A New NMR Approach for the Assignment of Symmetric Isomers

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Abstract: Irradiation of the ^{13}C satellite (1% natural abundance) of the NMR ^1H signals yields NOE effects on the spatially close hydrogens of the same isotopomer but not on the hydrogens of the 99% isotopomer having only ^{12}C atoms. In a DPFGSE-NOE sequence, the latter signals are completely canceled, and it is possible, therefore, to detect NOE effects experienced by isochronous lines that would not be otherwise observable. This allows the structural assignments of symmetric isomers to be unambiguously obtained. Examples are reported for the cases of the cis and trans dimethylstilbene, cis and trans stilbeneoxide, 2,5- and 3,4-dimethylthiophene, 1,8- and 1,5-dimethylnaphthalene, syn and anti 1,2-bis(2-methyl-1-naphthyl)-benzene, 1,3-cyclooctadiene, and cycloheptatriene.

It is well known that the structures of cis and trans ethylenic derivatives (RCH=CHR′) can be distinguished by NMR spectroscopy on the basis of a $^3J_{HH}$ coupling constant, which is larger in the trans than in the cis configuration.[1,2] In the case of symmetric derivatives (i.e., when R = R′), this coupling is invisible in the normal spectrum but can be detected by examining the ^{13}C satellites.[3] In derivatives bearing three or four substituents, there is not such a $^3J_{HH}$ coupling, but NOE experiments can be used for reliable assignments,[4] except in ethylenes bearing two pairs of equal substituents (i.e., RR′C=CR′R). We propose here a method to achieve, even in these cases, an unambiguous assignment by applying the NOE experiment to ^{13}C satellites.

Let us consider, for instance, the cis and trans isomers of dimethylstilbene (**1** and **2**, respectively). Contrary to the case of the unsubstituted stilbene, where the ^{13}C satellites provide the $^3J_{HH}$ couplings to be used for the identification, this coupling is not available in **1** and **2**. Furthermore, the NOE experiment cannot be applied for the assignment because in both isomers the methyl groups are homotopic and thus yield isochronous methyl signals. If, however, we take into consideration the ^{13}C isotope in natural abundance, we have a 1% proportion of the isotopomers **1a** and **2a**, as illustrated in Chart 1.

The ^1H NMR methyl signals of **1a** and **2a** comprise a doublet,[5] due to the $^{13}CH_3$ group ($^1J_{CH} = 126.5$ Hz), and a

Chart 1
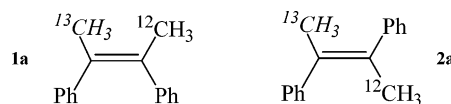
singlet,[5] due to the $^{12}CH_3$ group. The latter signal, however, is not observable because it is overlapped by the intense singlet (99%) of the isotopomer having two $^{12}CH_3$ groups (**1b**, cis and **2b**, trans). When the two $^{13}CH_3$ satellite signals are simultaneously saturated by a selective pulse, a NOE effect will be experienced by the $^{12}CH_3$ signal of **1a** but not for that of **2a** because the average distance between the methyl hydrogens of the trans is too large (4.90 Å)[6a] as compared to that of the cis isomer (3.61 Å).[6b] Likewise, the NOE effect will not be experienced by the isotopomers **1b** and **2b** because, with two $^{12}CH_3$ groups, there is not any $^{13}CH_3$ signal to be irradiated. In a double pulsed field gradient spin−echo NOE (DPFGSE-NOE) sequence,[7] the signals not experiencing a NOE effect are eliminated, so this approach would provide a clear-cut distinction between **1a**, which will show a NOE effect, and **2a**, where this effect is not present. The result of this experiment is shown in Figure 1. On the top is reported the ^1H methyl signal of the cis (left) and trans (right) isomers **1b** and **2b** taken at 600 MHz in CDCl₃: in the wings are also displayed the satellite signals of **1a** and **2a** in a 100-fold intensified scale. Underneath are shown the NOE spectra obtained by saturation of the ^{13}C satellite signals: as predicted, a positive NOE effect is clearly observed

(1) Abraham, R. J.; Fisher, J.; Loftus, P. *Introduction to NMR Spectroscopy*, 2nd ed.; Wiley: Chichester, 1988; p 41.
(2) Lambert, J. B.; Shurvell, H. F.; Lightner, D. A.; Cooks, R. C. *Organic Structural Spectroscopy*; Prentice Hall: Upper Saddle River, NJ, 1998; Chapter 4, p 74.
(3) (a) Jackman, L. M.; Sternhell, S. *Application of NMR Spectroscopy to Organic Chemistry*, 2nd ed.; Pergamon: Oxford, 1969; p 140. (b) Goldstein, J. H.; Watts, V. S.; Rattet, L. S. *Prog. Nucl. Magn. Reson. Spectrosc.* **1971**, *8*, 103−162.
(4) Claridge, T. D. W. *High-Resolution NMR Techniques in Organic Chemistry*; Pergamon, Elsevier Science: Oxford, 1999; p 297.
(5) These satellites actually appear as a pair of 1:3:3:1 quartets, due to the long-range coupling with the hydrogens of the $^{12}CH_3$ group ($^5J_{HH} = 0.9$ and 1.3 Hz for **1a** and **2a**, respectively).

