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Internally Referenced Diffusion Coefficient−Formula Weight (D-FW) Analysis of ^{31}P Diffusion-Ordered NMR Spectroscopy (DOSY)

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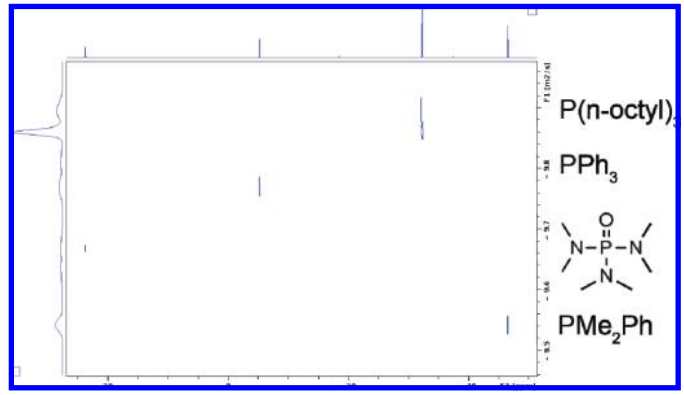
ABSTRACT



The development of ^{31}P DOSY NMR with diffusion coefficient−formula weight (D-FW) analysis is reported. Commercially available trialkyl phosphine internal references were used in a model system to establish the molecular weight of a phosphorous containing organolithium compound. The feasibility of ^{31}P DOSY D-FW studies is established. This extension of DOSY D-FW analysis expands its applicability to solution structure studies of a wide variety of compounds.

The expansion of diffusion-ordered spectroscopy (DOSY) methodology and the application of this technique to structure analysis in solution is a main focus of our research. Our group has comprehensively developed ^{1}H and ^{13}C DOSY techniques and diffusion coefficient-formula weight (D-FW) correlation analysis into useful tools for the analysis of formula weights of complexes in solution.[1] This DOSY toolbox has allowed the solution state characterization of several systems not amenable to conventional mass spectrometric techniques, including reactive, water, and air sensitive small molecules, for instance, organolithium compounds.

An extension of the DOSY toolbox is the establishment of the method in other nuclei. ^{31}P is a good choice due to its wide use with organometallic ligands, sharp peaks in the proton decoupled ^{31}P NMR spectrum, 100% natural abundance, and spin of $^{1}/_{2}$. Potentially, ^{31}P DOSY combines the best traits of ^{1}H and ^{13}C DOSY. That is, like the ^{1}H DOSY, it is very fast to acquire, and like the ^{13}C DOSY, sharp, widely separated peaks make individual peak picking for signal attenuation curve analysis facile. A major detriment to DOSY D-FW analysis is overlapping resonances in the chemical shift dimension leading to misleading data in the

‡ These researchers contributed equally to this report.

(1) (a) Li, D.; Keresztes, I.; Hopson, R.; Williard, P. G. *Acc. Chem. Res.* **2009**, *42*, 270–280. (b) Li, D.; Kagan, G.; Hopson, R.; Williard, P. G. *J. Am. Chem. Soc.* **2009**, *131*, 5627–5634. (c) Li, D.; Sun, C.; Williard, P. G. *J. Am. Chem. Soc.* **2008**, *130*, 11726–11736. (d) Li, D.; Sun, C.; Liu, J.; Hopson, R.; Li, W.; Williard, P. G. *J. Org. Chem.* **2008**, *73*, 2373–2381. (e) Li, D.; Hopson, R.; Li, W.; Liu, J.; Williard, P. G. *Org. Lett.* **2008**, *10*, 909–911.

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diffusion dimension. The very wide ^{31}P spectrum provides ample separation between relatively similar compounds.

Only a few examples of ^{31}P diffusion spectroscopy have been successfully applied to compounds as an aid to solution structure analysis and solution composition.[2]

We chose a model system of dimethylphenylphosphine **1** (PMe_2Ph, 138.15 g/mol, −46.6 ppm), triphenylphosphine **2** (PPh_3, 262.29 g/mol, −5.26 ppm), and tri-*n*-octylphosphine **3** ($P(n\text{-octyl})_3$, 370.64 g/mol, −32.3 ppm) at equimolar concentration in toluene-d_8 as internal references and hexamethylphosphoramide **4** (HMPA, 179.2 g/mol, 23.7 ppm) as an analyte to validate the methodology.

