Supplementary materials

Synthesis, Complexation Properties, and Evaluation of New Aminodiphosphonic Acids as Vector Molecules for ^{68}Ga Radiopharmaceuticals

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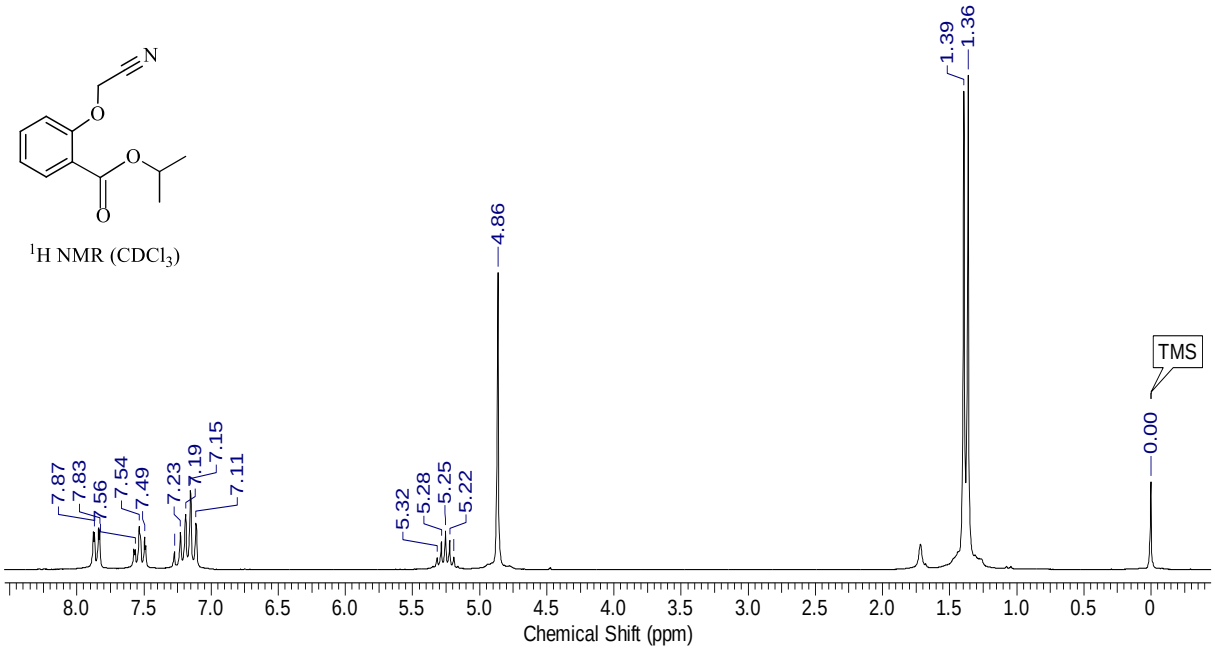
Contents **Page**

Figure S1. ^{1}H and ^{13}C NMR of nitrile **6a**.



