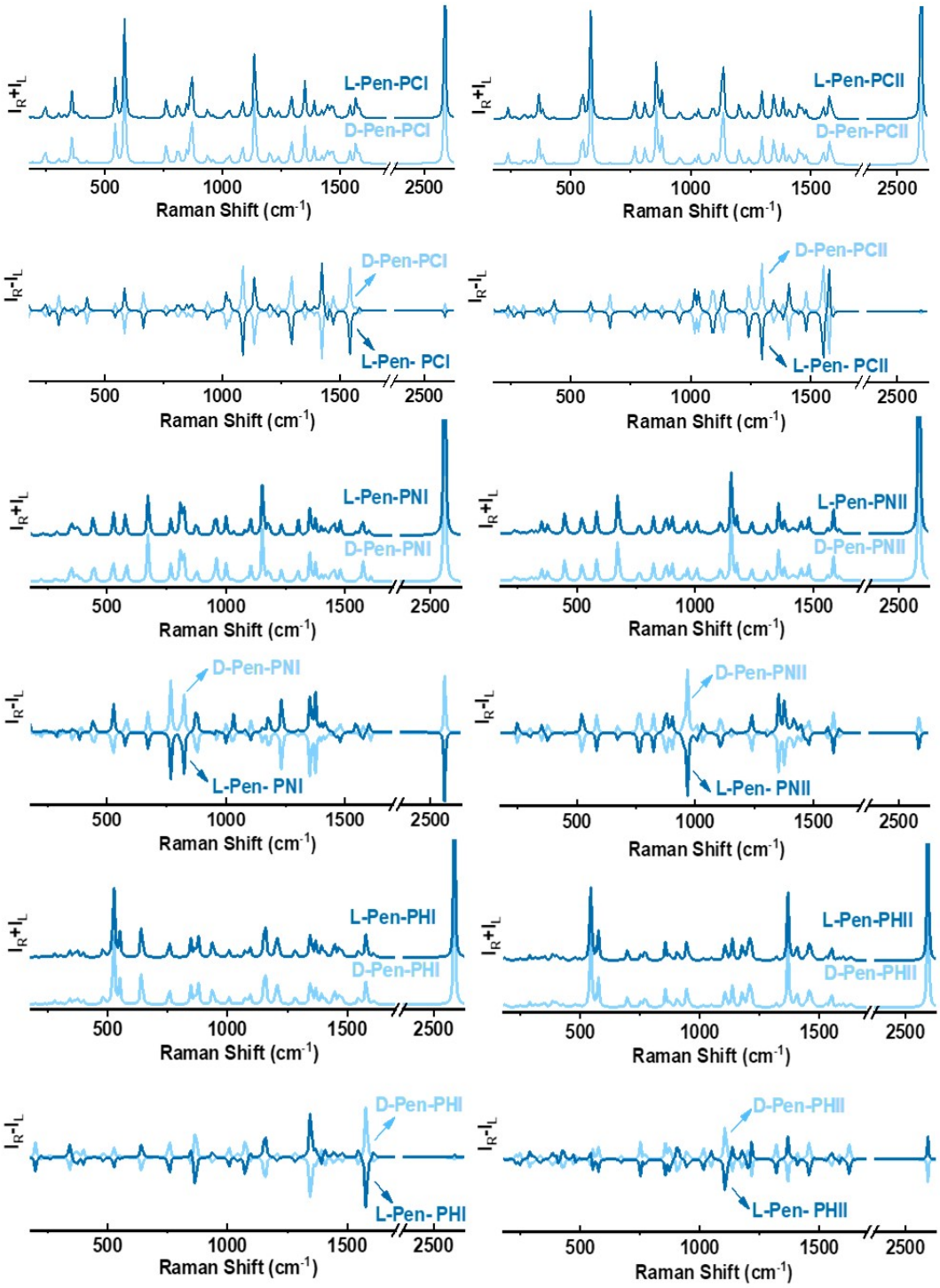


Figure S3. Raman and ROA theoretical spectra corresponding to the six stable conformations of penicillamine in H_2O

