Supplementary Information (SI) for Physical Chemistry Chemical Physics.

Supplementary Information for
Hydrophobic Hydration of Analgesics and Diltiazem Complexes Explored by Electrochemical Impedance Spectroscopy and NMR Diffusion-Ordered Spectroscopy

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(a)

(b)

Figure S1. (a) Overview of the electrochemical measurement instrument consisted of a triode cell, a potentiostat (Vertex 1A), and an analysis PC (IviumSoft). (b) Triode glass cell (HX-111), containing a working electrode of glassy carbon (HX-W8, center), a counter electrode with platinum (HX-C13, left), and the reference electrode of Ag/AgCl (HX-R14, right).

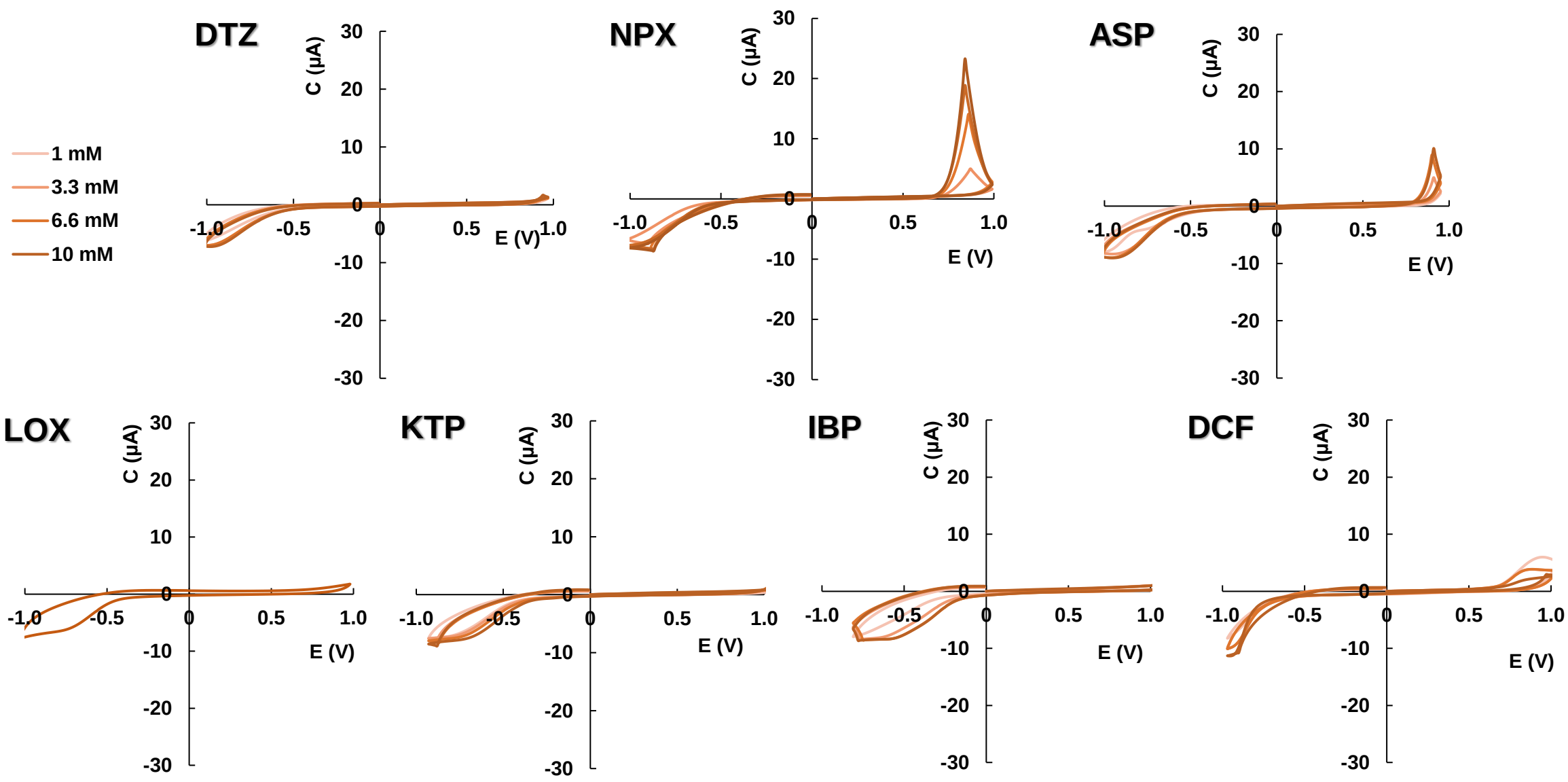
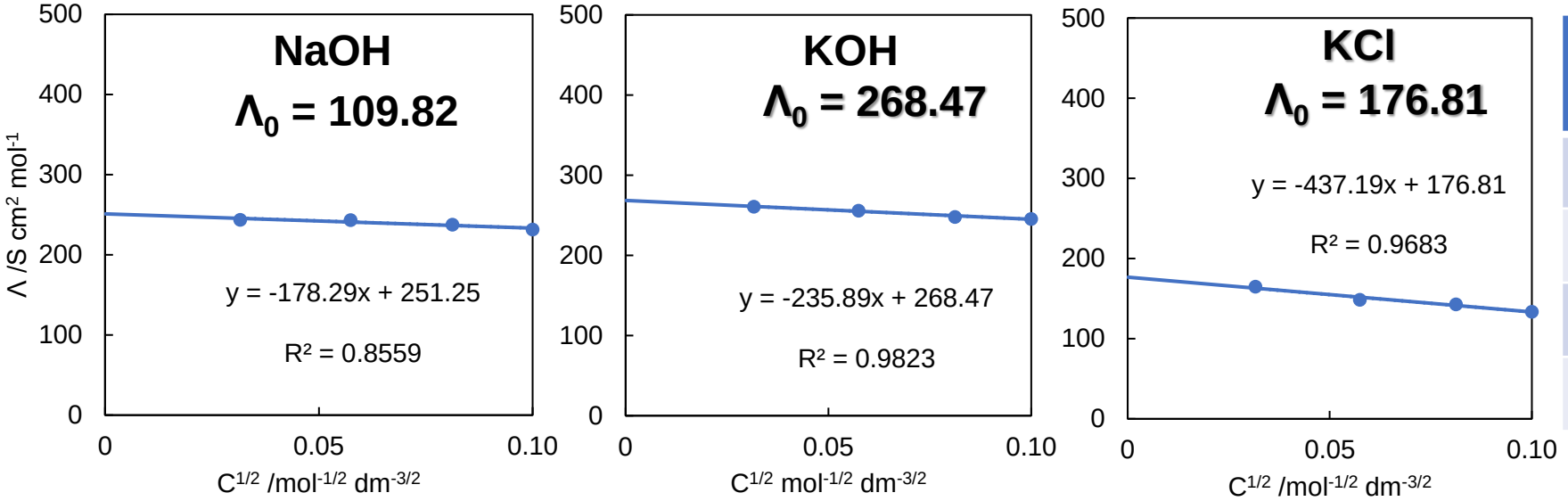


Figure S2. CV current-voltage diagrams for basic DTZ and acidic analgesics, NPX, ASP, LOX, KTP, IBP, and DCF. No redox signals were observed for the drug samples in the applied voltage range.



ion	Theoretical S cm² mol⁻¹	Observed S cm² mol⁻¹
Na^+	50.1	57.265
K^+	73.5	77.737
Cl^-	76.3	96.902
OH^-	199.1	191.37

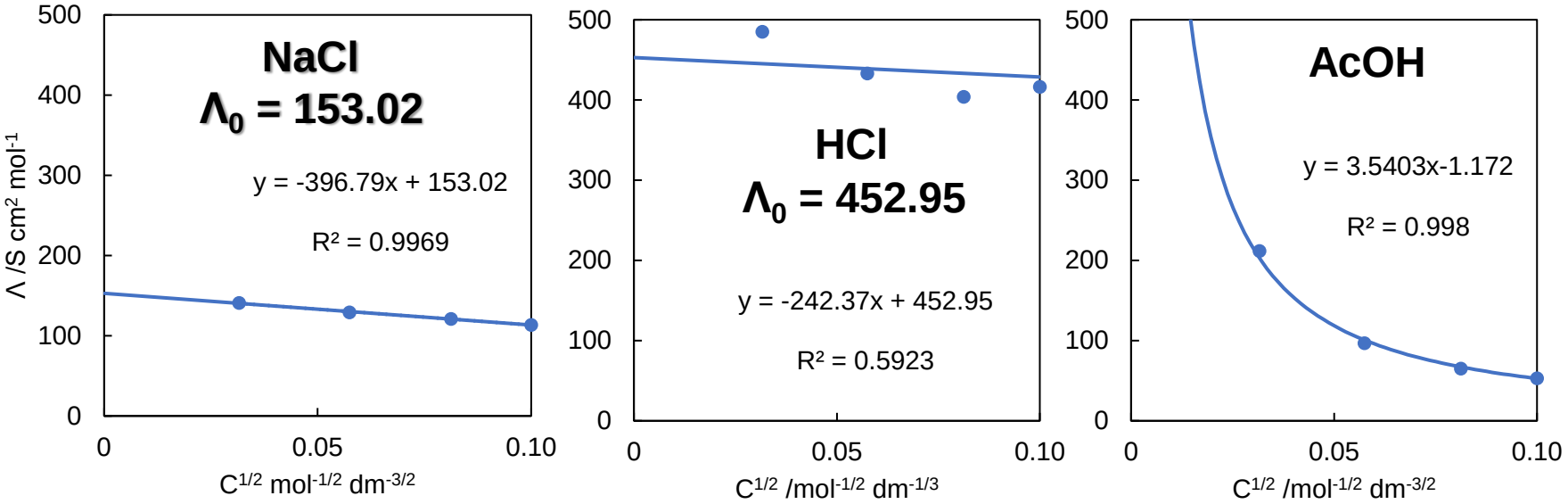


Figure S3. Molar electrical conductivity for inorganic electrolytes and acetic acid (AcOH). Ion transportation numbers for Na^+, K^+, Cl^-, and OH^- were calculated using Hittorf's equation.