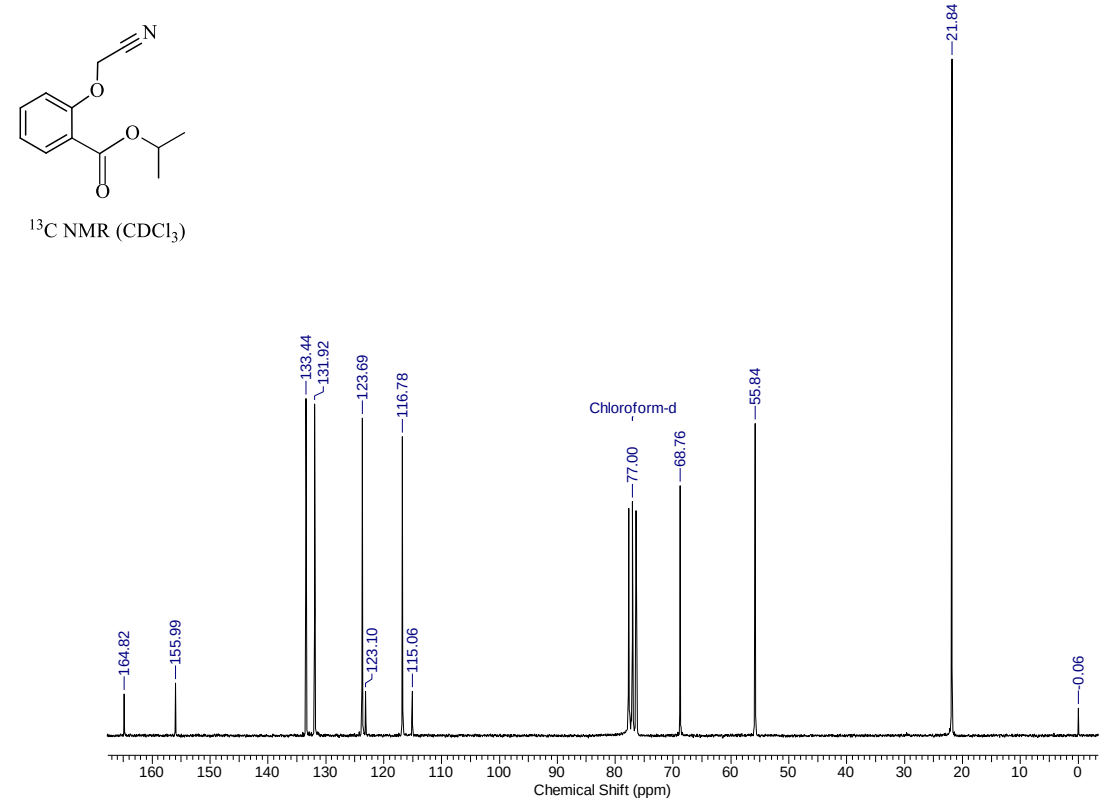


Figure S2. ^{1}H, ^{13}C and ^{31}P NMR of nitrile **6b**.

