

${}^6\text{Li}$ - ${}^{15}\text{N}$ Heteronuclear Multiple Quantum Correlation (HMQC) Spectroscopy: Application to the Structure Determination of Lithium 2,2,6,6-Tetramethylpiperidide Mixed Aggregates

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A heteronuclear multiple quantum correlation (HMQC) experiment was used to correlate the ${}^6\text{Li}$ and ${}^{15}\text{N}$ chemical shifts of mixed aggregates of [${}^6\text{Li}$, ${}^{15}\text{N}$]lithium 2,2,6,6-tetramethylpiperidide with [${}^6\text{Li}$]LiBr, [${}^6\text{Li}$]LiCl, and [${}^6\text{Li}$]lithium cyclohexenolate. Optimization of the experiment to spin systems containing more than one weak spin is discussed. The two-dimensional correlations represent a substantial improvement in sensitivity and resolution relative to one-dimensional methods.

KEY WORDS ${}^6\text{Li}$ - ${}^{15}\text{N}$ HMQC spectroscopy Lithium tetramethylpiperidide mixed aggregates

INTRODUCTION

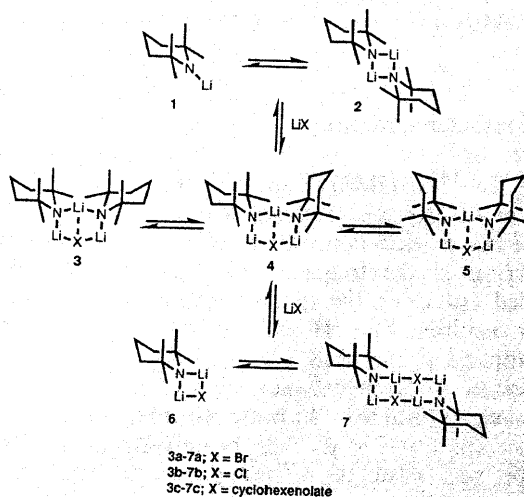
As part of a general program to elucidate the determinants of lithium amide reactivities and selectivities, we have been exploring the potential of ${}^6\text{Li}$ and ${}^{15}\text{N}$ NMR spectroscopy for elucidating the solution structures of *N*-lithiated species.¹ Recent studies of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) mixed aggregates² and hexamethylphosphoramide (HMPA) solvates of LiTMP³ highlighted the importance of having access to unequivocal ${}^6\text{Li}$ - ${}^{15}\text{N}$ resonance correlations (atomic connectivities); single-frequency decoupling methods⁴ allowed us to unravel solution equilibria containing as many as ten discrete structural forms. Nevertheless, limited sensitivity and the poor chemical shift dispersion of the signals of interest rendered the experiments difficult and tedious.

Heteronuclear multiple quantum correlation (HMQC) spectroscopy,^{5,6} originally developed for the measurement of ${}^1\text{H}$ - ${}^{13}\text{C}$ and ${}^1\text{H}$ - ${}^{15}\text{N}$ heteronuclear chemical shift correlations, has been used to correlate several pairs of non-proton nuclei.⁷ Of special significance to the work described here, Günther and co-workers⁸ applied ${}^6\text{Li}$ - ${}^{13}\text{C}$ HMQC spectroscopy to the solution structure determinations of some very complex dilithiated species. In this paper we describe ${}^6\text{Li}$ - ${}^{15}\text{N}$ HMQC experiments. The technique is presented in the context of LiTMP-LiX mixed aggregates (Scheme 1) characterized previously by ${}^6\text{Li}$ and ${}^{15}\text{N}$ one-dimensional NMR spectroscopic methods.