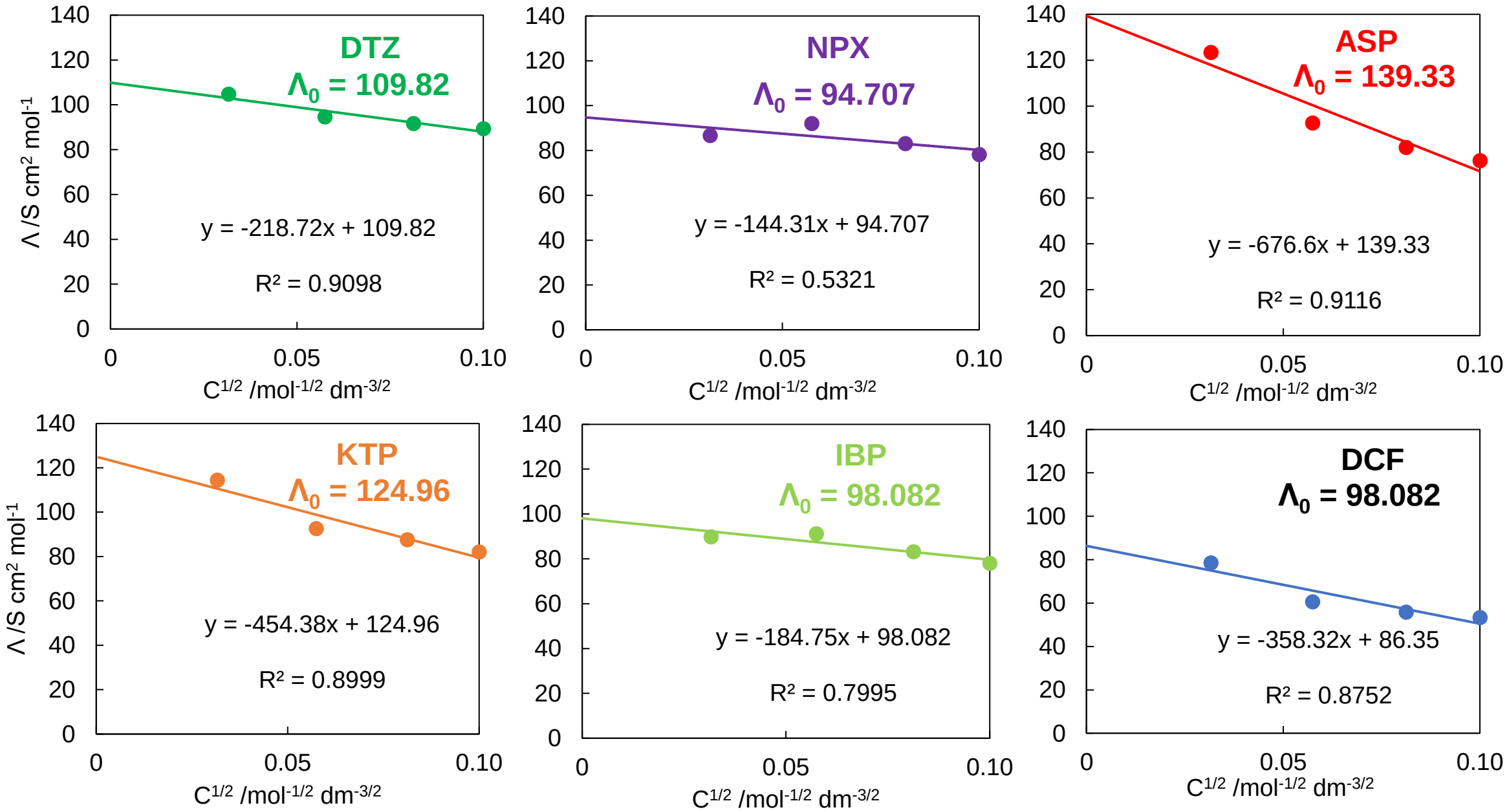


Figure S4. Molar electrical conductivity for basic DTZ and acidic analgesics and their calibrations.

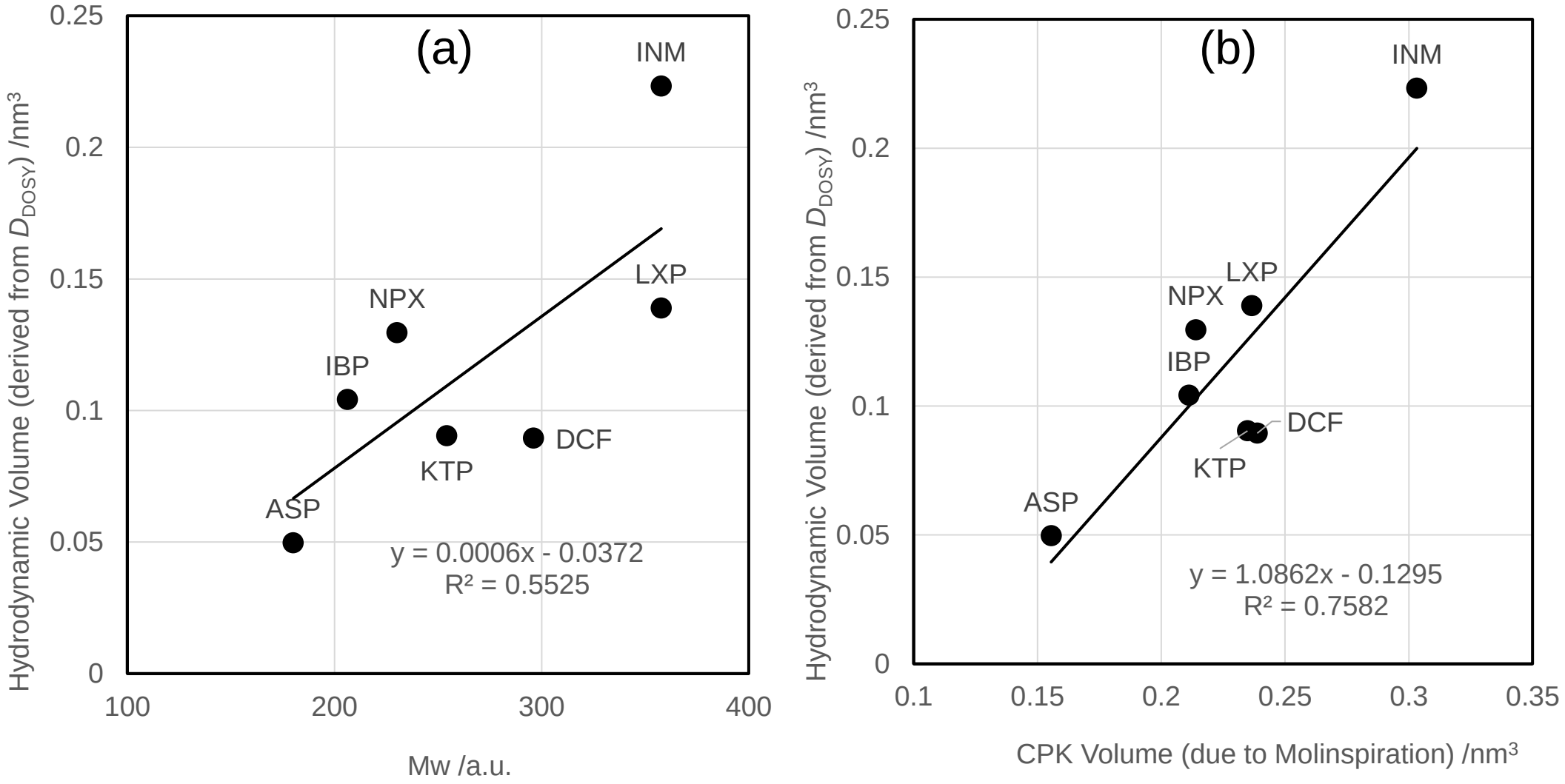


Figure S5. Correlations of the hydrodynamic volumes derived from D_{DOSY} to Mw of NSAIDs (a) and molecular volume of NSAIDs (b). Supposing that the Mw of ASP, IBP, NPX, and INM correlated to the hydrodynamic volumes, those of KTP, DCF, and LXP were lower than expected from their Mw. The CPK volumes were calculated using https://www.molinspiration.com/services/volume.html; the hydrodynamic volumes of KTP and DCF were smaller than predicted based on their CPK volumes.

