On the Recovery of $^{3}J_{H,H}$ and the Reduction of Molecular Symmetry by Simple NMR Inverse Detection Experiments

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Simple $^{1}H,^{13}C$ correlation spectra obtained by inverse detection techniques provide useful evidence of molecular symmetry. The emblematic case of *cis*- and *trans*-stilbenes together with that of a symmetric terthiophene are reported as examples. The effects of a reduction of symmetry on both direct and long-range correlations are reported.

Introduction

A distinction between *cis* and *trans* symmetrically disubstituted ethylenes, such as *cis*- and *trans*-stilbene, can be made through a plethora of physical methods and spectroscopic techniques,[1] among which ^{1}H and ^{13}C NMR spectroscopy are amongst the most commonly used. Here, the distinction can be based on empirical substituent and configurational effects on the chemical shifts of the ^{1}H and ^{13}C signals[1−3] or on the measurement of the $^{3}J_{C,H}$ coupling constant between carbon and the proton bonded to the double bond, owing to the relationship $^{3}J_{C,H(trans)} > {}^{3}J_{C,H(cis)}$.[1,3] Another NMR experimental parameter very sensitive to the double bond configuration and more readily accessible from an experimental point of view exists: the coupling constant $^{3}J_{H,H}$ between the two ethylenic protons. It is well established[1,3−5] that $^{3}J_{H,H}$ for a *trans*-disubstituted ethylene is always higher than that for the corresponding *cis*-disubstituted ethylene. Unfortunately, this precious information is lost in the ^{1}H NMR spectra of symmetrically disubstituted ethylenes, for which the two ethylene protons are isochronous as in A_2 systems.

In this report we point out that when a simple H,C inverse-detection spectrum is acquired without carbon decoupling during acquisition, $^{3}J_{H,H}$ is recovered and can be utilized to correctly assign the double bond configuration without any previous knowledge other than that $^{3}J_{H,H(trans)} > {}^{3}J_{H,H(cis)}$. The effects of symmetry on long range $^{1}H,^{13}C$ correlations are also discussed.

Results and Discussion

Figure 1 displays the partial spectra of *cis*- and *trans*-stilbene obtained through common 2D heteronuclear multiple quantum coherence (HMQC)[6] experiments with inverse detection. Similar results are obtained from other H,C correlation experiments in inverse detection, such as those based on heteronuclear single quantum coherence (HSQC).[7]

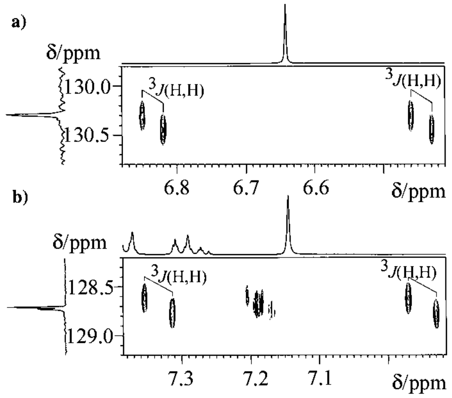

Figure 1. Comparison between partial HMQC spectra of: a) *cis*- and b) *trans*-stilbene, respectively; in b) the high-field half of the H_{ortho},C_{ortho} cross peak is also present

It is apparent that the H,C correlation involving the ethylenic hydrogen and carbon is modulated not only by the expected $^{1}J_{H,C}$ coupling in the f_2 dimension, but also by $^{3}J_{H,H}$, both in the f_1 and f_2 dimensions,[8] as in the A contribution to an AMX spectrum. The $^{3}J_{H,H}$ modulation remains only in the f_2 dimension in the HSQC spectrum, whereas it is lost if ^{13}C is decoupled during acquisition. Acquisition parameters corresponding to a digital resolution of about 0.5−1 Hz in the f_2 dimension enable the measurement of $^{3}J_{H,H}$ to be achieved with sufficient accuracy to be able to distinguish a *cis* isomer from a *trans* isomer: coupling constants of 12.0 and 16.5 Hz are obtained from

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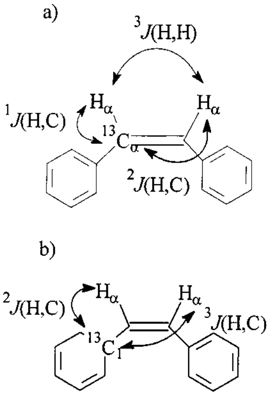
HMQC experiments for *cis*- and *trans*-stilbene, respectively.