EXPERIMENTAL

Pure sequence

The pulse sequence shown below has been analyzed in detail elsewhere.^{6,9} We briefly highlight here some details relevant to its application to spin systems containing more than one *S* spin. The application of the HMQC sequence to IS_n spin systems ($n > 1$) has been discussed previously;¹⁰ see also Refs. 7 and 8a. The



Scheme 1

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analysis follows the product operator formalism.¹¹

I : $90-\Delta-$ $-t_1/2-180t_1/2-$ $-FID$

S : $-90-$ $-90-$

1H : $---$ broadband decouple $---$

Following the 90° I -spin preparation pulse in the above sequence, the evolution of I -spin magnetization of an IS_2 spin system under scalar I - S coupling during the preparation delay Δ is described by the equation

$$\begin{aligned}
 & -I_u \xrightarrow{\pi J_{I,S1} \Delta 2I_z S_{z,1} + \pi J_{I,S2} \Delta 2I_z S_{z,2}} \\
 & -I_y (\cos \pi J_{I,S1} \Delta) (\cos \pi J_{I,S2} \Delta) \\
 & + 2I_x S_{z,1} (\sin \pi J_{I,S1} \Delta) (\cos \pi J_{I,S2} \Delta) \\
 & + 2I_x S_{z,2} (\sin \pi J_{I,S2} \Delta) (\cos \pi J_{I,S1} \Delta) \\
 & + 4I_y S_{z,1} S_{z,2} (\sin \pi J_{I,S1} \Delta) (\sin \pi J_{I,S2} \Delta) \quad (1)
 \end{aligned}$$

where I_u and $S_{v,n}$ ($u, v = x, y, z$; $n = 1, 2$) are the one-spin Cartesian operators corresponding to the spins I , S_n , J_{ISn} are the heteronuclear coupling constants between I and the spin S_n and Δ is the length of the preparation delay. The first term on the right-hand side of Eqn. (1) has not developed scalar coupling to S spins and cannot lead to evolution of S -spin chemical shift in t_1 . The fourth term will evolve under the chemical shifts in both S spins upon application of a 90° S -spin pulse, giving results analogous to an S -spin double- or zero-quantum experiment. A ^{15}N zero-quantum experiment distinguishes lithium dialkylamide cyclic dimers from higher oligomers.¹² The second and third terms in Eqn. (1), however, evolve in analogy to I -spin doublets. After the evolution period and the S -spin 90° reconversion pulse, I -spin triplets will be labeled with the chemical shifts of the S spin to which they developed scalar coupling in the preparation period. The coefficients of $2I_x S_{z,1}$ and $2I_x S_{z,2}$ in Eqn. (1) will (for identical coupling constants) reach their maximum value at a time $\Delta = 1/4J(I, S)$, and disappear at $1/2J(I, S)$. Therefore, a preparation delay of *ca.* 50 ms was employed for samples displaying triplets with fairly uniform coupling constants of *ca.* 5 Hz.

The center lines of triplets correspond to non-selected order of coherence and are cancelled by the phase cycle. The $-1:0:1$ intensity pattern takes on the appearance of a widely spaced doublet in the two-dimensional spectrum.

Spectrometer hardware

The 6Li - ^{15}N HMQC spectra were recorded on a Bruker AC-300 spectrometer with an Aspect 3000 computer and process controller. Pulsing, phase shifting and detection at the frequency of 6Li (44.17 MHz) were carried out using the spectrometer's standard multinuclear facilities. The 2H lock coil of a modified 10 mm broadband probe head, tuned to a frequency of 6Li as described previously,⁴ served as the 6Li observed channel. Typical 90° 6Li pulse widths with this configuration are 150–170 μs . The broadband channel of the probe was used to deliver pulses to the indirectly detected ^{15}N spins. Pulses at the frequency of ^{15}N (30.42 MHz) were generated by a BSV-3 BX hetero-

nuclear decoupler with a PTS-160 frequency synthesizer. Typical ^{15}N 90° decoupler pulse widths were 70–75 μs .

6Li - ^{15}N HMQC spectra were acquired using non-spinning 10 mm samples without field-frequency locking. The magnetic field homogeneity was adjusted using 1H NMR spectra and free induction decays. The ^{15}N transmitter was placed in the center of the ^{15}N spectrum. The phase cycle provided with Bruker's Aspect-3000 software selects S -spin chemical shifts, gives quadrature detection in f_1 and rejects I -spin signals actively coupled to even numbers of S spins. We employed a straightforward modification of the Bruker cycle, permuting both 90° S -spin pulses through four phases. Spectra were processed in magnitude mode with squared sine bells weighting in f_1 and Lorentz-Gaussian resolution enhancement in f_2 .