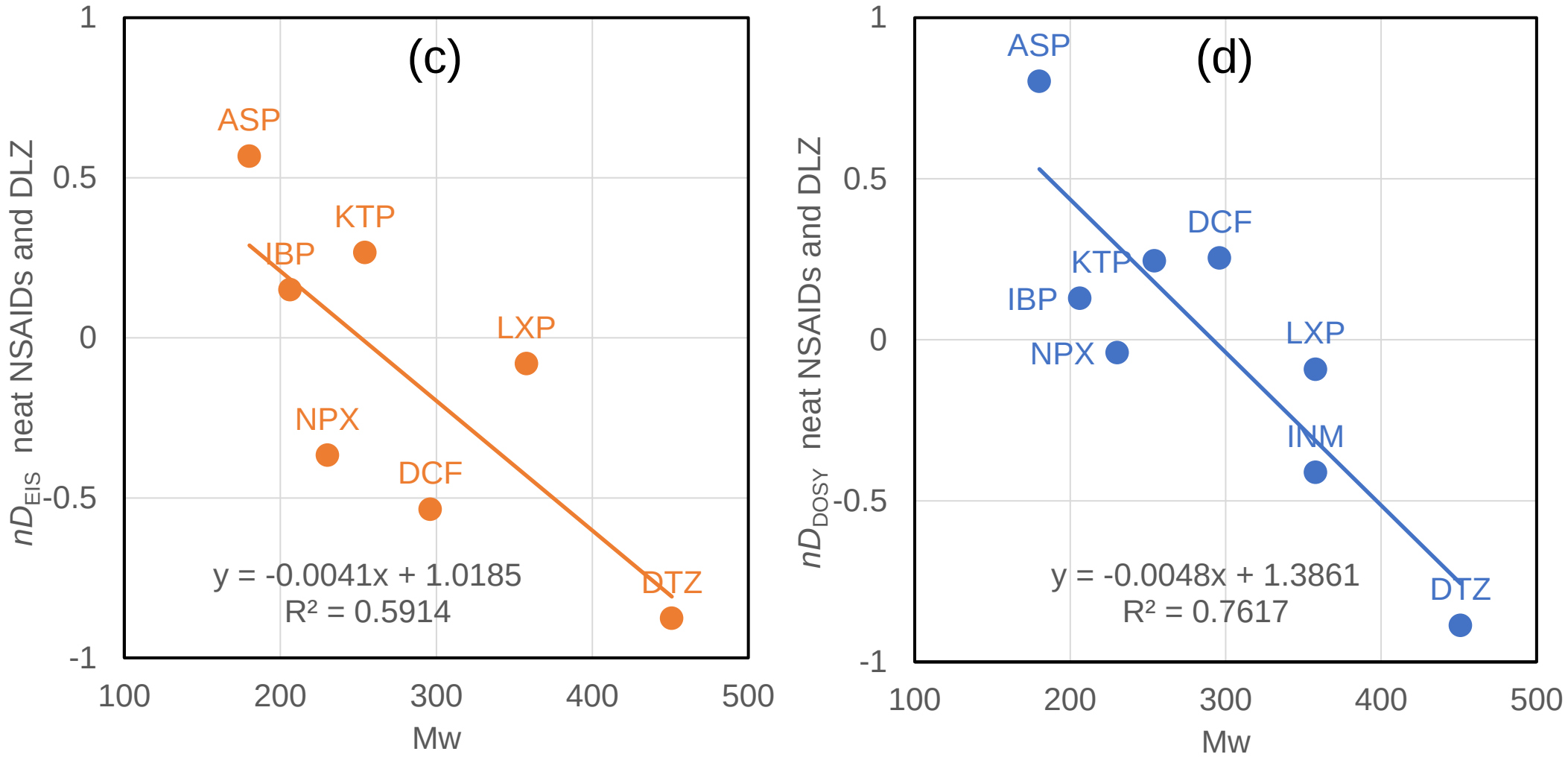
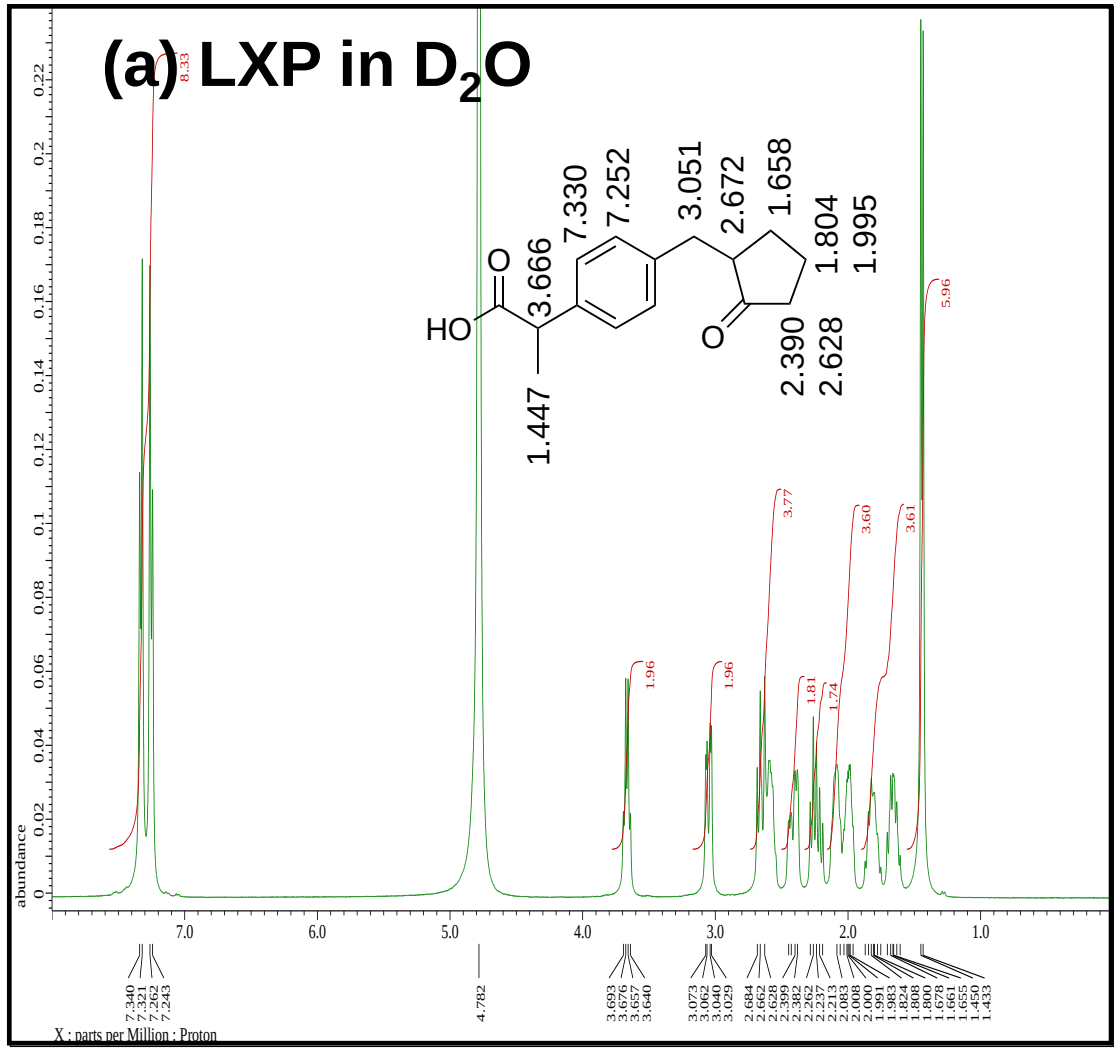
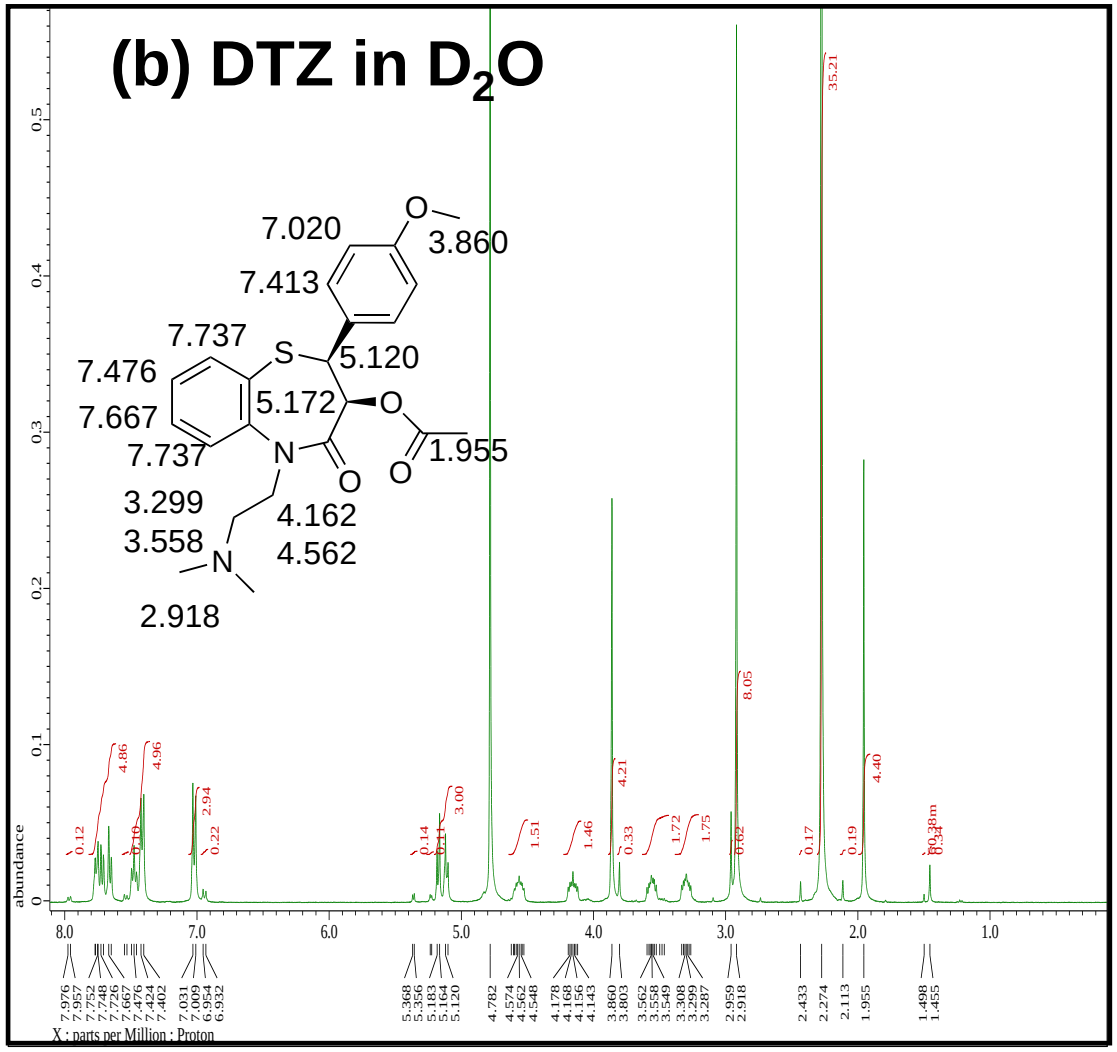