Initial results were promising. Parameters for the standard Bruker stegp1s DOSY pulse program were optimized for ^{31}P DOSY, and the resulting spectrum (Figure 1a) was

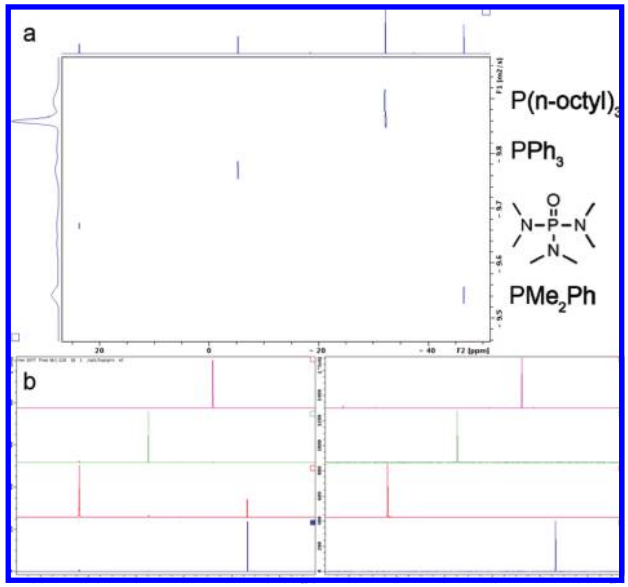

Figure 1. (a) ^{31}P DOSY spectrum of a mixture of compounds **1**−**4** in toluene-d_8. (b) Slices of the DOSY diffusion axis (left) as compared to spectra of pure compounds (right).

consistent with the expected diffusion order of compounds in solution, with lighter compounds diffusing more rapidly than heavier compounds. Sharp peaks typical of ^{31}P NMR produced crisp and clear signals along the diffusion axis, and slices taken at each of the four major diffusion levels reproduced the individual ^{31}P spectra of the separate compounds (Figure 1b). The DOSY spectrum shows excellent separation of all components in the diffusion dimension.

Diffusion coefficients were generated by using curve fitting of signal attenuation data.[3] The signal attenuation curves of peak intensity provide some insight into the performance of the pulse program, and in this case full signal attenuation was attained after 32 steps of increasing gradient strength from 2% to 95% linearly (Figure 2).

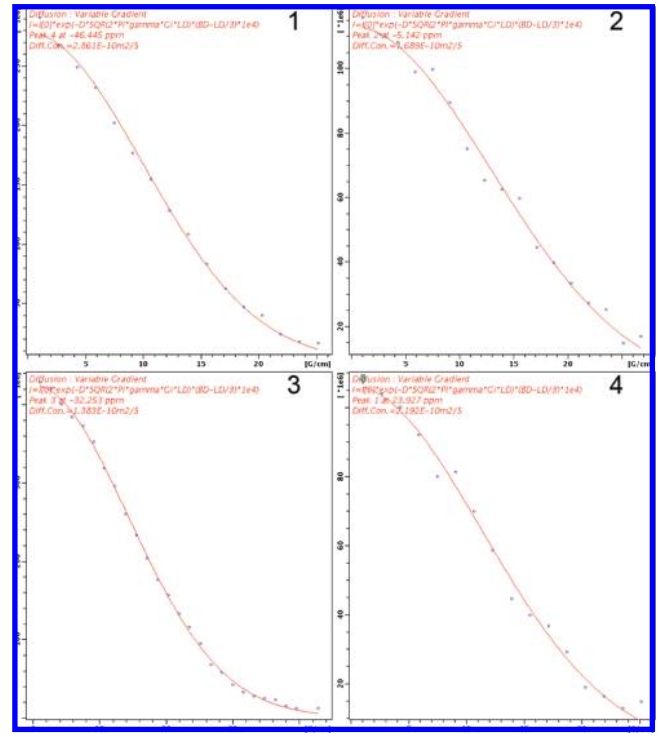

Figure 2. Signal attenuation curves for ^{31}P DOSY data of a mixture of compounds **1**−**4** in toluene-d_8.

A D-FW analysis was performed on the data and the predicted formula weights were in good agreement with calculated values, as shown in Figure 3 and Table 1.

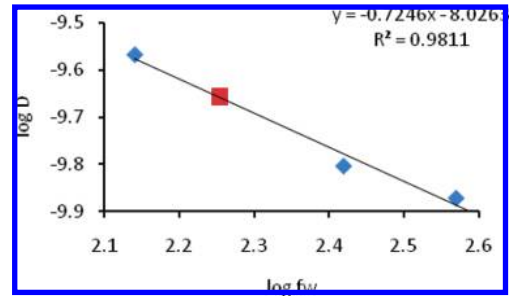

Figure 3. D-FW analysis of ^{31}P DOSY data of a mixture of compounds **1**−**4** in toluene-d_8.