RESULTS AND DISCUSSION

Structure assignments

The mixed aggregates in [6Li , ^{15}N]LiTMP-LiX mixtures (99% ^{15}N , 95.5% 6Li) have been characterized with the aid of single-frequency 6Li and ^{15}N decoupling.⁴ Details of the assignments will not be reiterated.² The labels on the 6Li and ^{15}N one-dimensional spectra depicted along the 6Li - ^{15}N HMQC axes correspond to the previously determined structures. Distinction between conformational isomers **3a-c** and **5a-c** was not made. To simplify the discussion, we shall arbitrarily refer to the observed species as **3a-c**.

LiTMP

Figure 1 shows the 6Li - ^{15}N HMQC spectrum of a 0.1 M solution of [6Li , ^{15}N]LiTMP in the THF-pentane (3:1) at $-115^\circ C$ acquired in 25 min. The upper trace is a 6Li spectrum displaying a triplet corresponding to LiTMP dimer **2** and a doublet corresponding to LiTMP monomer **1**.² As explained under Experimental, the center line of the 6Li triplet corresponding to dimer **2** does not show a cross-peak in the two-dimensional spectrum.

LiTMP-LiX mixed aggregates

The equilibria resulting from mixed aggregation of LiTMP with added LiX salts provides a more revealing test of the 6Li - ^{15}N HMQC experiment. Figures 2–4 depict 6Li - ^{15}N HMQC spectra recorded for [6Li , ^{15}N]LiTMP-LiBr, [6Li , ^{15}N]LiTMP-LiCl and [6Li , ^{15}N]LiTMP-lithium cyclohexenolate, respectively. The 6Li and ^{15}N traces along the axes correspond to spectra recorded using standard one-dimensional methods. Many of the 6Li - ^{15}N correlations are immediately apparent and require little comment. However, some of the strengths and weaknesses of the 6Li - ^{15}N HMQC

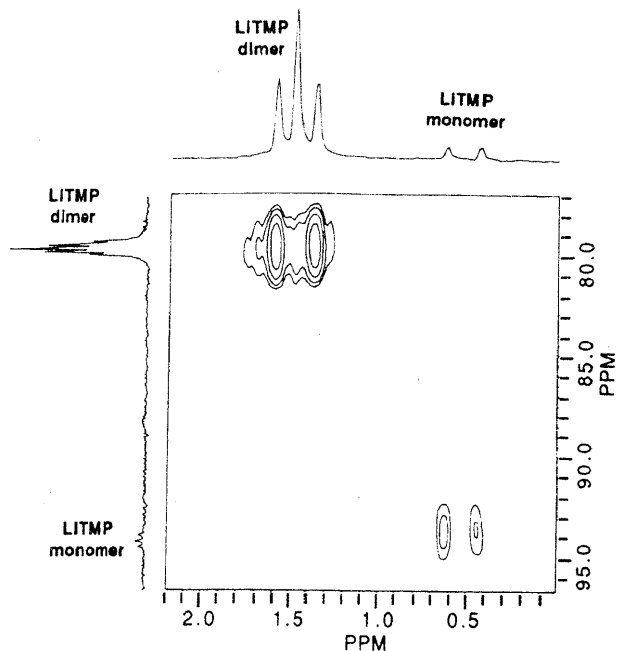


Figure 1. ^6Li - ^{15}N HMQC spectrum of 0.1 M $[\text{}^6\text{Li}, \text{}^{15}\text{N}]\text{LiTMP}$ in 3:1 THF-pentane at -115°C . The upper and left-hand traces are the one-dimensional ^6Li and ^{15}N $\{^1\text{H}\}$ NMR spectra, respectively, recorded under the same conditions. Sixteen t_1 increments were acquired with 32 transients per increment. Total time, 25 min.