Figure S5. Normalized diffusion constants (*nD*) for APIs, obtained from EIS (c) and DOSY (d) measurements, correlated to their molecular weights (Mw). nD_{EIS} values were correlated to Mw with the determination constant $r^2 = 0.5914$, whereas nD_{DOSY} had $r^2 = 0.7617$. After excluding NPX and DCF as outliers, the nD_{EIS} for $n = 5$ improved to have an r^2 of 0.8815 (Figure 3b). With NPX and IBP as outliers, the nD_{DOSY} for $n = 5$ improved to have an r^2 of 0.9483 (Figure 3c).



Chemical shift /ppm



Chemical shift /ppm

Figure S6. ^{1}H-NMR 1D-spectra of DTZ and LXP and their signal assignments in D_2O. (see ref[13])

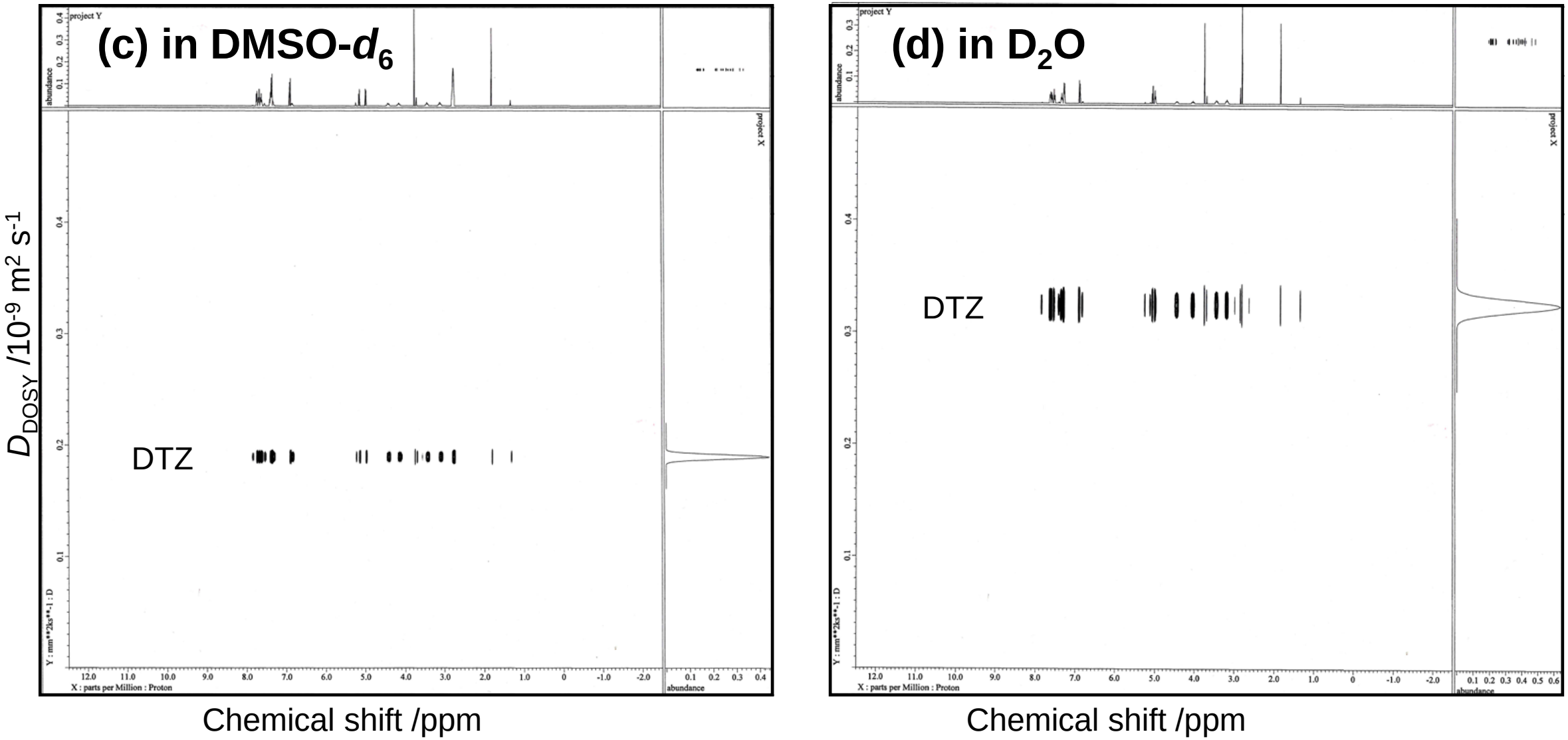


Figure S6 (continued). DOSY spectra of DTZ measured in (c) DMSO-d_6, (d) D_2O.