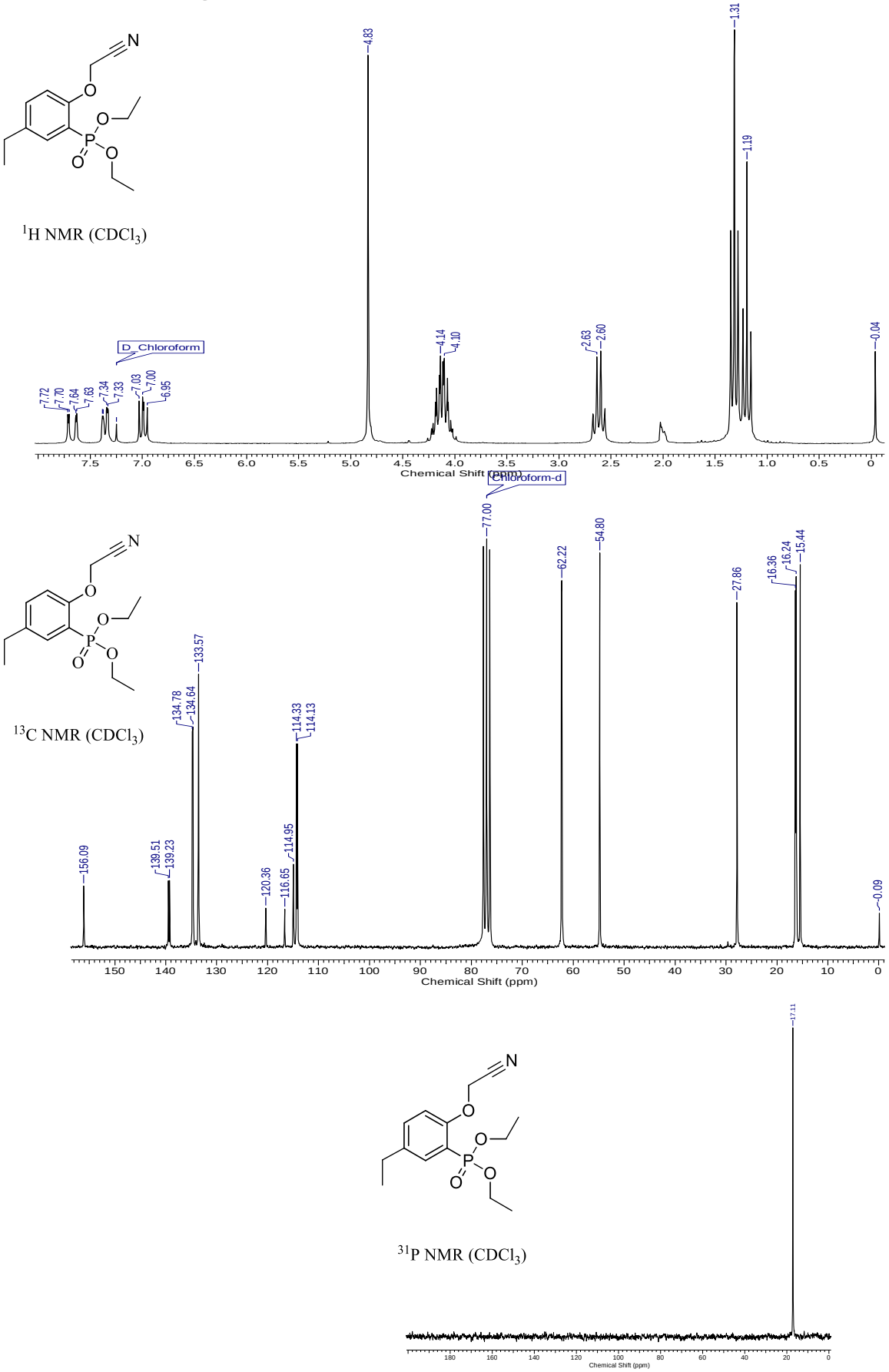


Figure S3. ^{1}H, ^{13}C and ^{31}P NMR of aminodiphosphonic acid **7a**.

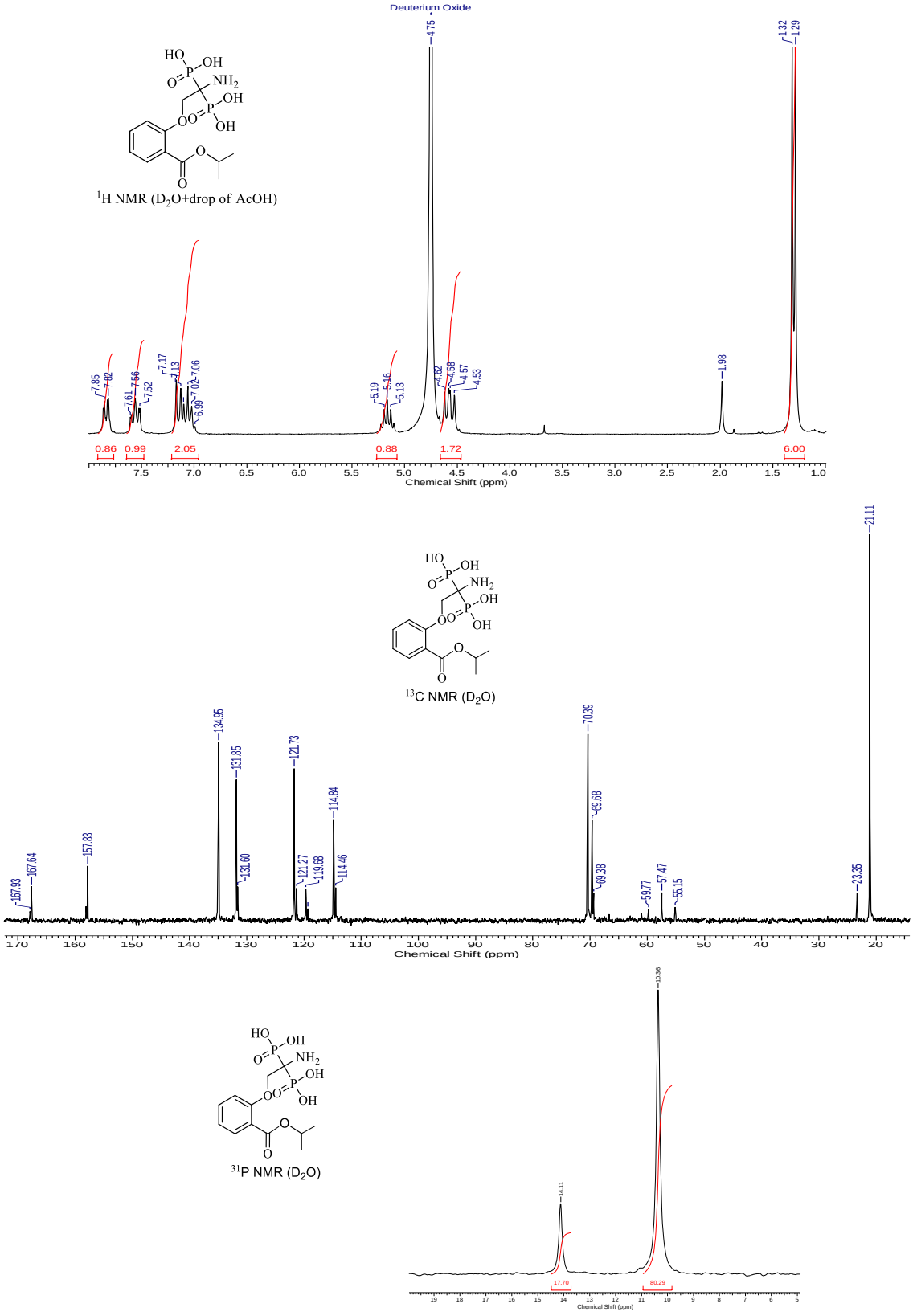