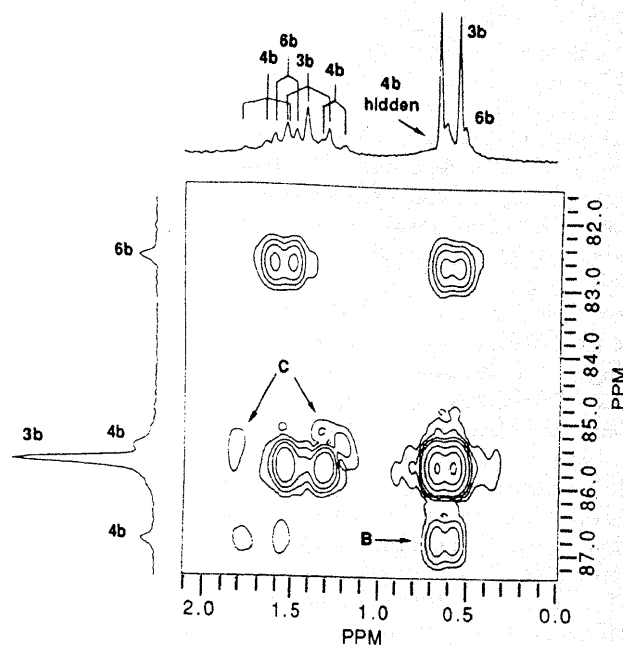


Figure 3. ^6Li - ^{15}N HMQC spectrum of a sample containing 0.1 M $[\text{}^6\text{Li}, \text{}^{15}\text{N}]\text{LiTMP}$ in 3:1 THF-pentane with 0.5 equivalent of $[\text{}^6\text{Li}]\text{LiCl}$ added at -105°C . The upper and left-hand traces are the one-dimensional ^6Li and ^{15}N $\{^1\text{H}\}$ NMR spectra, respectively. The ^{15}N spectrum is broadband ^6Li decoupled to show the upfield ^{15}N resonance of **4b** more clearly. Thirty t_1 increments were acquired with 256 transients per increment. Total experiment time, 5.75 h.

method over the corresponding one-dimensional methods warrant further comment.

Despite an excellent spectral dispersion in the one-dimensional ^{15}N spectrum recorded on the $[\text{}^6\text{Li}, \text{}^{15}\text{N}]$

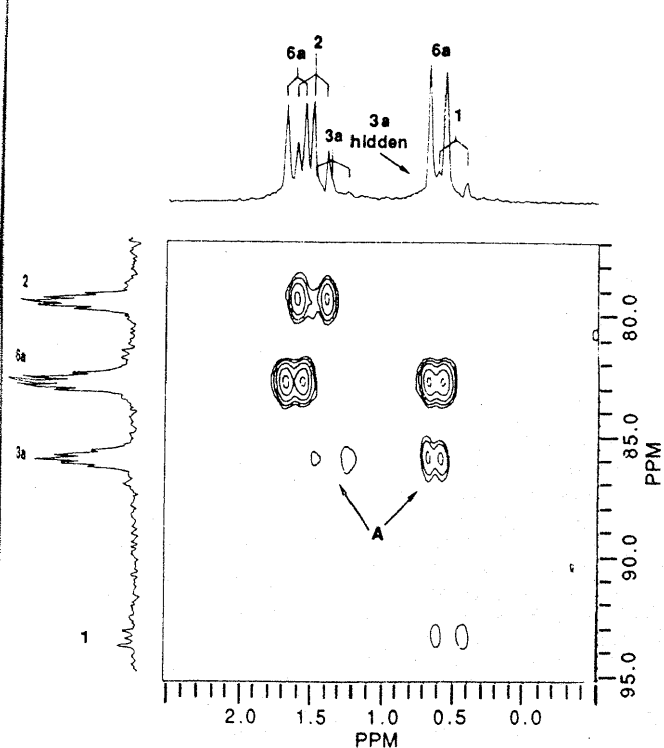


Figure 2. ^6Li - ^{15}N HMQC spectrum of a sample containing 0.1 M $[\text{}^6\text{Li}, \text{}^{15}\text{N}]\text{LiTMP}$ in 3:1 THF-pentane with equivalent of $[\text{}^6\text{Li}]\text{LiBr}$ added at -120°C . The upper and left-hand traces are the one-dimensional ^6Li and ^{15}N $\{^1\text{H}\}$ NMR spectra, respectively, recorded under the same conditions. Thirty-two t_1 increments were acquired with 64 transients per increment. Total time, 90 min.