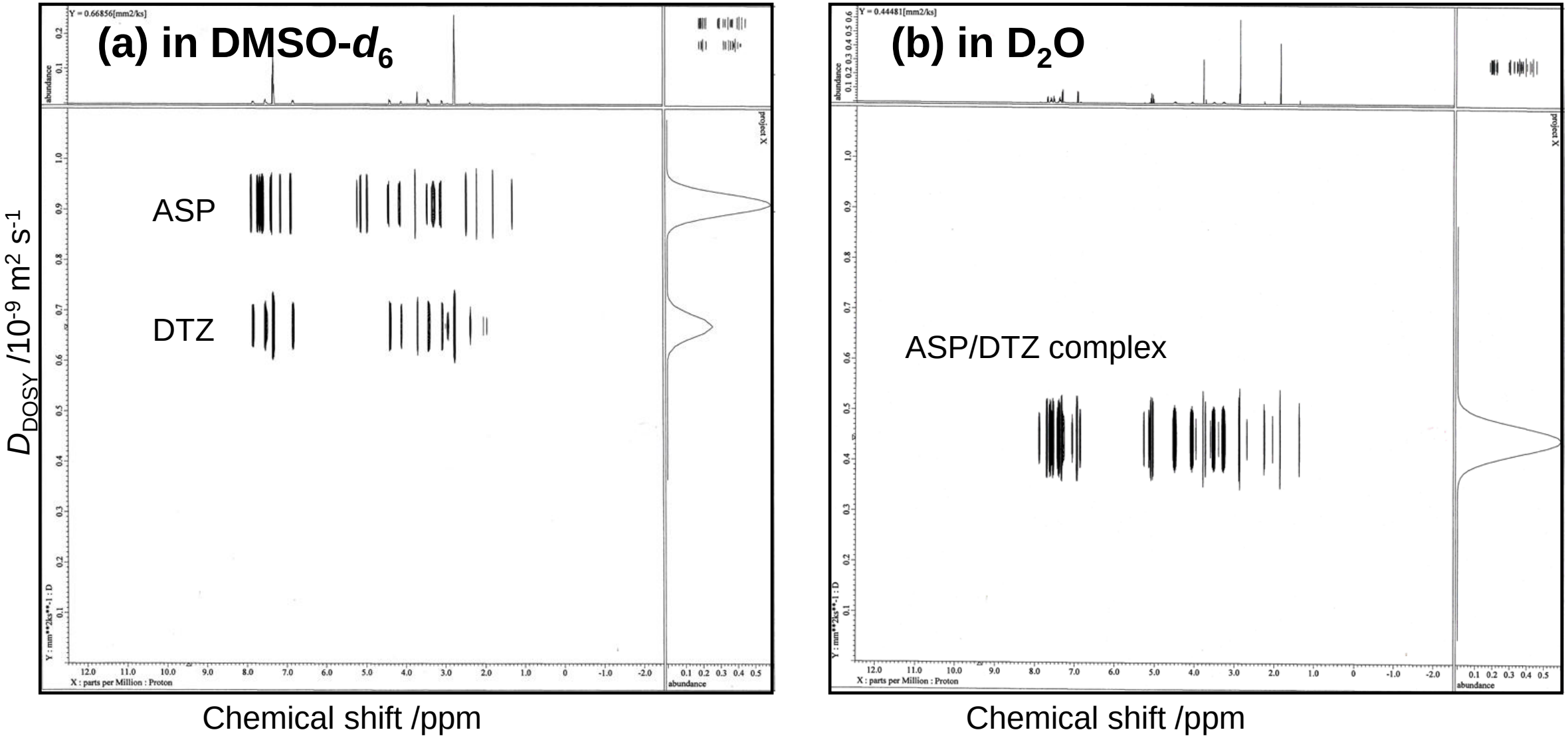


Figure S7. DOSY spectra of ASP/DTZ equimolar mixture measured in (a) DMSO-d_6, (b) D_2O.

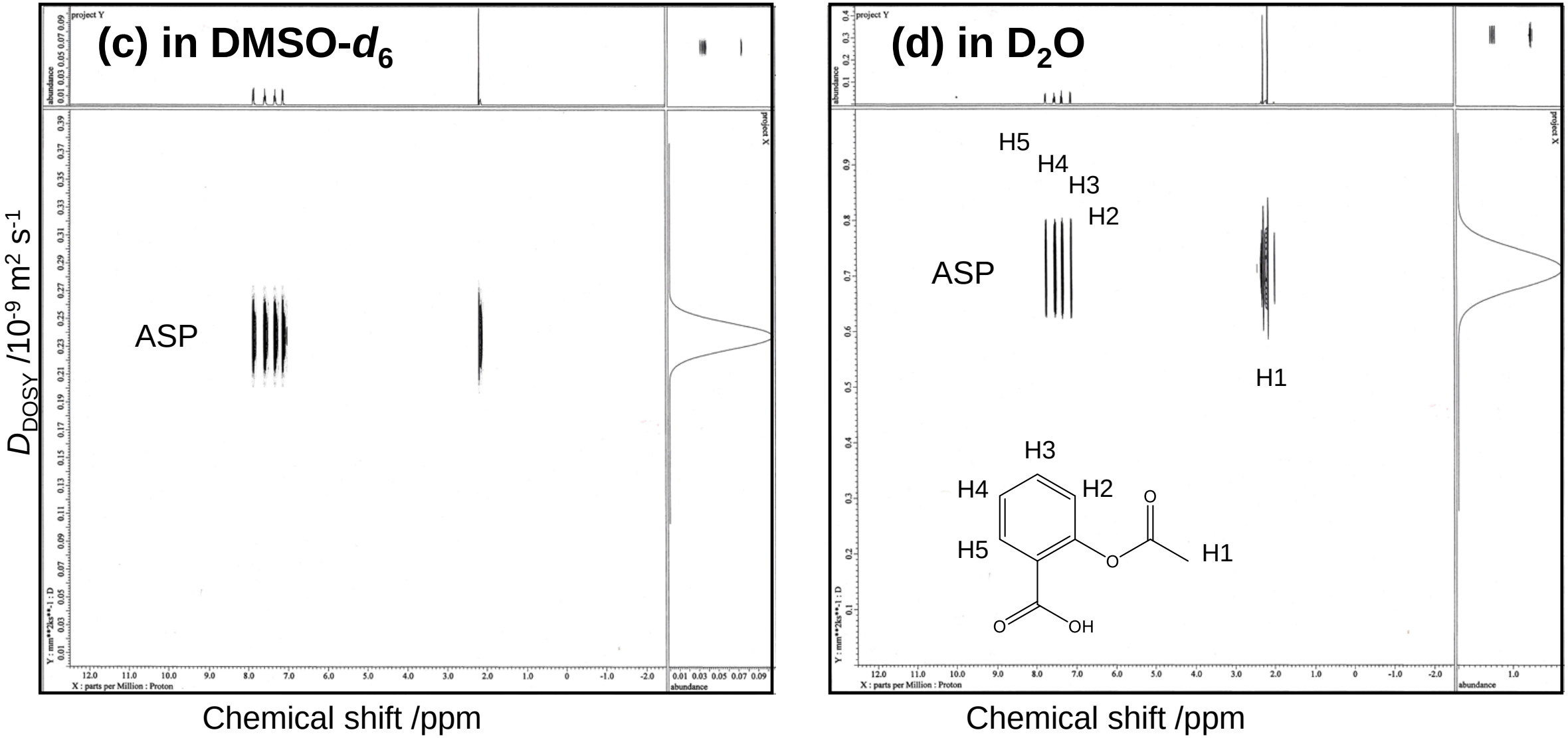


Figure S7 (continued). DOSY spectra of ASP measured in (c) DMSO-d_6, (d) D_2O. [13]

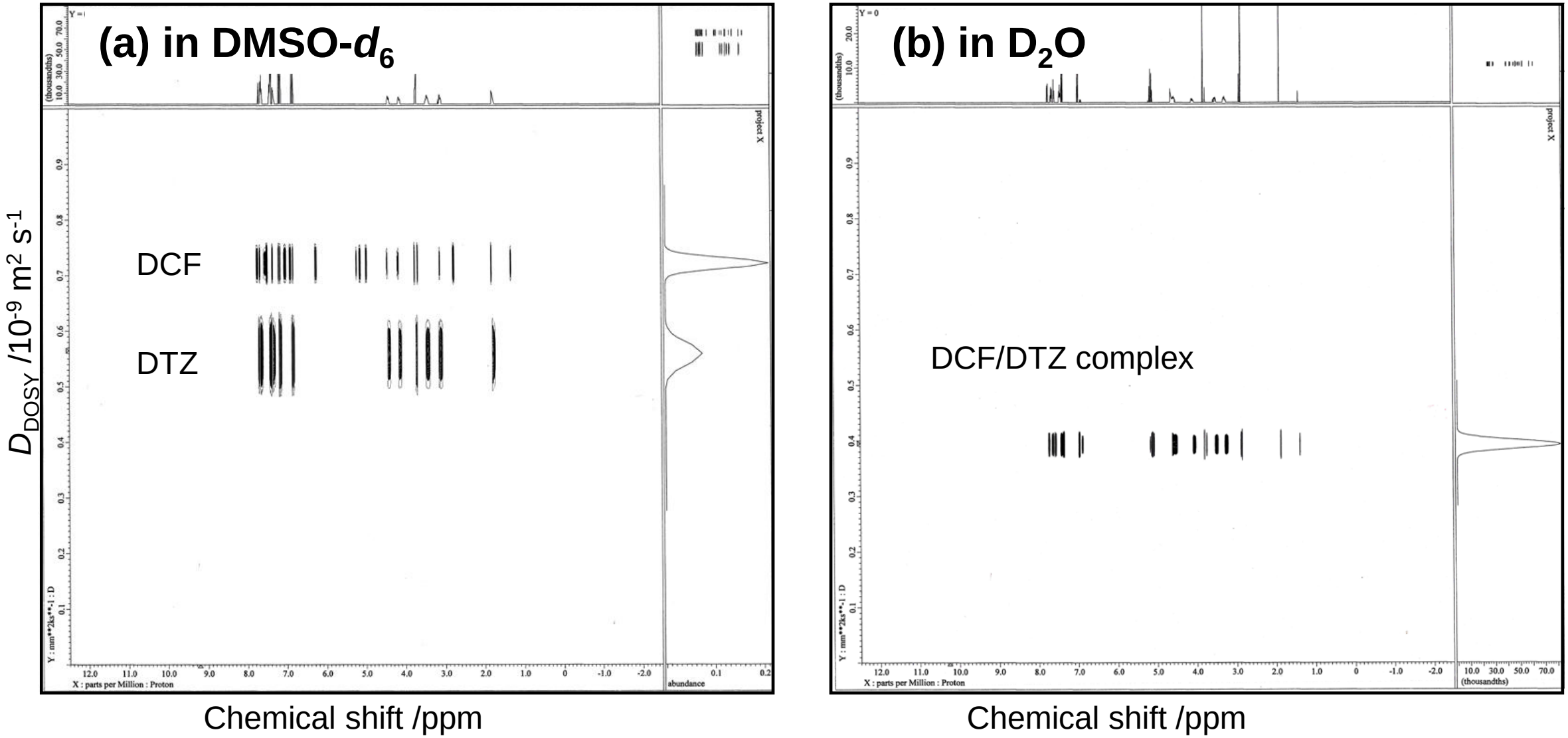


Figure S8. DOSY spectra of DCF/DTZ equimolar mixture measured in (a) DMSO-d_6, (b) D_2O.