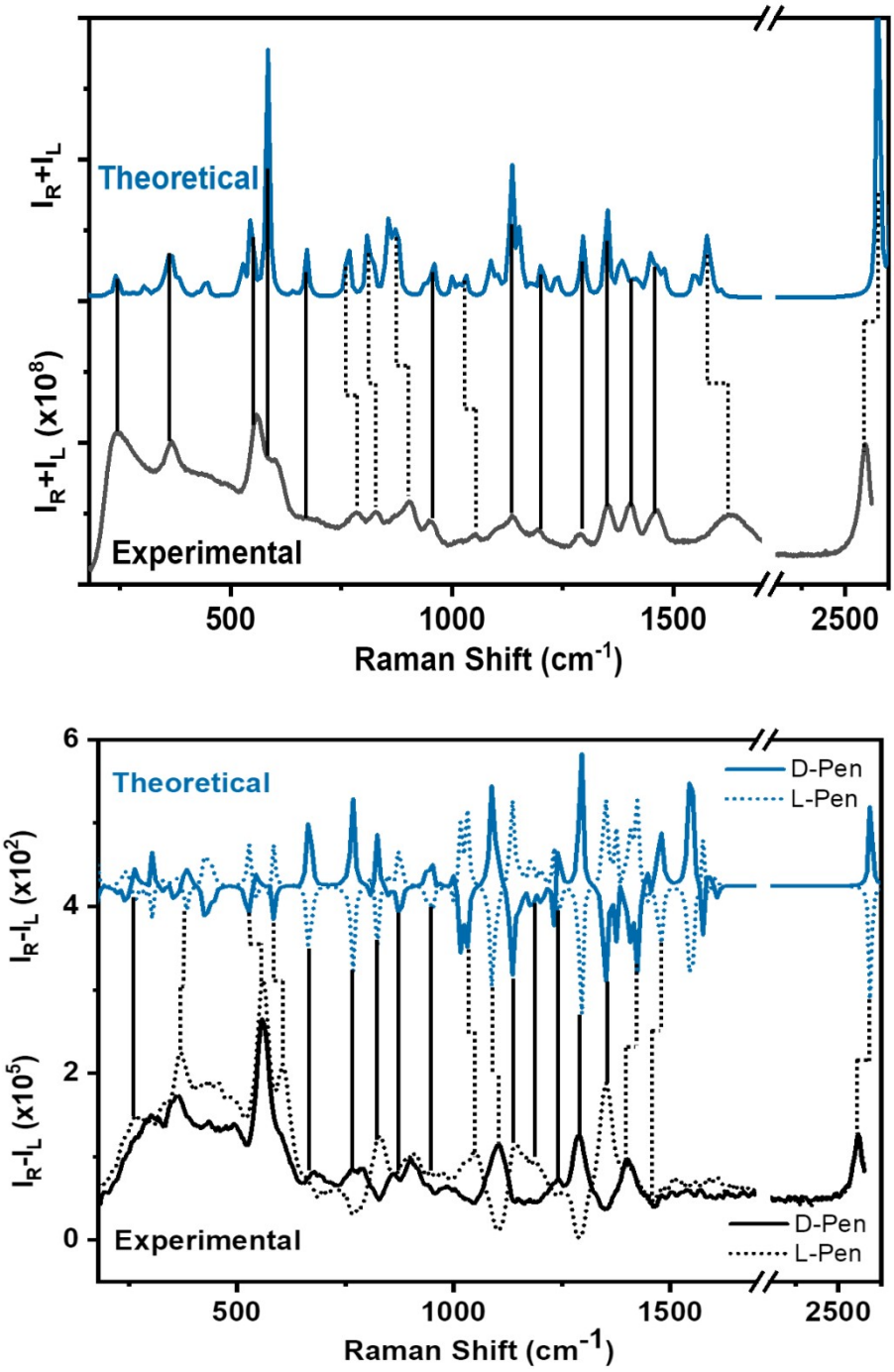


Figure S4. Correspondence peaks between experimental and simulated Raman (D-Pen) and ROA spectra (D-Pen & L-Pen)

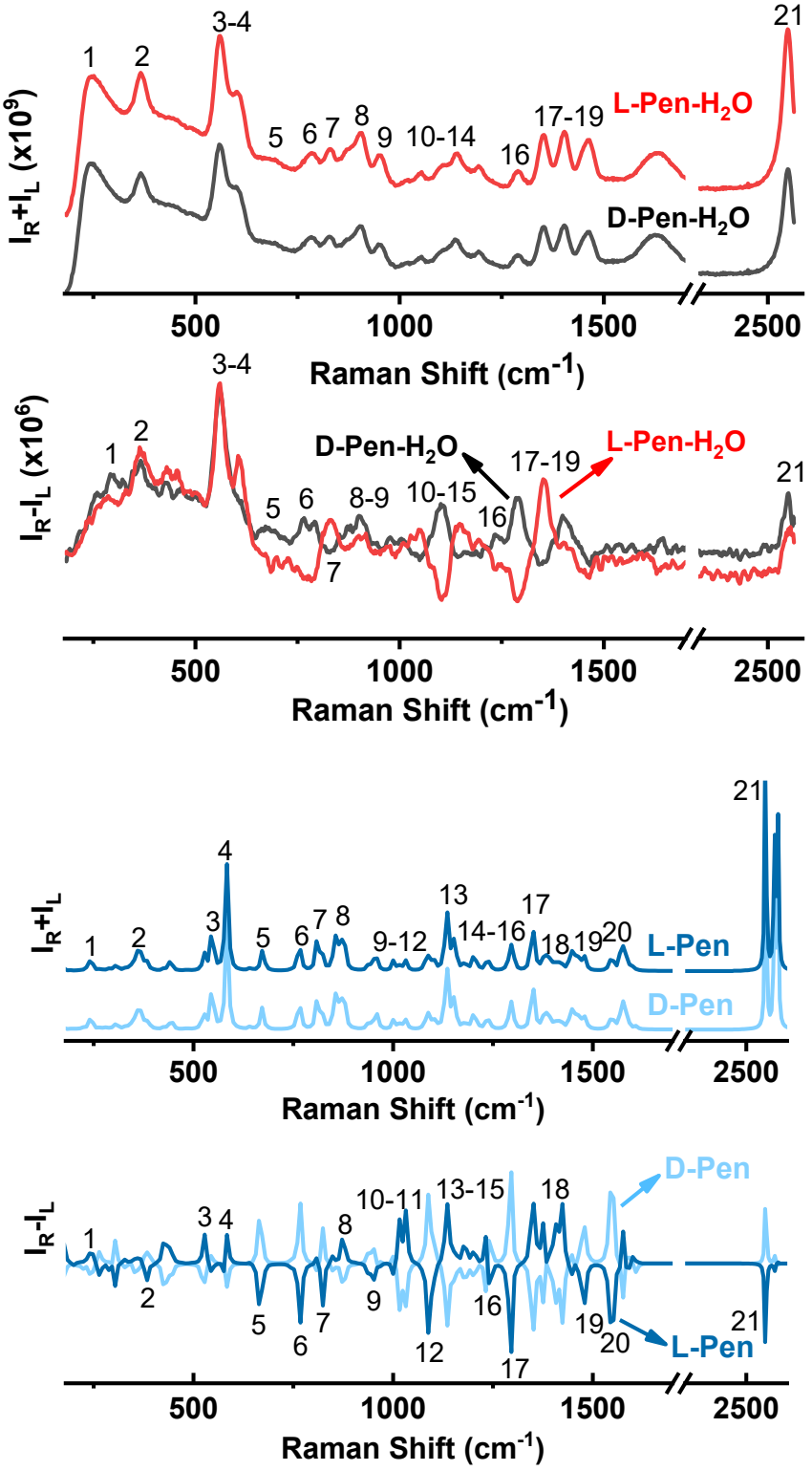
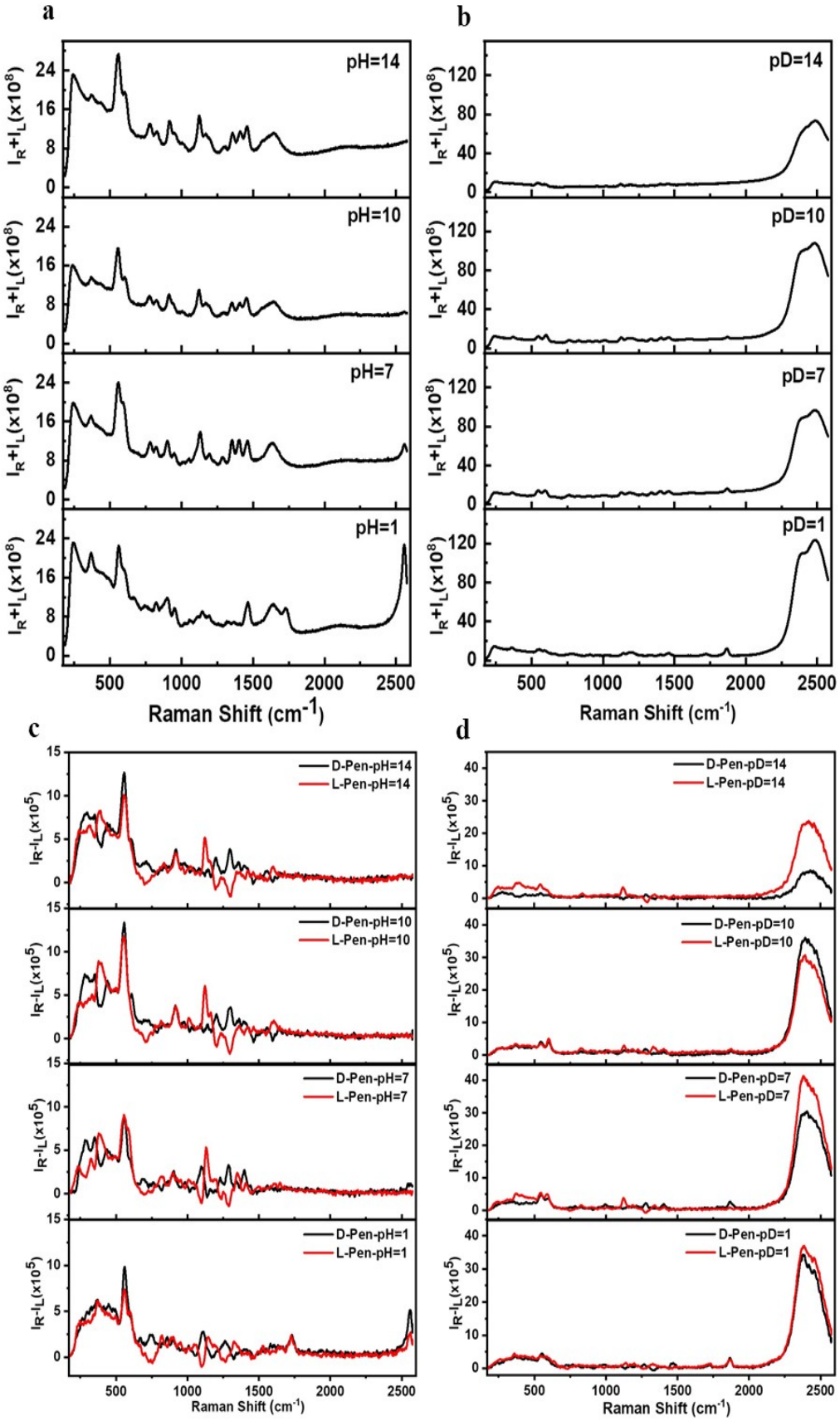