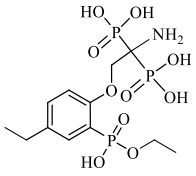
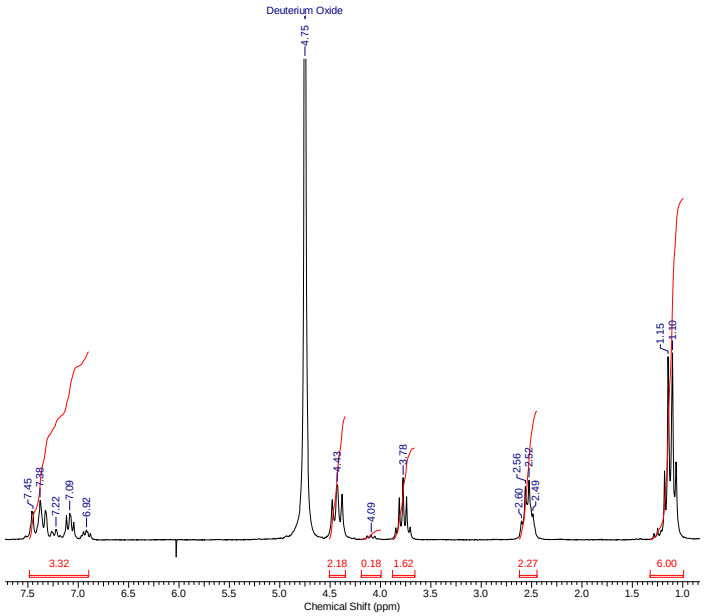
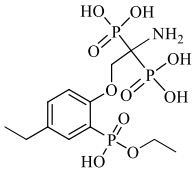