Diffusion coefficients were generated from the signal attenuation data of peak integration. Values for M and B are based on the linear line of best fit $\log D = A(\log \text{fw}) + C$ of a plot of the logarithm of the formula weight versus the logarithm of the diffusion coefficient.[1a] This shows a good correlation of the values of the internal references (in blue) and a good prediction of the analyte HMPA, in red, with a

(2) (a) Kapur, G. S.; Berger, S. *TriboTest* **2000**, *6*, 323–336. (b) Martinez-Viviente, E.; Rüegger, H.; Pregosin, P. S.; Lopez-Serrano, J. *Organometallics* **2002**, *21*, 5841–5846. (c) Nama, D.; Kumar, P. G. A.; Pregosin, P. S. *Magn. Reson. Chem.* **2005**, *43*, 246–250. (d) Segev, O.; Columbus, I.; Ashani, Y.; Cohen, Y. *J. Org. Chem.* **2005**, *70*, 309–314.

Table 1. D-FW Analysis of ^{31}P DOSY Data of a Mixture of Compounds **1**−**4** in Toluene-d_8[a]

entry	compd	fw (g/mol)	$10^{-10}D$ (m^2/s)	log fw	log D	fw*	% error
1	$P(Me)_2Ph$	138.15	2.701	2.1404	−9.5685	134	2.7
2	PPh_3	262.29	1.571	2.4188	−9.8038	284	−8.2
3	$P(n\text{-octyl})_3$	370.64	1.344	2.5690	−9.8716	352	5.0
4	HMPA	179.2	2.205	2.2533	−9.6566	178	0.8
					average dev		4.1

[a] $A = -0.72461$; $C = -8.02627$.

very high r^2 value of 0.98. The average deviation of formula weight prediction was 4.1% overall, with only a 0.8% error in the prediction of the analyte formula weight. This example established confidence in the chosen set of internal references as a means to predict formula weights by the D-FW method in ^{31}P DOSY spectra.

Encouraged by these results, we proceeded to characterize a complex of lithium hexamethyldisilazide (LiHMDS) and HMPA **5**. Crystals of (LiHMDS)·(HMPA) complex were grown, washed in dry pentane, and dissolved in toluene-d_8. This solution was added to a previously prepared NMR tube containing the internal references PMe_2Ph, PPh_3, and $P(n\text{-octyl})_3$, titrated to similar signal strength in the ^{31}P spectrum.

Solutions of LiHMDS and HMPA have been studied previously by several groups, notably Collum.[4] Extensive evidence for the solvation of lithium by HMPA and other phosphine oxides by $J_{^6\text{LiP}}$ and $J_{^7\text{LiP}}$ coupling have been presented by Reich and co-workers,[5] as well as a single crystal structure by Snaith.[6]

It was noted that apparently bound HMPA had the same chemical shift in the phosphorus spectrum as that of free HMPA, perhaps surprising considering the widely varying chemical shifts of phosphorus nuclei for apparently similar compounds. This seems to indicate that if a complex between lithium and HMPA is formed, it is, unsurprisingly, formed through the oxygen of HMPA rather than the phosphorus. The ^{31}P DOSY results are striking, in that the HMPA has moved very far up the diffusion axis to become the slowest diffusing compound in solution, indicative of a substantial increase in formula weight, thus indicating that it remains complexed with LiHMDS in solution (Figure 4).

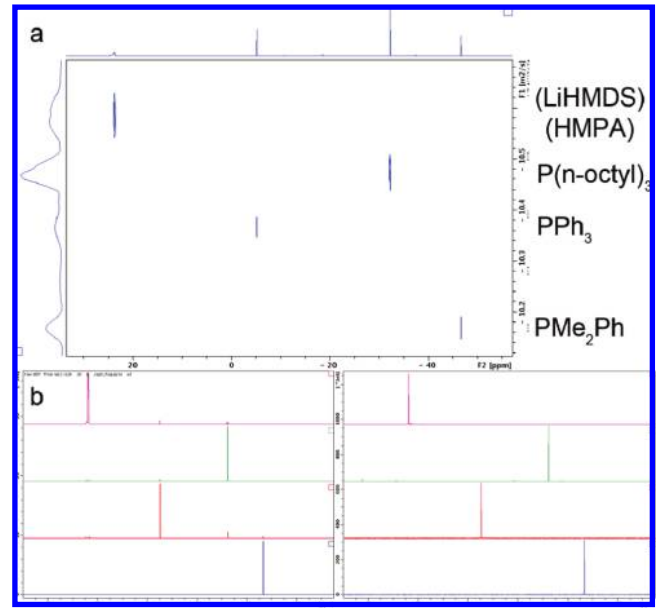

Figure 4. (a) ^{31}P DOSY spectrum of a mixture of compounds **1**−**3** and **5** in toluene-d_8. (b) Slices of the DOSY diffusion axis (left) as compared to spectra of pure compounds (right).