Figure S5. Experimental and theoretical Raman& ROA spectra of penicillamine in H_2O (Labels in the figure are marked according to the assignment in the table below. Test conditions：pH=5; 1mol/L; 24 mW; 1.029 s; 400 min；Calculated parameters：B3LYP/aug-cc-PVDZ; SMD)


a
b
pH=14
pH=10
pH=7
pH=1
pD=14
pD=10
pD=7
pD=1
$I_R+I_L(x10^8)$
Raman Shift (cm^{-1})
c
d
D-Pen-pH=14
L-Pen-pH=14
D-Pen-pH=10
L-Pen-pH=10
D-Pen-pH=7
L-Pen-pH=7
D-Pen-pH=1
L-Pen-pH=1
D-Pen-pD=14
L-Pen-pD=14
D-Pen-pD=10
L-Pen-pD=10
D-Pen-pD=7
L-Pen-pD=7
D-Pen-pD=1
L-Pen-pD=1
$I_R-I_L(x10^5)$
Raman Shift (cm^{-1})

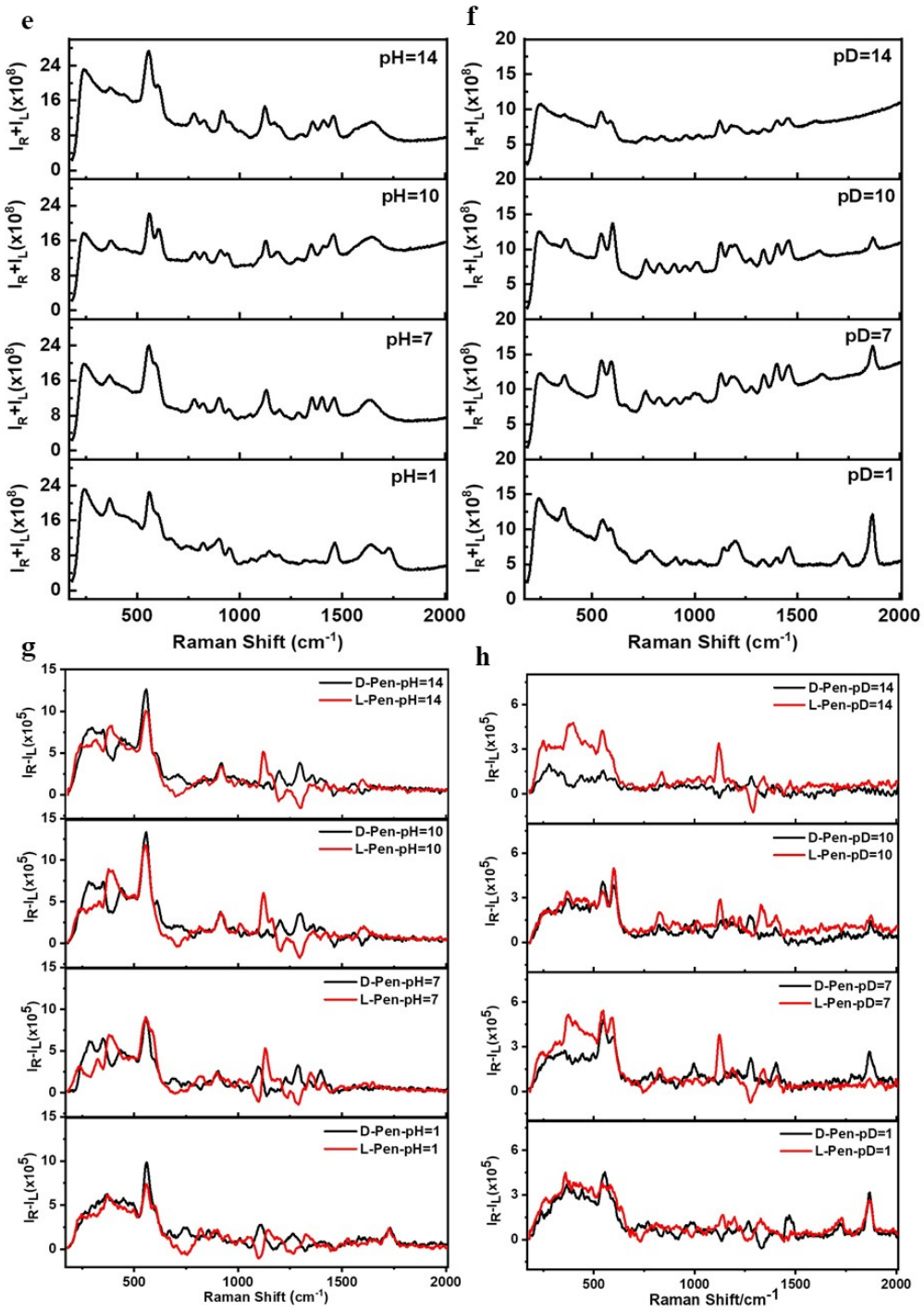
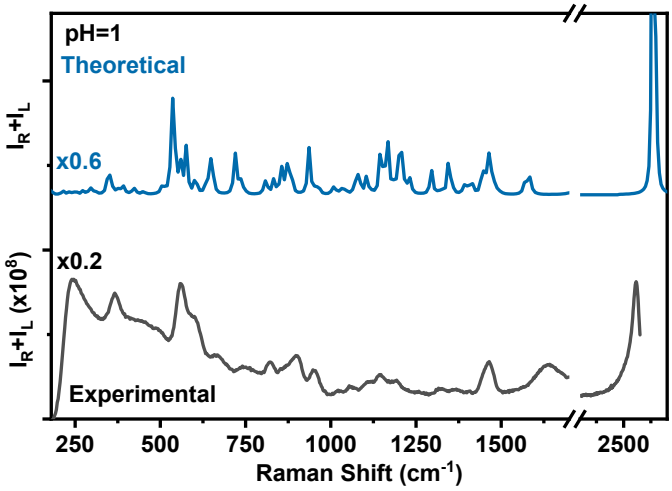
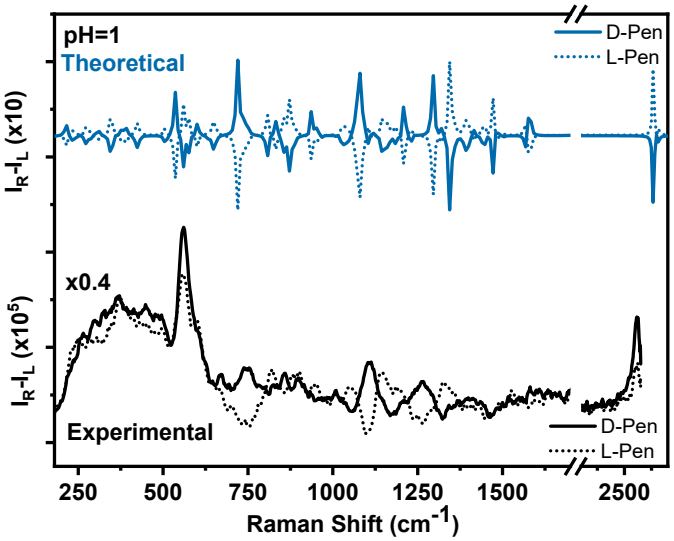


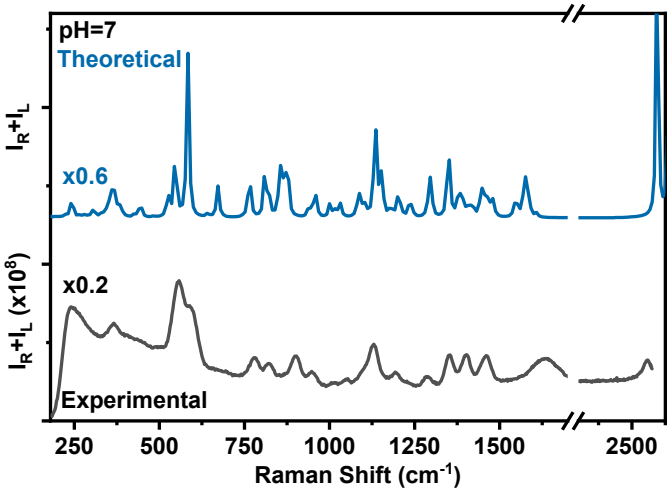
Figure S6. (a-b & e-f) Raman spectra of D-penicillamine in H_2O in pH=1,7,10,14（Test conditions：0.75 mol/L; 24 mW; 1.029 s ; 600 min）and in D_2O in pD=1,7,10,14 (0.55 mol/L; 24 mW; 1.029 s ; 400 min;); (c-d & g-h) ROA experimental spectra of D- and L-penicillamine in H_2O in pH=1,7,10,14 and in D_2O in pD=1,7,10,14（Test conditions is as the same as Raman test）;The wavenumber range of spectra (a,b,c,d) is 180~2600 cm^{-1} and the wavenumber range of spectra (e,f,g,h) is 180~2010 cm^{-1}) and ROA spectra (D-Pen & L-Pen)



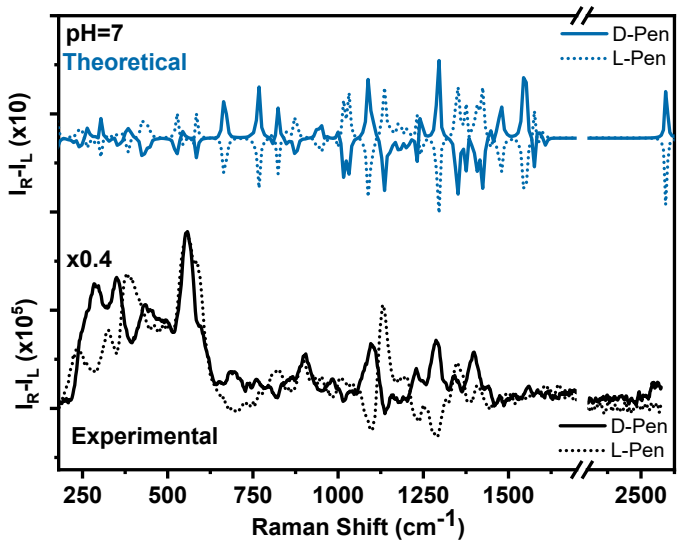
The theoretical and experimental Raman spectra of penicillamine at pH=1