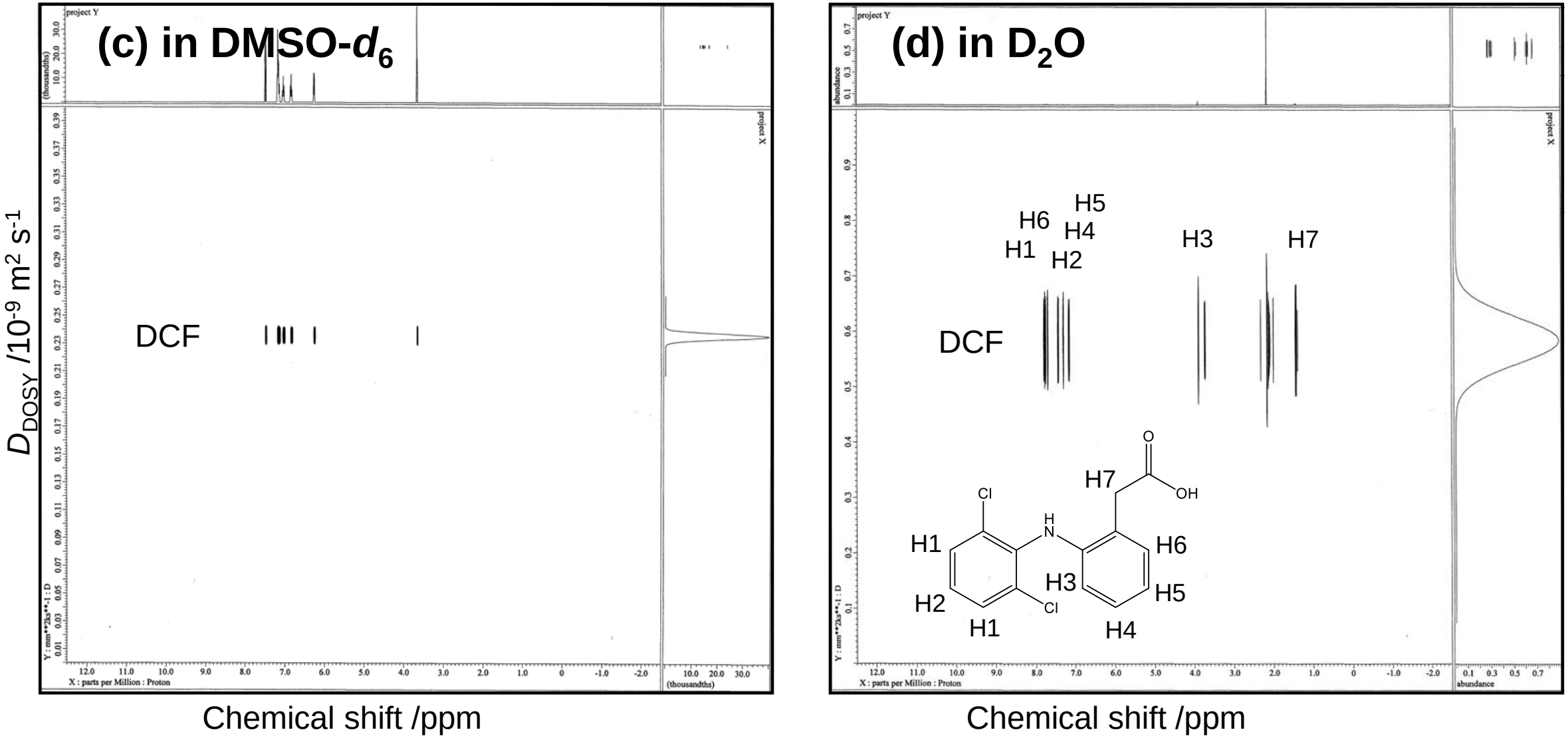


Figure S8 (continued). DOSY spectra of DCF measured in (c) DMSO-d_6, (d) D_2O. [15]

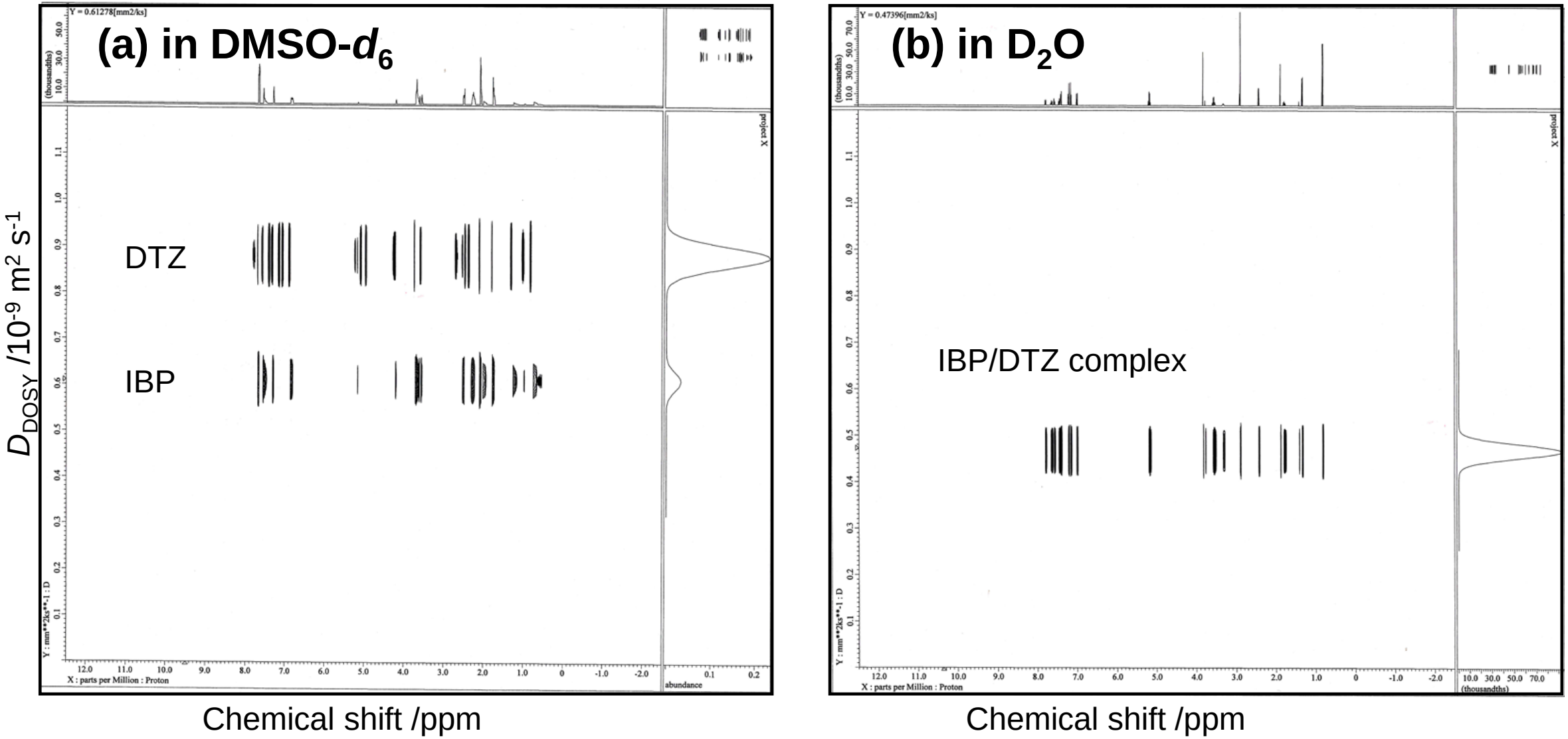


Figure S9. DOSY spectra of IBP/DTZ equimolar mixture measured in (a) DMSO-d_6, (b) D_2O.