Twenty microliters of *n*-butyllithium was added to the sample tube to regenerate (LiHMDS)·(HMPA), as it was observed that some LiHMDS was reprotonated during crystal manipulation, or on contact with the phosphine solution, which may not have been completely dry. Further addition of *n*-butyllithium did not have any effect on the diffusion coefficient of HMPA, the internal references, or the chemical shifts thereof.

D-FW correlation analysis performed on the diffusion data had a very high r^2 value of 1, and gave a predicted formula weight of HMPA of 598 g/mol, as compared to free HMPA at 179.2 g/mol. Average deviation for the internal references was only 0.2% overall (Figure 5, Table 2).

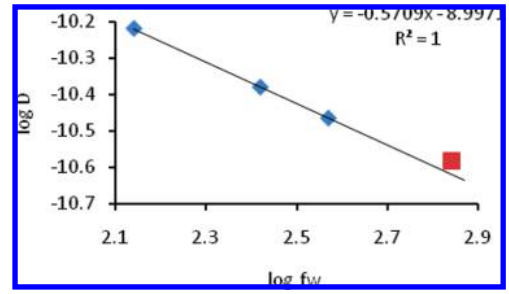

Figure 5. D-FW analysis of ^{31}P DOSY data of a mixture of compounds **1**−**4** in toluene-d_8.

(3) (a) Wu, D.; Chen, A.; Johnson, C. S., Jr. *Bull. Magn. Reson.* **1995**, *17*, 21–26. (b) Chen, A.; Wu, D.; Johnson, C. S., Jr. *J. Am. Chem. Soc.* **1995**, *117*, 7965–7970. (c) Johnson, C. S., Jr. *Understanding Chem. React.* **1994**, *8*, 455–488. (d) Morris, K. F.; Johnson, C. S., Jr. *J. Am. Chem. Soc.* **1993**, *115*, 4291–4299. (e) Morris, K. F.; Johnson, C. S., Jr. *J. Am. Chem. Soc.* **1992**, *114*, 776–777. (f) Morris, K. F.; Johnson, C. S., Jr. *J. Am. Chem. Soc.* **1992**, *114*, 3139–3141.

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Table 2. D-FW Analysis of ^{31}P DOSY Data of a Mixture of Compounds **1**−**3** and **5** in Toluene-d_8[a]

entry	compd	fw	$10^{-11}D$ (m^2/s)	log fw	log D	fw*	% error
1	$P(Me)_2Ph$	138.15	6.042	2.1404	−10.2188	138	0.1
2	PPh_3	262.29	4.181	2.4188	−10.3787	263	−0.3
3	$P(n\text{-octyl})_3$	370.64	3.441	2.5690	−10.4633	370	0.2
4	(LiHMDS)·(HMPA)		2.615	2.8408	−10.5825	598	
					average dev		0.2

[a] $A = -0.57093$; $B = -8.99706$.

Having formula weight data for a complex in solution is a valuable tool for the study of solution state structures of compounds. The predicted formula weight of (LiHMDS)·(HMPA) provides information about the nature of this complex in solution. From ^{1}H NMR integration, the stoichiometry of HMPA to LiHMDS is 1:1. Hence the formula of the complex should be $[(LiHMDS)\cdot(HMPA)]_m$. From D-FW results, we confirm that the species in solution is a disolvated LiHMDS dimer $(LiHMDS)_2\cdot(HMPA)_2$. This complex has a formula weight of 693.05 g/mol, a 14% difference in formula weight predicted from this analysis. The plot of the correlation is shown in Figure 5, with the internal references in blue and (LiHMDS)·(HMPA) in red as $(LiHMDS)_2\cdot(HMPA)_2$.

Limitations here include a larger extrapolation than is preferable, but this can be solved by the use of heavier internal references for higher weight species, and this process is under development. Of particular interest is the extension of this method to macromolecules such as DNA, RNA, and proteins under biological conditions.

In general, while these data alone do not prove with finality the solution structure of $(LiHMDS)_m\cdot(HMPA)_n$ in this system, they do give valuable insight into the role of HMPA in lithium solvation and demonstrate the application of ^{31}P DOSY to formula weight analysis by using the D-FW approach with internal references. This, coupled with ^{1}H and ^{13}C DOSY methods, provides an extensive toolbox for the study of reactive and sensitive complexes in solution not amenable to traditional methods of study such as mass spectrometry and 1D NMR analysis.

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Supporting Information Available: Full spectroscopic data for NMR experiments as well as diffusion data. This material is available free of charge via the Internet at http://pubs.acs.org.

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