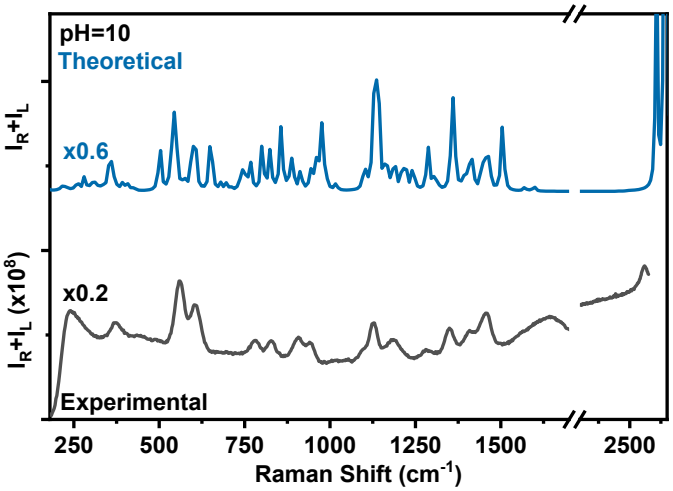
The theoretical and experimental ROA spectra of penicillamine at pH=1



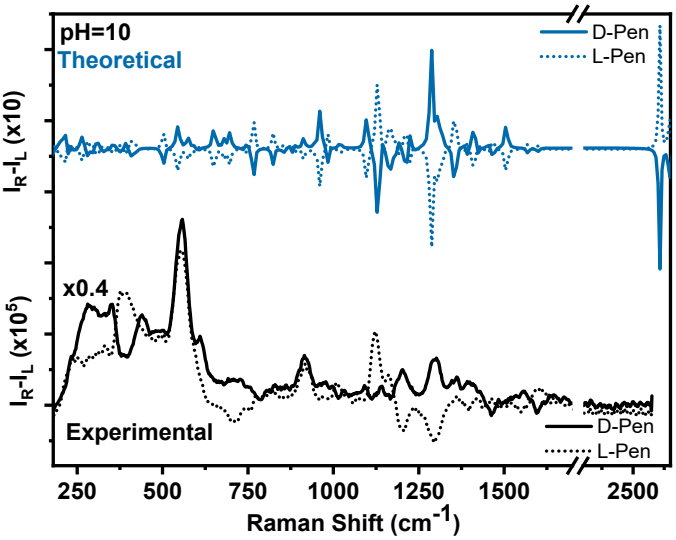
The theoretical and experimental Raman spectra of penicillamine at pH=7



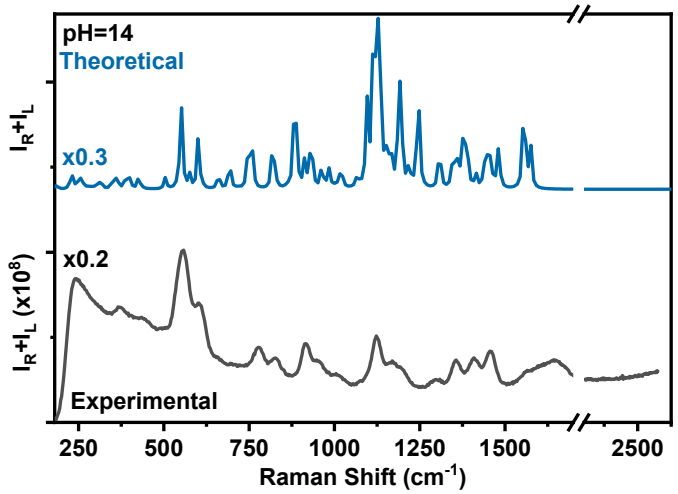
The theoretical and experimental ROA spectra of penicillamine at pH=7



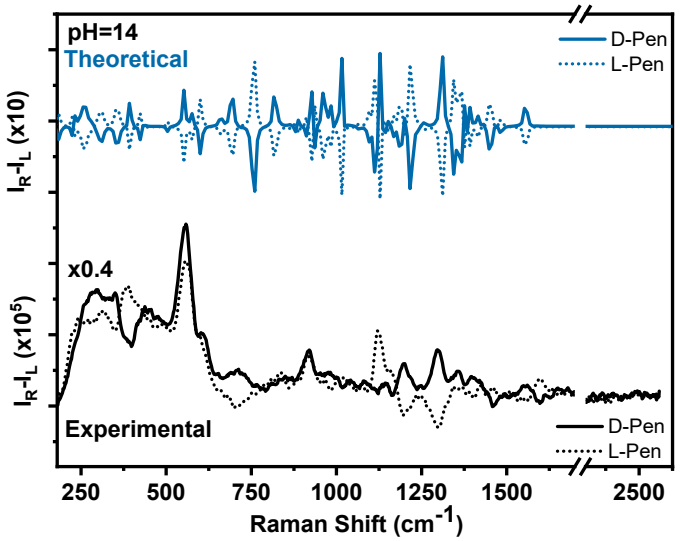
The theoretical and experimental Raman spectra of penicillamine at pH=10



The theoretical and experimental ROA spectra of penicillamine at pH=10



The theoretical and experimental Raman spectra of penicillamine at pH=14



The theoretical and experimental ROA spectra of penicillamine at pH=14

Figure S7. The theoretical and experimental Raman and ROA spectra of penicillamine under different pH conditions (The spectra at pH=7 and pH=5 are identical because of the same zwitterionic state in solution; To better compare the theoretical and experimental peak intensities, some peaks are multiplied by proper scaling factors which are labeled in spectra)