Similar results are also obtained through classical C,H heterocorrelated experiments such as HETCOR,[9] although these experiments need an acquisition time about fifteen times that required by HMQC experiment to obtain a similar resolution in the ^1H dimension.

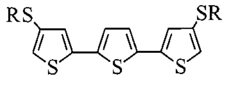
The presence of a homonuclear $^3J_{H,H}$ coupling constant between equivalent protons in the inverse-detected H,C correlation spectra can be explained by considering that the technique suppresses the large component due to signals coming from H bonded to ^{12}C, which represents 99% of the total in normal ^1H NMR spectra, through phase cycling, and the signal acquired is only due to protons bonded to ^{13}C. It is known that homonuclear coupling constants appear in the ^{13}C satellites of symmetrical molecules — such as symmetrically disubstituted ethylenes, di- or tetrasubstituted ethanes and benzenes[10,11] — that are characterized by a single resonance in their ^1H NMR spectra. This splitting derives from the loss of proton magnetic equivalence due to the presence of a magnetically active ^{13}C in place of an inactive ^{12}C (Scheme 1a), which gives rise to an ABX system. ^{13}C (X) decoupling induces magnetic equivalence of the two protons, explaining why no $^3J_{H,H}$ splitting is observed in the HMQC or HSQC spectra of symmetric molecules acquired under decoupling conditions. A number of modern texts on NMR and/or stereochemistry seem, with some exceptions,[1,12,13] to have forgotten this important structural information which was once known and accessible through long ^{13}C satellites studies, often involving enriched samples.



Scheme 1. Relevant *cis*-stilbene isotopomers and coupling patterns

Modern NMR instrumentation has made experiments on ^{13}C natural abundance samples readily accessible, and nowadays inverse-detected H,C correlation experiments allow us to rapidly observe this important structural information, i.e. to isolate, from a spectral point of view, the A (or B) part of these ABX systems, depending on the experiment employed. More generally, the appearance in HMQC, HSQC or Heteronuclear Multiple Bond Correlation (HMBC)[14] spectra of a homonuclear $^nJ_{H,H}$ coupling constant between chemically equivalent protons is direct proof of the existence of a symmetry element in the molecule relating the equivalent protons. Furthermore, these spectra enable the geometrical information implied in the numerical value of the coupling constant to be obtained. More sophisticated experiments can be employed[15] when a high accuracy in the determination of the $^3J_{H,H}$ coupling constant is required.

Terthiophene **1**[16] (Scheme 2) is another example showing the generality of this approach. The HMQC spectrum of **1** (Figure 2) displays an $^3J_{H,H}$ coupling of 4.0 Hz which is absent in the ^1H NMR spectrum (top trace), indicating,[4] together with a $^1J_{H,C}$ coupling of 167 Hz, typical of a thiophene β-CH fragment,[5] the presence in the structure of a thiophene ring symmetrically disubstituted in the 2- and 5-positions.



1 R = n–C_8H_{17}

Scheme 2. 4,4′′-Bis(octylsulfanyl)-2,2′:5′,2′′-terthiophene (**1**)

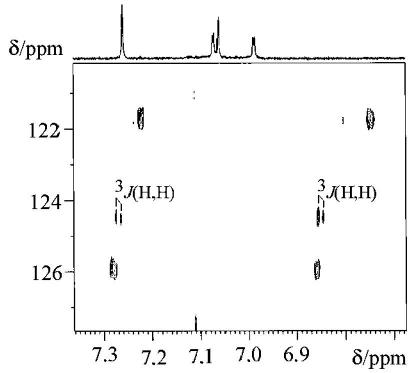


Figure 2. HMQC spectrum of terthiophene **1**; the correlation between the singlet at δ = 7.07 and the carbon at δ = 124.5 (^{13}C NMR spectrum was not directly acquired) shows the modulation due to the $^1J_{H,C}$ coupling in $f2$ and that deriving from $^3J_{H,H}$ coupling with the symmetrical proton in $f2$ and $f1$