Figure S4a. ^{1}H NMR of aminodiphosphonic acid **7b**.

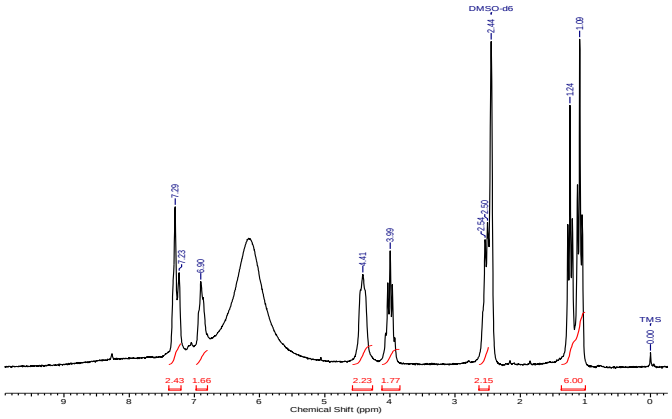


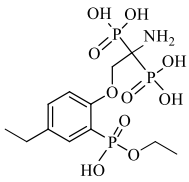
^{1}H NMR (D_2O)





^{1}H NMR (DMSO-d_6)





^{1}H NMR (DMSO-d_6 + drop of TFA)

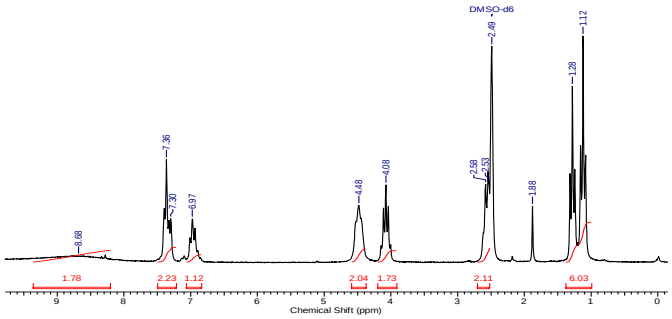
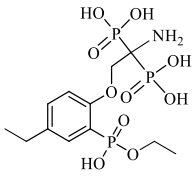
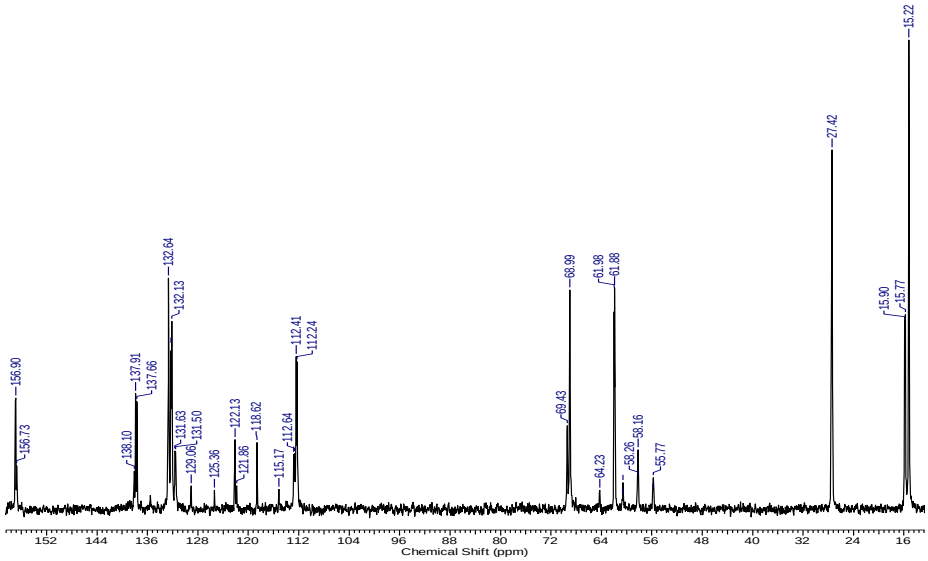
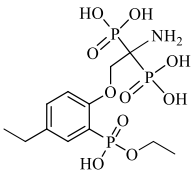


Figure S4b. ^{13}C and ^{31}P NMR of aminodiphosphonic acid **7b**.

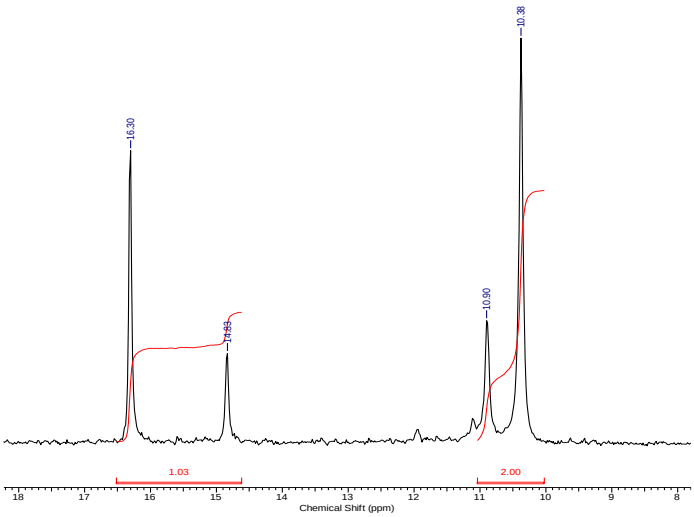


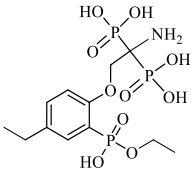
^{13}C NMR (D_2O)





^{31}P NMR (DMSO d_6)





^{31}P NMR (D_2O)