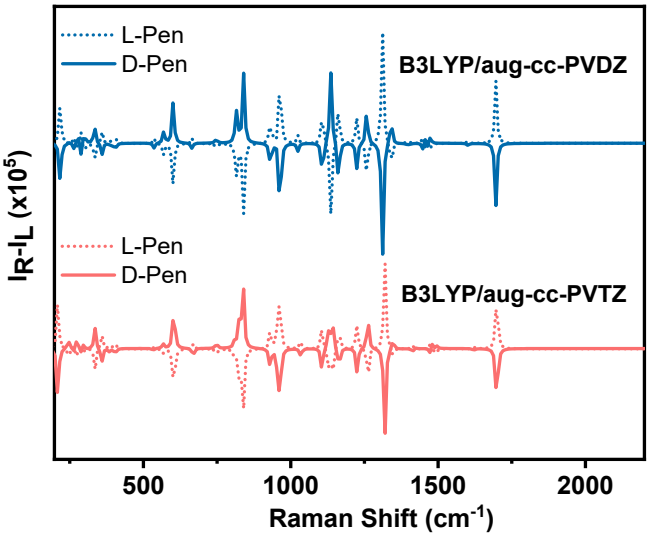


Figure S8. The theoretical ROA spectra of the D- and L-penicillamine using B3LYP/aug-cc-PVDZ and B3LYP/aug-cc-PVTZ (Take one of the conformations as the example; The Figure shows that the higher order one (aug-cc-PVTZ) produces similar results to another one (aug-cc-PVDZ), and the blue one (aug-cc-PVDZ) displays more clear peaks, for example, the peaks in the range of 500 cm^{-1}-900 cm^{-1}.)

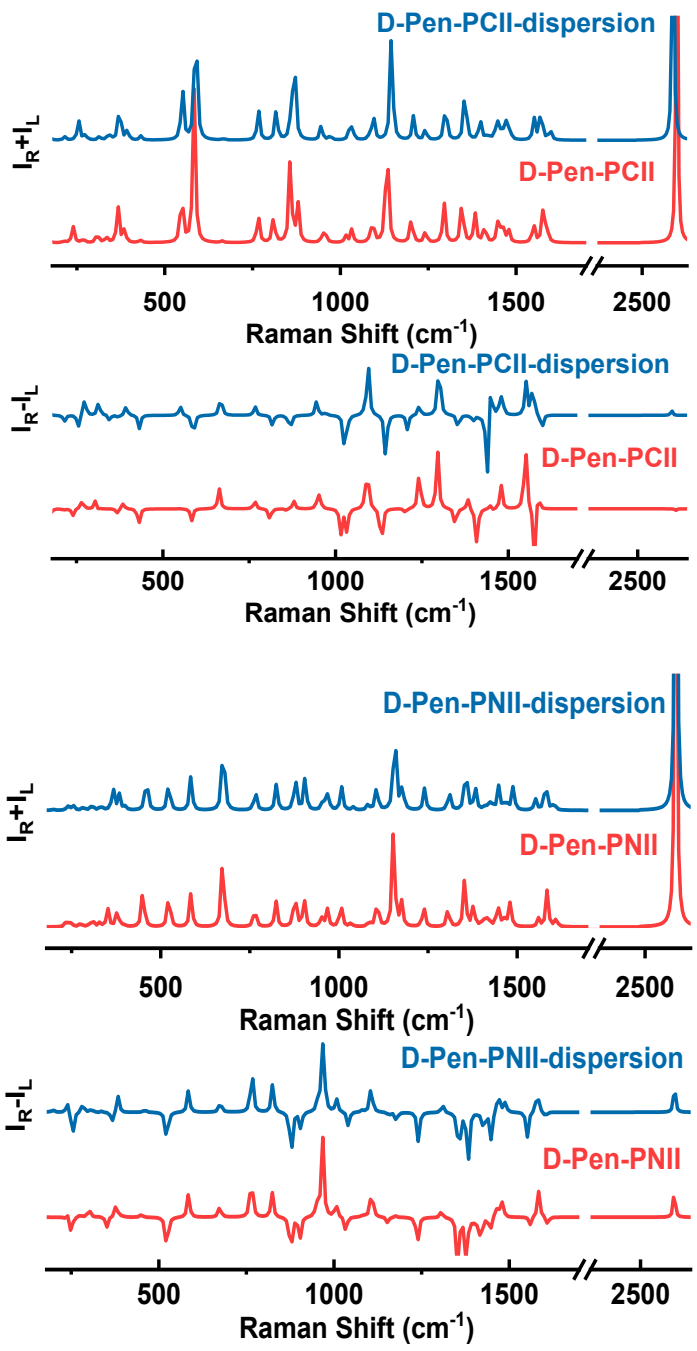


Figure S9. The theoretical Raman and ROA spectra of the D-penicillamine with and without dispersion correction (Take P_C^{II} and P_N^{II} conformations as the example and the spectra are both calculated by using B3LYP/aug-cc-PVDZ and SMD. The blue one is the spectra with dispersion correction and the red one is the spectra without dispersion correction.)

We also considered the explicit solvation model (the penicillamine molecule was surrounded by five, water molecules), which implied that interaction between molecules and surroundings. (The optimized models are shown in **Figure S10**. In the fingerprint region, the theoretical results using a single implicit SMD (**Figure S11c**) showed higher agreement with the experimental results **(Figure S11a)** than that with an implicit solvation model and explicit water molecules (**Figure S11b**) in **Figure S11**. And the peaks in **Figure S11b** are more complicated than the peaks in **Figure S11c.** Therefore, only the SMD implicit solvation model was applied to the calculations.