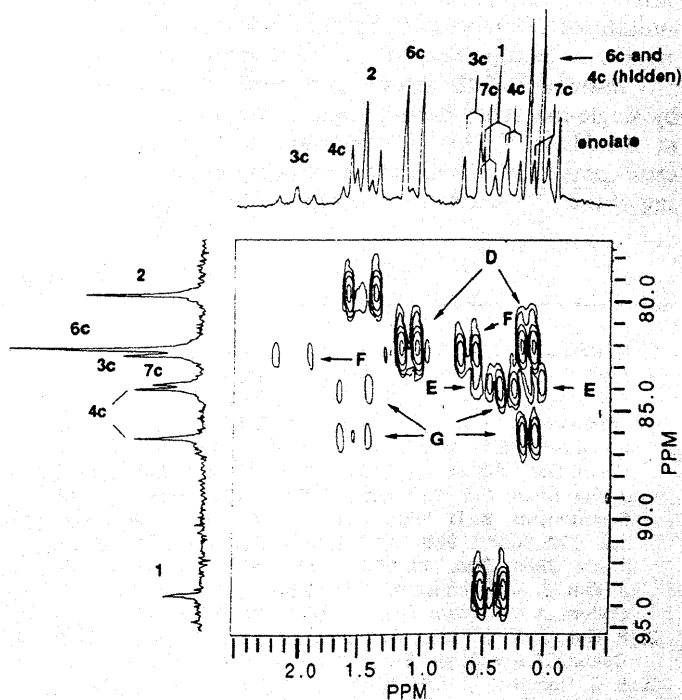


Figure 4. ^6Li - ^{15}N HMQC spectrum of a sample containing 0.2 M $[\text{}^6\text{Li}, \text{}^{15}\text{N}]\text{LiTMP}$ in 3:1 THF-pentane with 0.7 equivalent of $[\text{}^6\text{Li}]\text{lithium cyclohexenolate}$ added¹³ at -105°C . The upper and left-hand traces are the one-dimensional ^6Li and ^{15}N $\{^1\text{H}\}$ NMR spectra, respectively. The ^{15}N spectrum is broadband ^6Li decoupled. Thirty-two increments were acquired with 512 transients per increment. Total time, 12 h. The minor signal at 1.1 ppm in the ^6Li spectrum is unique to this sample.⁶

LiTMP–LiBr mixture (see the vertical projection of Fig. 2), the low sensitivity of the lock channel for observing ^6Li posed problems in the previously described single-frequency decoupling studies. Specially, the doublet of **3a** (labeled 'hidden' in Fig. 2) is completely obscured by the doublet of **6a** in the one-dimensional spectrum in the absence of single-frequency irradiations. Further, a long acquisition was required to determine unambiguously that the triplet corresponding to **3a** had collapsed on irradiation of the corresponding ^{15}N resonance. In the ^6Li – ^{15}N HMQC spectrum (Fig. 2), both ^6Li resonances of **3a** show clear correlations with a single ^{15}N resonance (arrows A). Moreover, the 90 min ^6Li – ^{15}N HMQC acquisition represents a substantial decrease in experiment time.