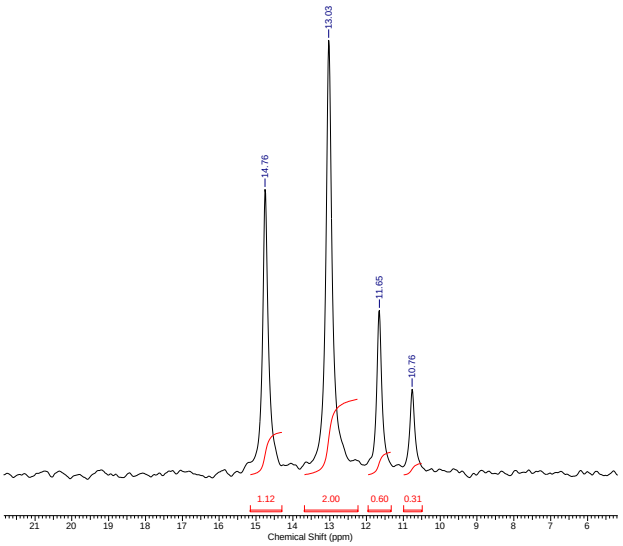
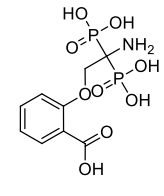


Figure S5. ^{1}H, ^{13}C and ^{31}P NMR of aminodiphosphonic acid **8**.



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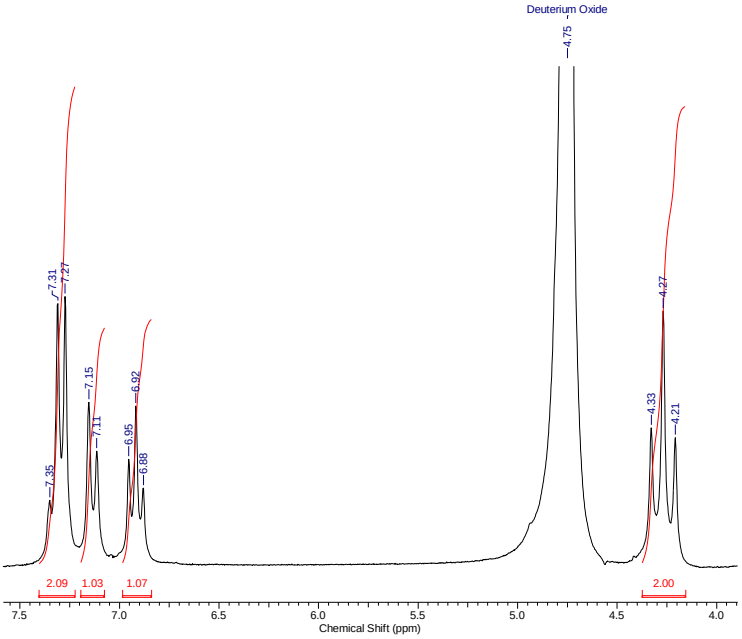
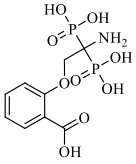
NMR ^{1}H (D_2O, pH~10)





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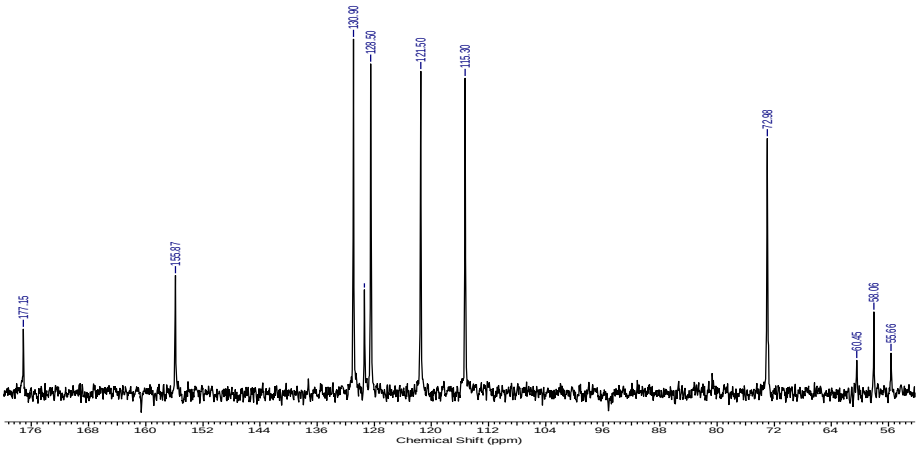
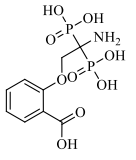
NMR ^{13}C (D_2O, pH~10)