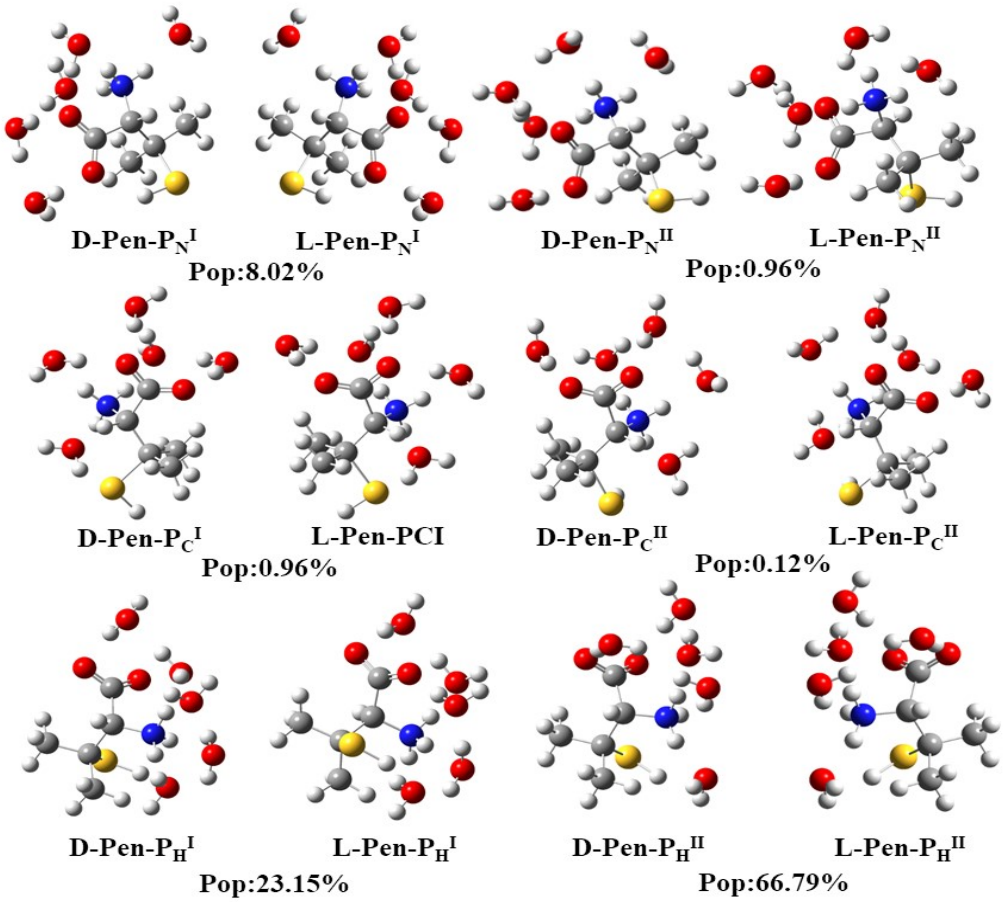


Figure S10. Optimized conformations of D- and L-penicillamine with implicit solvation model (SMD) and explicit water molecules in H_2O. (The populations of conformations were labeled in Figure)

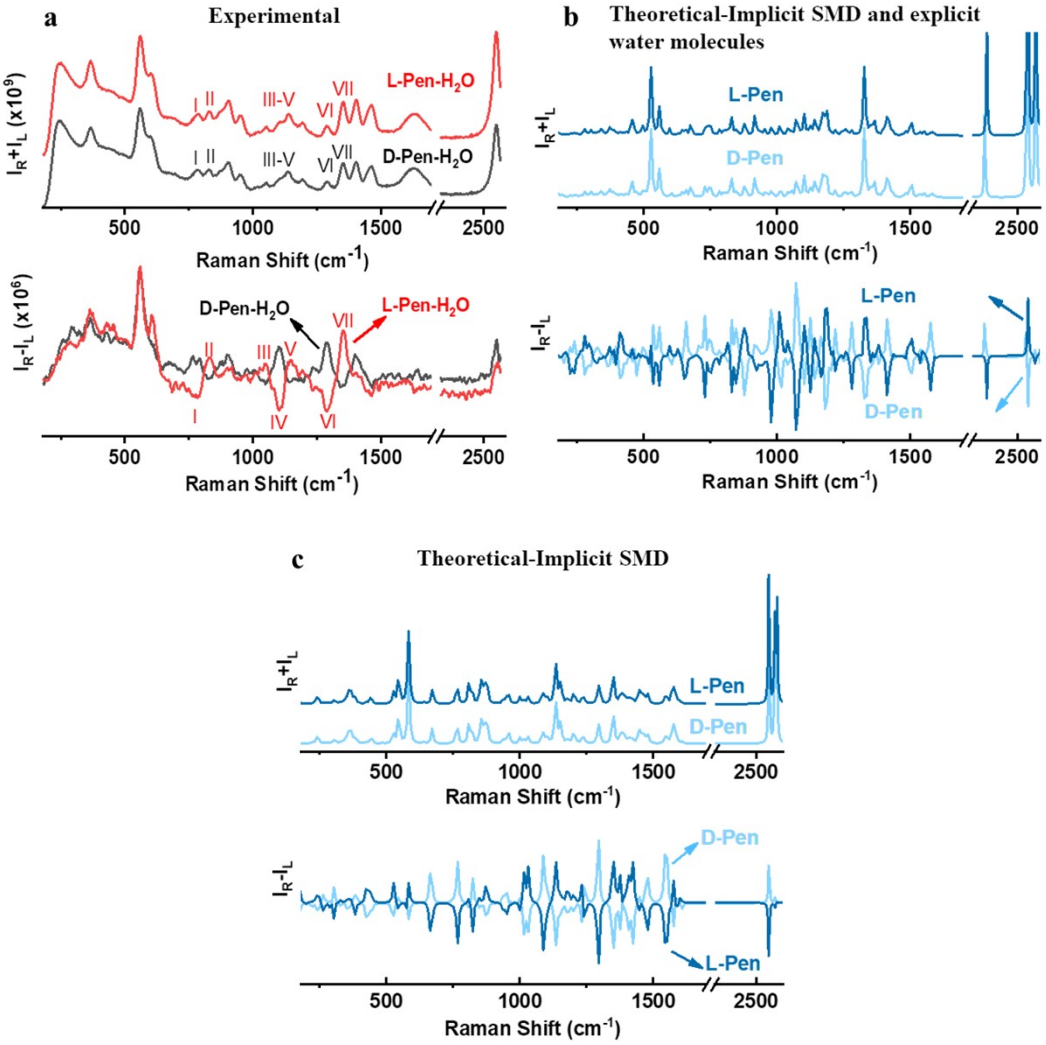


Figure S11. The theoretical Raman and ROA spectra of D- and L-penicillamine with different solvation models in H_2O. (a. The experimental spectra of D-/L- Pen and this is also the Figure 5a; b. The theoretical spectra of D-/L-Pen with implicit solvation model (SMD) and five explicit water molecules; c. The theoretical spectra of D-/L-Pen with only SMD and this is also the Figure 5b.)