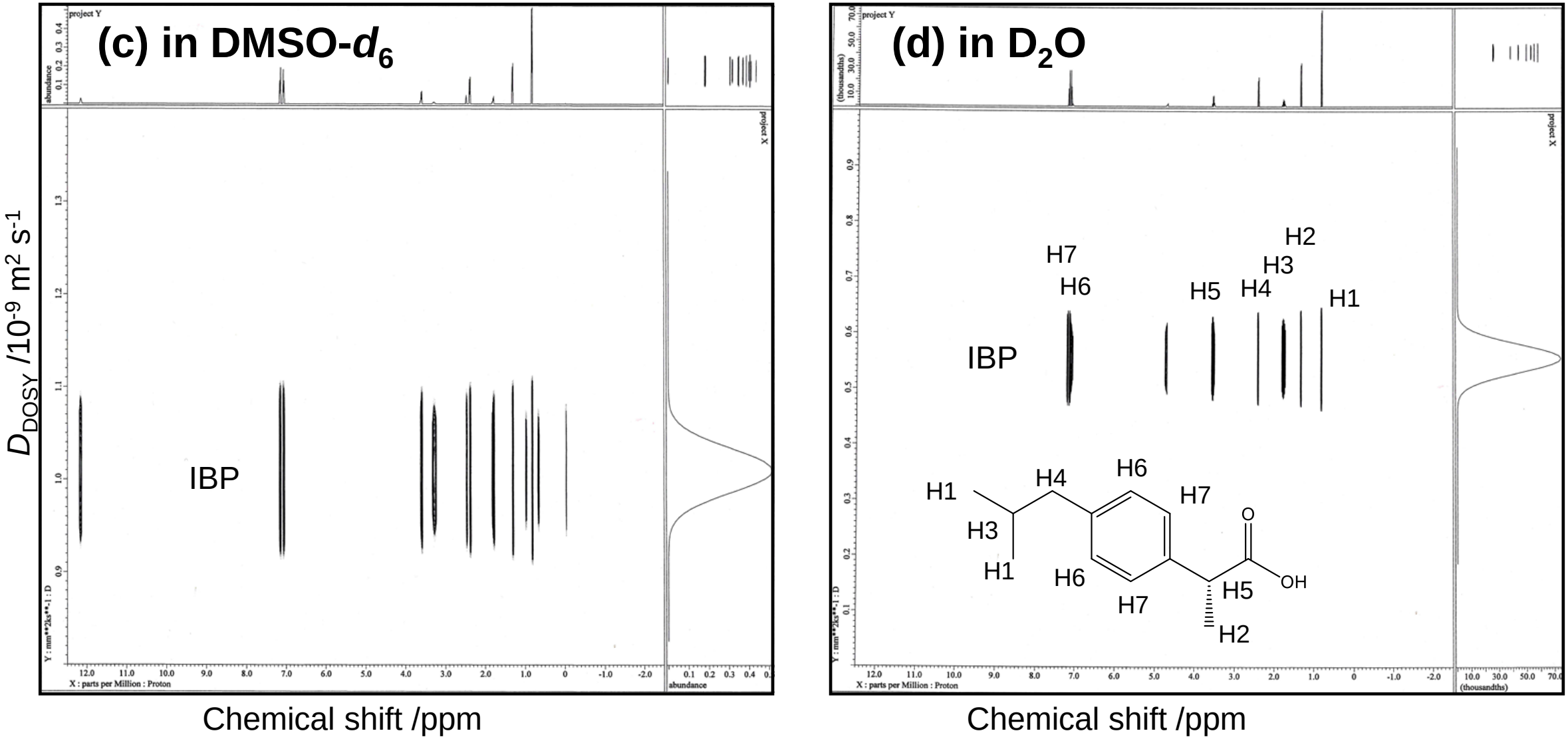


Figure S9 (continued). DOSY spectra of IBP measured in (c) DMSO-d_6, (d) D_2O. [13]

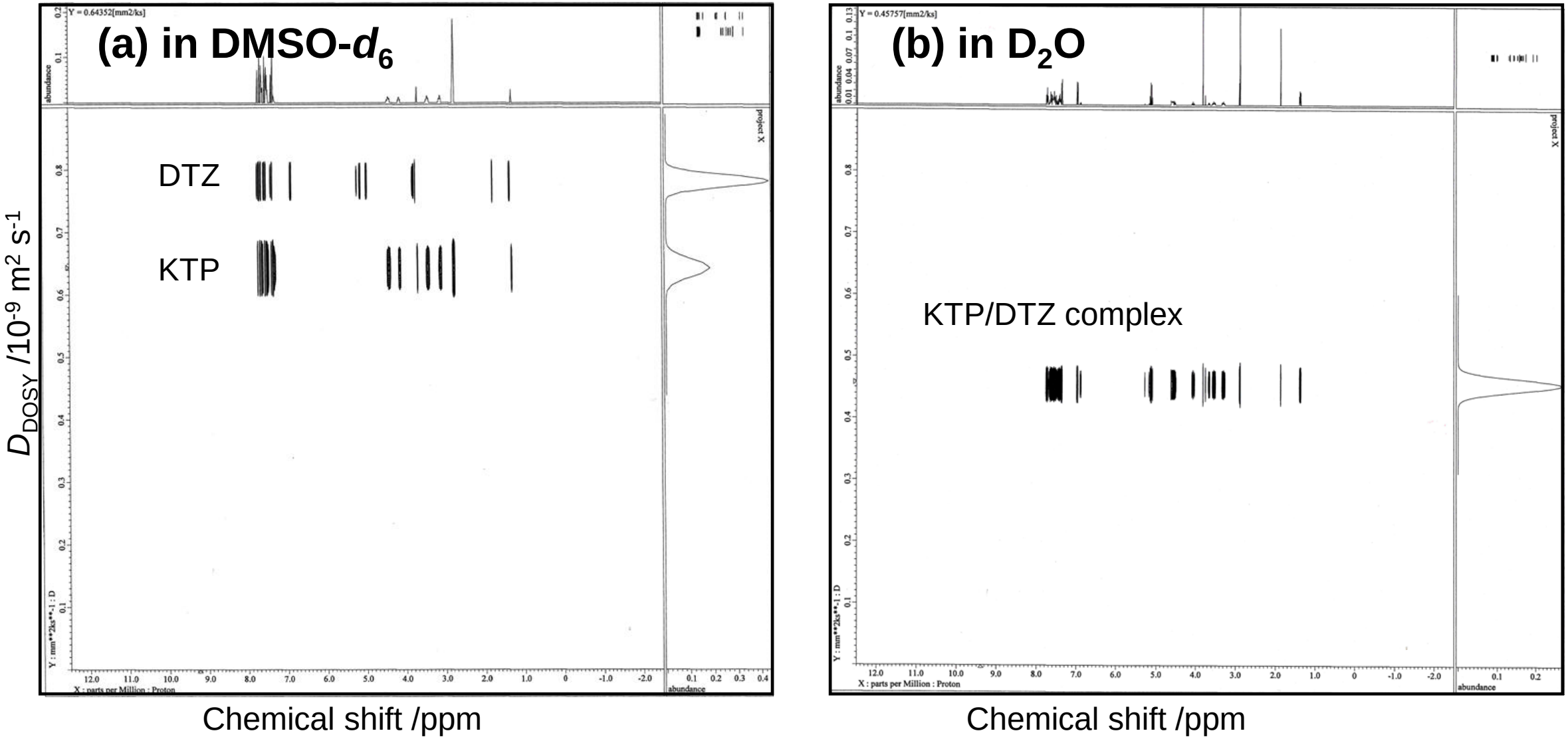


Figure S10. DOSY spectra of KTP/DTZ equimolar mixture measured in (a) DMSO-d_6, (b) D_2O.