Figure 3 shows the ^6Li – ^{15}N HMQC spectrum of a 2:1 mixture of [^6Li , ^{15}N]LiTMP and [^6Li]LiCl. We have inserted a ^6Li broadband decoupled ^{15}N projection in Fig. 3 to illustrate more clearly the second ^{15}N resonance of **4b** partially obscured by the **3b** resonance. The increased structural complexity resulting from the existence of two discrete 2:1 mixed aggregates, **3b** and **4b**, and the narrow separation of their ^{15}N resonances posed a significant challenge using one-dimensional methods. In addition, the upfield ^6Li doublet of **4b** (labeled 'hidden' in Fig. 3) was never observed directly in the ^6Li NMR spectrum with or without the aid of single-frequency decouplings. Its existence was inferred from the collapse of the downfield ^{15}N resonance of **4b** on irradiation of the most upfield-shifted envelope of ^6Li resonances. The detection and correlation of the hidden ^6Li resonance of **4b** are very clear in Fig. 3 (arrow B). However, inspection of Fig. 3 also reveals limitations of processing the ^6Li – ^{15}N HMQC data in magnitude mode. The two correlations of the upfield ^{15}N resonance of **4b** (arrows C) were readily determined by single-frequency decoupling, but are poorly resolved in the ^6Li – ^{15}N HMQC spectrum. Distortions in the cross-peaks (arrows C) and previously noted broadening of the ^{15}N resonances are suggestive of rapid chemi-

cal exchange. The 6 h acquisition time again represents a substantial reduction in the time expended on the spectrometer.

The ^6Li – ^{15}N HMQC spectrum of a solution of [^6Li , ^{15}N]LiTMP with 0.70 equivalent of [^6Li]lithium cyclohexenolate¹³ is shown in Fig. 4. We again chose to display broadband ^6Li decoupled ^{15}N projections to show the ^{15}N resonances more clearly. Mixed aggregate **6c** appears as a pair of doublets in the ^6Li spectrum that correlate with a single ^{15}N multiplet (arrows D). Another pair of doublets correspond to the mixed aggregate assigned the ladder structure **7c**. These doublets both correlate with a single ^{15}N resonance (arrows E). Most notably, the correlations of **3c** and **4c** (arrows F and G, respectively) in the ^6Li – ^{15}N HMQC spectrum are substantially clearer than those obtained by the single-frequency irradiations.

CONCLUSIONS

The ^6Li – ^{15}N HMQC experiment has been shown to correlate ^6Li and ^{15}N resonances in some relatively complex mixtures of lithium amide mixed aggregates. The ^6Li – ^{15}N HMQC experiment typically requires substantially less spectrometer time and provides greater selectivity than the single-frequency decoupling method applied previously.