Finally, as anticipated above, useful signs of molecular symmetry can be found in HMBC spectra. In this case the long-range correlations are involved rather than the direct correlations. The HMBC spectrum of *cis*-stilbene (Figure 3) shows the presence of modulations due to $^3J_{H,H}$ in the f_1 and f_2 dimensions in the cross peak between H_α and C_α (δ = 130.3), and a modulation of 2.5 Hz due to $^2J(H_\alpha,C_\alpha)$ in the f_2 dimension. A double $^nJ_{H,C}$ modulation only in f_2 dimension is also evidenced in the cross peak between H_α and C_1 (δ = 137.3).

Both these effects are ascribable to the lowering of molecule symmetry due to the presence of a magnetically active ^{13}C center in place of the inactive ^{12}C isotope (Scheme 1b). In particular, as far as the H_α,C_1 cross peak is concerned, we observe that the presence of a magnetically active ^{13}C not directly bonded to H_α does not produce modulations due to $^3J_{H,H}$ (distinguishable by the typical slanting appearance of the cross peak in multiple quantum spectra), but instead provides a more subtle symptom of symmetry, i.e.

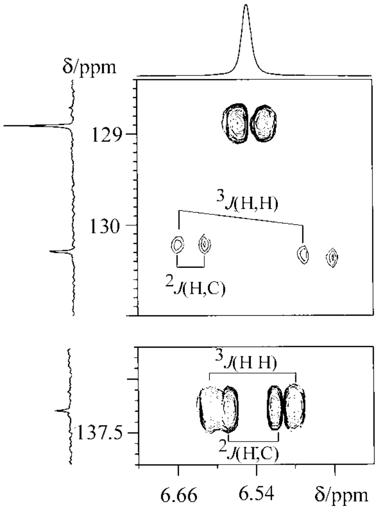


Figure 3. Partial HMBC spectrum of *cis*-stilbene; correlations between H_α and C_{ortho} at δ = 128.9, C_α at δ = 130.3 and C_1 at δ = 137.3 are shown

two overlapping H,C correlations centered at the ethylenic proton chemical shift (one doublet is formed by the two inner peaks and the other by the two outer peaks). These are due to the double coupling path between H_α and C_1, over two and three bonds, with coupling constants of 4.5 and 8.0 Hz, respectively. This double coupling path can be found in other symmetrical molecules such as oligothiophenes formed by an even number of thiophene rings, for which an excess of multiplicity is found in the H,C long-range correlations between the thiophene proton and the quaternary carbon closest to the symmetry element.[17]

Conclusion

The appearance of homonuclear $^3J_{H,H}$ couplings in H,C inverse-detection spectra between protons that are isochronous in the 1D ^1H NMR spectrum represents a rapid and valuable tool for the structural elucidation of symmetrical organic molecules not only for NMR spectroscopists but also for the majority of organic chemists who nowadays have more and more opportunities to use modern spectrometers.

Experimental Section

General Remarks: Commercially available stilbenes were used. NMR spectra were recorded on a Bruker AMX 400 spectrometer, equipped with an inverse probe, operating at 400.13 and 100.61 MHz for ^1H and ^{13}C, respectively. The proton chemical shifts in $CDCl_3$ solutions are referred to the residue signal of $CHCl_3$ at δ = 7.26, and the carbon chemical shifts are referred to the ^{13}C signal of $CDCl_3$ at δ = 77.0. HMQC and HSQC parameters for *cis*-stilbene spectra (0.4 M solutions) are: spectral width($f2$) 1.4 ppm; 1k points; spectral width ($f1$) 20 ppm; 64 t_1 increments with 8 scans per t_1 value; relaxation and evolution delays = 0.5 s and 3.125 ms or 1.562 ms, respectively; zero filling and linear prediction in $f1$, squared sine function in $f1$ and $f2$ were applied before Fourier transformation. HMBC parameters are the same as HMQC except: 70 ms evolution delay and squared cosine function in $f1$ applied before Fourier transformation. Similar acquisition parameters were used for HMQC spectrum of 1 ($2 \cdot 10^{-3}$ M) except for the number of scans which was 64 per t_1 value and for the 2.78 ms evolution time.

Acknowledgments

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