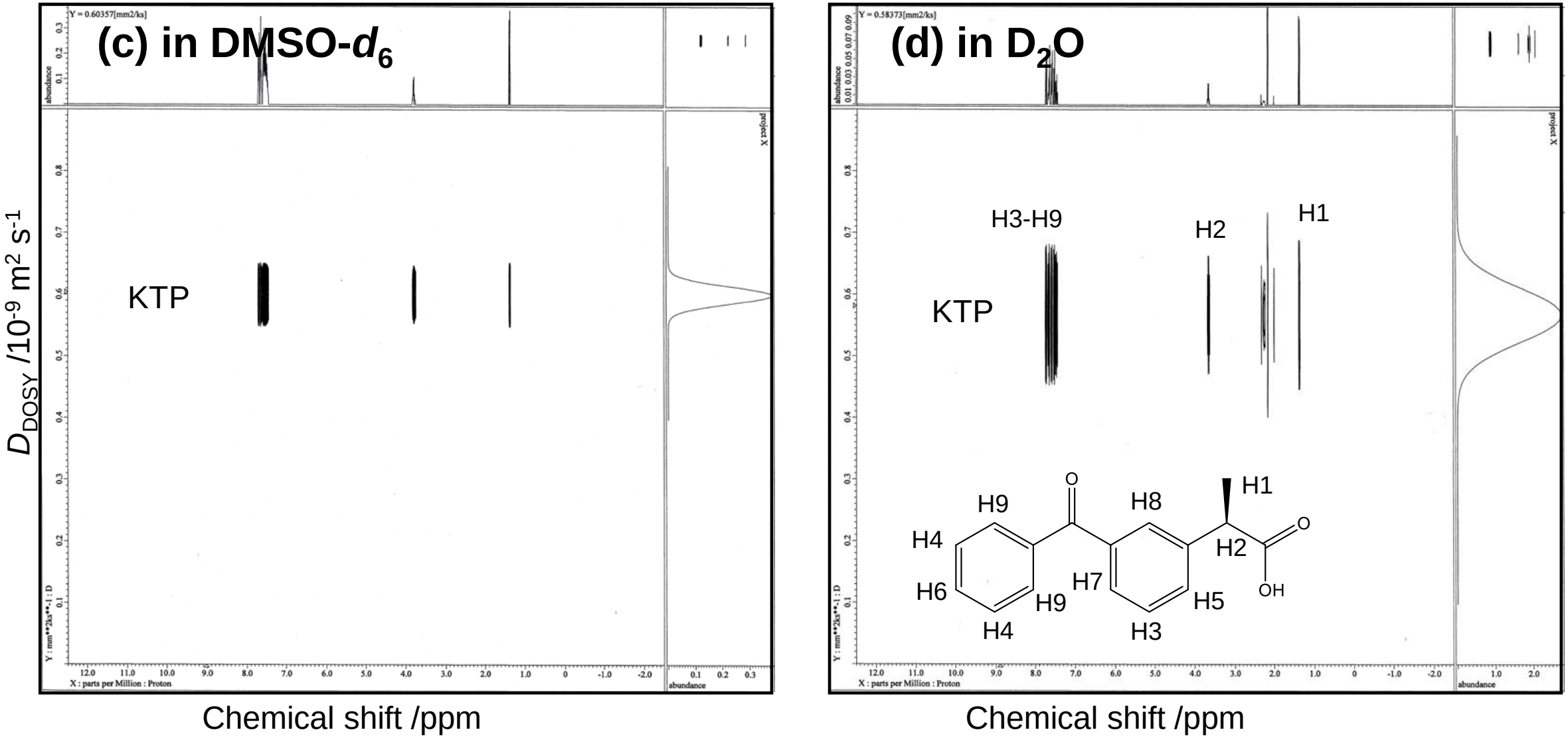


Figure S10 (continued). DOSY spectra of KTP measured in (c) DMSO-d_6, (d) D_2O. [13]

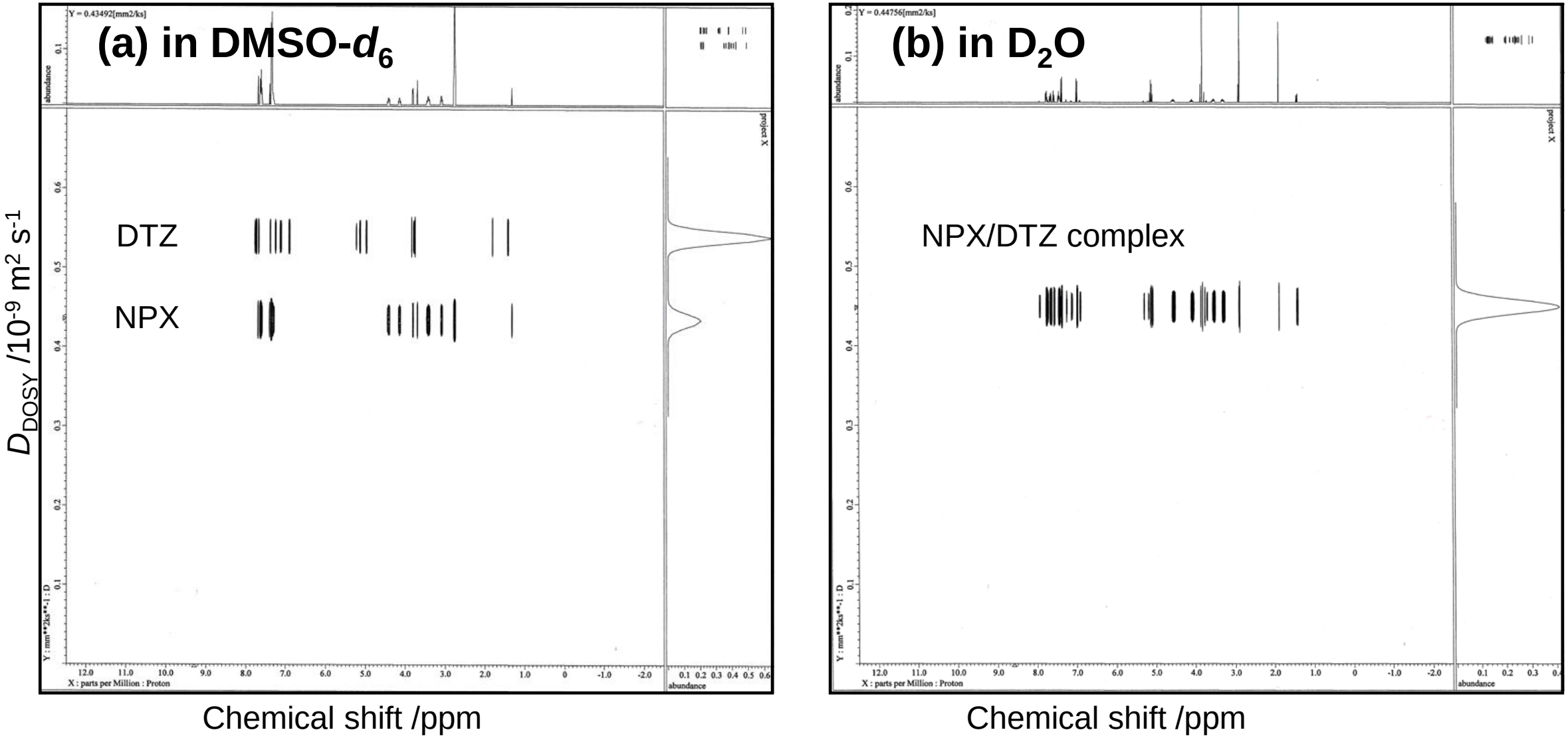


Figure S11. DOSY spectra of NPX/DTZ equimolar mixture measured in (a) DMSO-d_6, (b) D_2O.

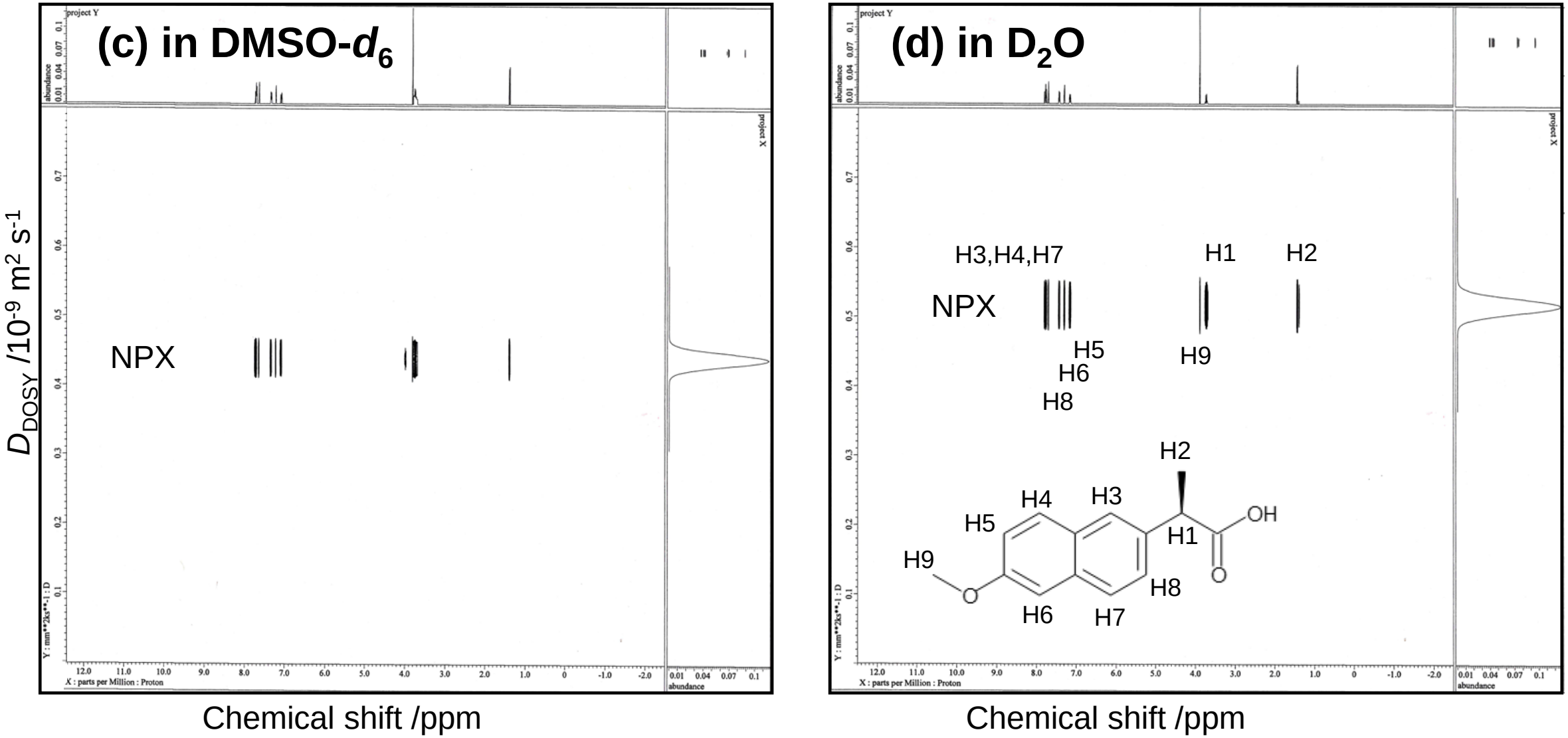


Figure S11 (continued). DOSY spectra of NPX measured in (c) DMSO-d_6, (d) D_2O.