Table S1. Dihedral angles of theoretical six conformations of L-penicillamine

conformer	P_N^I	P_N^{II}	P_C^I	P_C^{II}	P_H^I	P_H^{II}
Ψ_{a1}	-171.7	-175.2	-59.6	-63.2	64.9	60.7
Ψ_{a2}	-47.8	-51.4	64.8	61.4	-174.3	-178.7
Ψ_{a3}	74.1	68.4	179.3	177.6	-52.6	-59.0
Ψ_{b1}	-49.2	-52.5	61.0	57.1	-171.6	-178.0
Ψ_{b2}	74.7	71.2	-174.7	-178.3	-50.7	-57.4
Ψ_{b3}	-163.4	-169.0	-60.2	-62.0	70.9	62.3
Ψ_{c1}	66.4	63.4	178.4	175.0	-55.9	-60.7
Ψ_{c2}	-169.7	-172.8	-57.2	-60.4	65.0	59.9
Ψ_{c3}	-47.8	-53.0	57.3	55.9	-173.4	179.6
Ψ_{d1}	-49.6	145.4	94.4	139.5	-87.9	-160.5
Ψ_{d2}	-167.5	27.7	-29.1	18.1	151.7	79.5
Ψ_{d3}	73.4	-93.1	-148.3	-102.5	34.0	-40.2

Definition of Torsion angles: $\Psi_{a1}(C^1\text{-}C^2\text{-}C^3\text{-}C^5)$, $\Psi_{a2}(C^1\text{-}C^2\text{-}C^3\text{-}C^4)$, $\Psi_{a3}(C^1\text{-}C^2\text{-}C^3\text{-}S^6)$; $\Psi_{b1}(N^7\text{-}C^2\text{-}C^3\text{-}C^5)$, $\Psi_{b2}(N^7\text{-}C^2\text{-}C^3\text{-}C^4)$, $\Psi_{b3}(N^7\text{-}C^2\text{-}C^3\text{-}S^6)$; $\Psi_{c1}(H^9\text{-}C^2\text{-}C^3\text{-}C^5)$, $\Psi_{c2}(H^9\text{-}C^2\text{-}C^3\text{-}C^4)$, $\Psi_{c3}(H^9\text{-}C^2\text{-}C^3\text{-}S^6)$; $\Psi_{d1}(H^8\text{-}S^6\text{-}C^3\text{-}C^2)$, $\Psi_{d2}(H^8\text{-}S^6\text{-}C^3\text{-}C^5)$, $\Psi_{d3}(H^8\text{-}S^6\text{-}C^3\text{-}C^4)$. The data are recorded via Gauss View 5.0.

Table S2. △G and Boltzmann distributions of theoretical conformations of penicillamine under different pH conditions

conformer	Distribution,% (pH<1.9)		Distribution,% (1.9≤pH<7.9)		Distribution,% (7.9≤pH<10.7)		Distribution,% (pH≥10.7)	
	D-Pen	L-Pen	D-Pen	L-Pen	D-Pen	L-Pen	D-Pen	L-Pen
P_N^I	2.93	2.94	28.01	30.48	21.01	21.23	9.16	9.00
P_N^{II}	8.28	8.56	0.77	0.75	10.57	10.48	9.22	9.24
P_C^I	12.69	12.60	30.95	29.94	40.32	40.31	57.04	57.12
P_C^{II}	12.65	12.67	32.94	31.80	9.28	9.34	1.56	1.57
P_H^I	56.51	55.93	4.35	4.32	11.03	10.93	0.10	0.10
P_H^{II}	6.93	7.30	2.99	2.71	7.78	7.72	22.93	22.98

Table S3. Assignments of vibrational modes of penicillamine in H_2O

	Raman		ROA (Expt)		ROA (Theo)		Assignments
NO.	Expt	Theo	D-Pen	L-Pen	D-Pen	L-Pen	
1	246	240	275(+)	275(-)	240(-)	240(+)	β(C-C-S)
2	366	360	358(+)	368(+)	360(-)	360(+)	β(C-C-C)+β(C-C-S)+ν(C-S)
3	560	544	560(+)	560(+)	544(+)	544(-)	ν(C*-N)+β(C*-C=O)+ν(C-C)
4	601	584	604(-)	604(+)	584(-)	584(+)	ν(C-S)+β(C-C-C)+β(C-C-S)
5	679	672	679(+)	684(-)	664(+)	664(-)	ν(C-S)+β(COO^-)+β(C-C-C) +β(C-C-S)
6	783	768	766(+)	766(-)	768(+)	768(-)	β(COO^-)+ν(C*-C)
7	832	808	827(-)	827(+)	808(-)	808(+)	β(COO^-)+ν(C-C)
8	902	872	902(+)	902(+)	872(-)	872(+)	ν(C*-C) +β(COO^-)
9	947	952	957(-)	957(-)	952(+)	952(-)	ρ(CH_3)+ν(C-C)+ν(C*-N)
10	1014	1016	1014(-)	1014(+)	1016(-)	1016(+)	ν(C*-N)+ρ(CH_3)
11	1054	1032	1046(-)	1046(+)	1032(-)	1032(+)	ν(C*-N)+ρ(NH_3^+)
12	1105	1088	1105(+)	1105(-)	1088(+)	1088(-)	ρ(NH_3^+)+β(C*-H)
13	1142	1136	1142(-)	1142(+)	1136(-)	1136(+)	ρ(CH_3)
14	1193	1200	1193(-)	1193(+)	1200(-)	1200(+)	ρ(CH_3)+ν(C-C)
15	/	1240	1241(+)	1241(-)	1240(+)	1240(-)	ν(C*-C)+ν(C-C)+ρ(CH_3)
16	1289	1296	1289(+)	1289(-)	1296(+)	1296(-)	β(C*-H)
17	1353	1352	1351(-)	1351(+)	1352(-)	1352(+)	ν_s(COO^-)+β(C*-H)
18	1403	1424	1401(+)	1401(+)	1424(-)	1424(+)	δ_{as}(NH_3^+)
19	1462	1480	1462(-)	1462(-)	1480(+)	1480(-)	δ_{as}(CH_3)
20	/	1544	/	/	1544(+)	1544(-)	ν_{as}(COO^-)+δ_{as}(NH_3^+)
21	2557	2592	2557(+)	2557(+)	2592(+)	2592(-)	ν(S-H)

The peaks represented in the Table are marked in Figure S5.

The Expt represents the experimental data while the Theo represents the Theoretical data.

ν, stretch; δ, deformation; ρ, rock; ω, wag; as, asymmetric; s, symmetric; β, bend.