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REFERENCES

- N. Kallman and D. B. Collum, *J. Am. Chem. Soc.* **109**, 7466 (1987); L. M. Jackman, L. M. Scarmoutzos and W. Porter, *J. Am. Chem. Soc.* **109**, 6524 (1987); L. M. Jackman and L. M. Scarmoutzos, *J. Am. Chem. Soc.* **109**, 5348 (1987); A. S. Galiano-Roth, E. M. Michaelides and D. B. Collum, *J. Am. Chem. Soc.* **110**, 2658 (1988); J. S. Depue and D. B. Collum, *J. Am. Chem. Soc.* **110**, 5524 (1988); L. M. Jackman, L. M. Scarmoutzos, B. D. Smith and P. G. Willard, *J. Am. Chem. Soc.* **110**, 6058 (1988); A. S. Galiano-Roth and D. B. Collum, *J. Am. Chem. Soc.* **111**, 6772 (1989); A. S. Galiano-Roth, Y. J. Kim, J. H. Gilchrist, A. T. Harrison, D. J. Fuller and D. B. Collum, *J. Am. Chem. Soc.* **113**, 5053 (1991).
- P. Hall, J. H. Gilchrist, A. T. Harrison, D. J. Fuller and D. B. Collum, *J. Am. Chem. Soc.* **113**, 9575 (1991).
- F. E. Romesberg, J. H. Gilchrist, A. T. Harrison, D. J. Fuller and D. B. Collum, *J. Am. Chem. Soc.* **113**, 5751 (1991).
- J. H. Gilchrist, A. T. Harrison, D. J. Fuller and D. B. Collum, *J. Am. Chem. Soc.* **112**, 4069 (1990).
- G. Bodenhausen and D. J. Ruben, *Chem. Phys. Lett.* **69**, 185 (1980).
- A. Bax, R. H. Griffey and B. L. Hawkins, *J. Magn. Reson.* **55**, 301 (1983); M. R. Bendall, D. T. Pegg and D. M. Doddrell, *J. Magn. Reson.* **52**, 81 (1983); L. Müller, *J. Am. Chem. Soc.* **101**, 4481 (1979).
- (a) R. Benn and A. Ruffinska, *Magn. Reson. Chem.* **26**, 895 (1988); (b) R. Benn, H. Brenneke, A. Frings, H. Lehmkuhl, G. Mehler, A. Ruffinska and T. Wildt, *J. Am. Chem. Soc.* **110**, 5661 (1988); (c) W. M. Westler, B. J. Stockman, J. L. Markley, Y. Hosoya, Y. Miyake and M. Kainosho, *J. Am. Chem. Soc.* **110**, 6256 (1988); (d) W. P. Niemczura, G. L. Helms, A. S. Chesnick, R. E. Moore and V. Bornemann, *J. Magn. Reson.* **81**, 635, 1989 (1989); (e) L. D. Sims, L. R. Soltero and G. E. Martin, *Magn. Reson. Chem.* **27**, 599 (1989); (f) S. J. Berners-Price, P. J. Sadler and C. Brevard, *Magn. Reson. Chem.* **28**, 145 (1990); (g) M. Bourdonneau and C. Brevard, *Inorg. Chem.* **29**, 3272 (1990); (h) R. Benn and C. Brevard, *J. Am. Chem. Soc.* **108**, 5622 (1986).
- D. Moskau, F. Brauers, H. Günther and A. Maercker, *J. Am. Chem. Soc.* **109**, 5532 (1987); H.-J. Gais, J. Vollhardt, H. Günther, D. Moskau, H. J. Lindner and S. Braun, *J. Am. Chem. Soc.* **110**, 978 (1988); H. Günther, D. Moskau, P. Bast and D. Schmalz, *Angew. Chem., Int. Ed. Engl.* **26**, 1212 (1987).
- H. K. Kessler, M. Gehrke and C. Griesinger, *Angew. Chem., Int. Ed. Engl.* **27**, 490 (1988).
- D. Nanz and W. von Philipsborn, *J. Magn. Reson.* **92**, 560 (1991); for related examples, see M. H. Frey, G. Wagner, M. Vašák, O. W. Sørensen, D. Neuhaus, Wörgötter, J. H. R. Kägi,

- R. R. Ernst and K. Wüthrich, *J. Am. Chem. Soc.* **107**, 6847 (1985); J. D. Otvos, H. R. Engseth and S. R. Wehrli, *J. Magn. Reson.* **61**, 579 (1985); D. Live, I. M. Armitage, D. C. Dalgarno and D. Cowburn, *J. Am. Chem. Soc.* **107**, 1175 (1985).
11. O. W. Sørensen, G. W. Eich, M. H. Levitt, G. Bodenhausen and R. R. Ernst, *Prog. Nucl. Magn. Reson. Spectrosc.*, edited by J. W. Emsley, J. Feeney and L. H. Sutcliffe, Pergamon Press, Oxford, **16**, 163 (1983); K. J. Packer, Wright, *Mol. Phys.* **50**, 797 (1983); F. J. M. van de Ven and C. W. Hilbers, *J. Magn. Reson.* **54**, 512 (1983); P.-K. Wang and C. P. Silch-ter, *Bull. Magn. Reson.* **8**, 3 (1986).
 12. J. H. Gilchrist and D. B. Collum, *J. Am. Chem. Soc.* **114**, 794 (1992).
 13. Y.-J. Kim, M. P. Bernstein, A. S. Galiano-Roth, F. E. Romesberg, P. G. Williard, D. J. Fuller, A. T. Harrison and D. B. Collum, *J. Org. Chem.* **56**, 4435 (1991).