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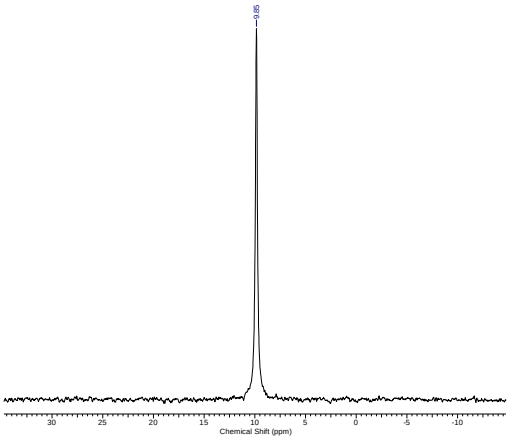
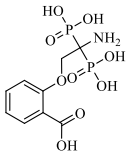
NMR ^{31}P (D_2O, pH~5)

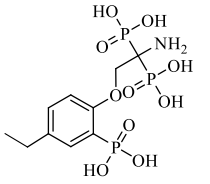




1

NMR ^{31}P (D_2O, pH~10)

Figure S6. ^{1}H, ^{13}C and ^{31}P NMR of aminodiphosphonic acid **9**.



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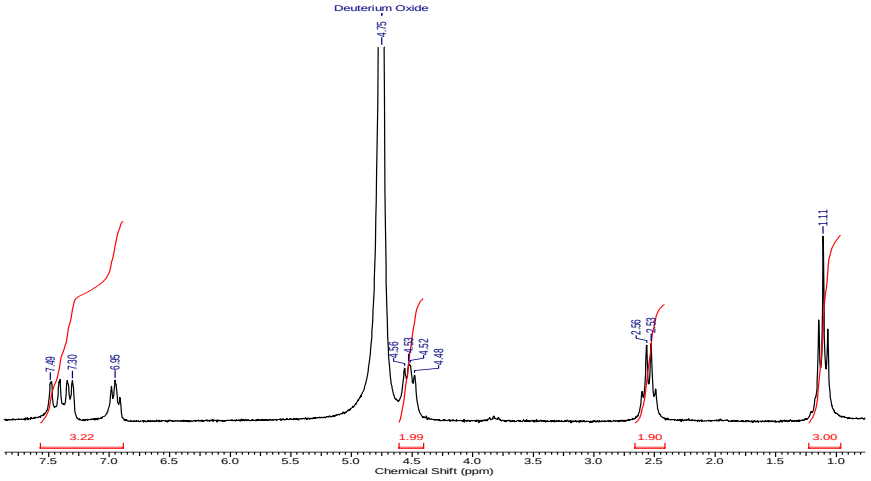
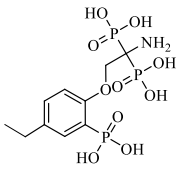
^{1}H NMR (D_2O, pH~5)





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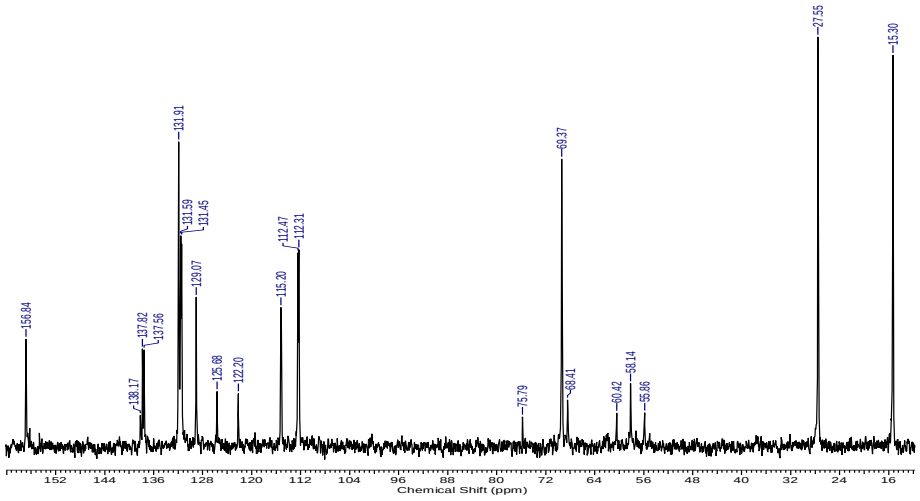
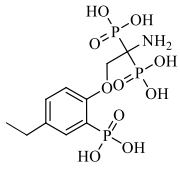
^{13}C NMR (D_2O, pH~5)





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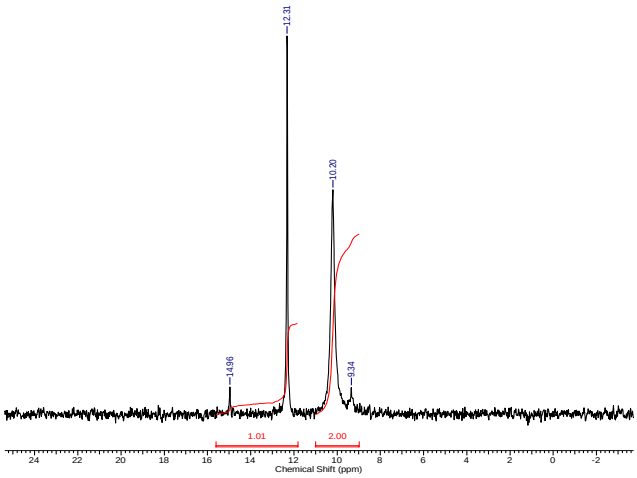
^{31}P NMR (D_2O, pH~5)



The presence of the second form of acid **9** is likely determined by the syn- or anti-orientation of the methyl group of the ethyl radical and the aminodiphosphonic function in molecule **9**, which is likely why the ratio of conformers, in this case, is ~ 1:10.

Table S1. Protonation constants of acids **8** (H_5L) and **9** (H_6L) in water at 298 K and ionic strength of I = 0.1 M KCl [a].

No.	Equilibrium	logβ [b]			
		8	**9**	MAMDP [c]	AEDP [c]
1	L + H = HL	10.88 ± 0.19	11.82 ± 0.29	13.4	11.5
2	L + 2H = H_2L	19.99 ± 0.18	22.47 ± 0.32	21.95	20.08
3	L + 3H = H_3L	25.64 ± 0.21	32.23 ± 0.32	26.81	25.45
4	L + 4H = H_4L	29.10 ± 0.15	40.73 ± 0.32	27.87	26.95
5	L + 5H = H_5L	32.09 ± 0.28	45.78 ± 0.33		
6	L + 6H = H_6L	-	48.52 ± 0.34		

[a] For simplicity, the charges of chemical forms in the equilibria are not indicated.
[b] logβ are full equilibrium constants, the errors in the lgβ values are evaluated by error propagation rule for the several titrations and applied algorithm calculations (see Experimental section)
[c] Protonation constants of similar known ligands [22]: (dimethylamino)methylenediphosphonic acid (MAMDP) and (aminoethylene)diphosphonic acid (AEDP), at 297 K and I = 0.2 M.

Table S2. Full stability constants of the Ga^{3+} complexes with **8** (H_5L) and **9** (H_6L) in water at 298 K and ionic strength of I = 0.1 M KCl [a].

No.	Equilibrium	logβ				
		8	**9**	GDPO [b]	EDDADPO [b]	EDTPO [b]
1	Ga + L = GaL	26.63 ± 0.24	31.92 ± 0.32	21.93	26.82	31.83
2	Ga + H +L = GaHL	34.91 ± 0.32	40.82 ± 0.51	26.02	31.92	38.48
3	Ga + 2H +L = GaH_2L	39.51 ± 0.29	49.10 ± 0.45	28.53	34.16	43.58
4	Ga + 3H +L = GaH_3L	42.76 ± 0.32	57.13 ± 0.46			46.87
5	Ga + 4H + L = GaH_4L	-	≈ 62			49.33

[a] See notes for Table S1.
[b] Full stability constants of the Ga^{3+} complexes with known multidentate ligands containing two or four phosphonic groups [23]: glycine-*N*,*N*-bis(methylenephosphonic) acid (GDPO), ethylenediamine-*N*,*N'*-diacetic-N,N'-bis(methylenephosphonic) acid (EDDADPO), and ethylenediamine-*N*,*N*,*N'*,*N'*-tetrakis(methylenephosphonic) acid (EDTPO), at 298 K and I = 0.1 M KNO_3.