(6) (a) Valle, G.; Busetti, G.; Galiazzo, G. *Acta Crystallogr., Sect. C* **1981**, *10*, 867−870. (b) Fronczek, F. R.; Swan, A. M.; Corkern, J. A.; Gandour, R. D. *Acta Crystallogr., Sect. C* **1984**, *40*, 1875−1876.
(7) (a) Stonehouse, J.; Adell, P.; Keeler, J.; Shaka, A. J. *J. Am. Chem. Soc.* **1994**, *116*, 6037−6038. (b) Stott, K.; Stonehouse, J.; Keeler, J.; Hwang, T. L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199−4200. (c) Stott, K.; Keeler, J.; Van, Q. N.; Shaka, A. J. *J. Magn. Reson.* **1997**, *125*, 302−324. (d) Van, Q. N.; Smith, E. M.; Shaka, A. J. *J. Magn. Reson.* **1999**, *141*, 191−194.
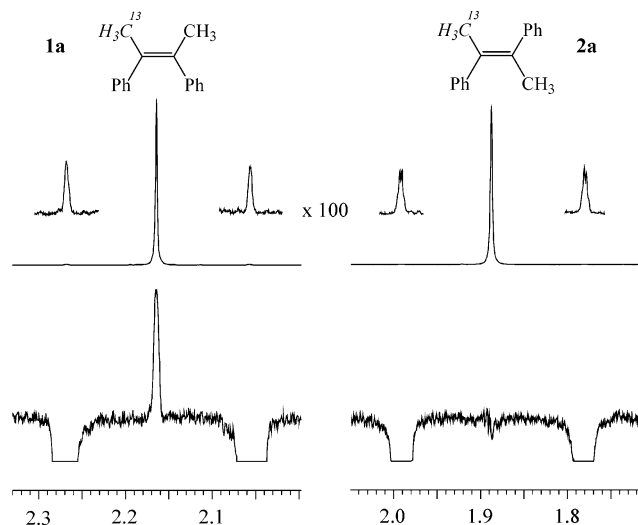
Figure 1. NOE experiments (600 MHz in CDCl$_3$) carried out by selective irradiation of the ^{13}C satellites of the methyl groups in the cis (left) and trans (right) isomers of dimethyl stilbene (see text).

for the cis isomer **1a** (left), but a null effect is observed for the trans isomer **2a** (right).

Also, the reverse experiment (i.e., irradiation of the ^{12}CH$_3$ signal and observation of positive or null NOE effect on the ^{13}C satellites) can, in principle, be carried out. However, the result is less favorable in that irradiation of the ^{12}CH$_3$ signal implies also irradiation of the large signal of the isotopomer with two ^{12}CH$_3$ groups (99%). This leads to an extremely intense negative signal, so that the small ^{13}C satellites experiencing the positive NOE appear somewhat distorted because they lie on the wings of such a large signal (an example is reported in the Supporting Information for the case of **1a**): although the distinction between a positive and a null NOE can still be observed, the effect is less evident.

Obviously this approach can also be applied when a $^3J_{HH}$ coupling is available and the method can be of some usefulness if the difference between the J values of the cis and trans isomers is small and might consequently make the assignment not completely certain. For instance, the isomers of stilbene oxide have $^3J_{HH}$ values equal to 4.3 Hz (isomer cis, **3**) and 1.7 Hz (isomer trans, **4**), as measured from the corresponding ^{13}C satellite spectra. Due to the proximity of the methine hydrogens, both isotopomers **3a** and **4a** (Figure 2) should display positive NOE effects in our experiment, but that observable in **3a** should be much greater than that of **4a** because the interproton distance in the cis (2.49 Å) is smaller than that in the trans isomer (3.23 Å). The NOE experienced by the ^{12}CH signal of **3a**, on irradiation of the ^{13}C satellites, was actually found to be 6.3 times larger[8] than that experienced by the ^{12}CH signal of **4a** (Figure 2): when this ratio is elevated to the $-^1/_6$ power,[9] the result (0.74) is in satisfactory agreement with the ratio of the cis/trans interproton distances (0.77). In this case, the assignment can be easily made on the basis of a large and of a small NOE effect, as in the usual case of asymmetric derivatives.

(8) The 6.3:1 ratio was estimated by comparing the integrated positive NOE signals of **3a** and **4a**. To guarantee as much as possible equal conditions for the two experiments, a unique sample, containing equimolecular amounts of the two compounds, was used, and identical parameters were employed in the DPFGSE-NOE sequence.

(9) Neuhaus, D.; Williamson, M. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH: New York, 1989.
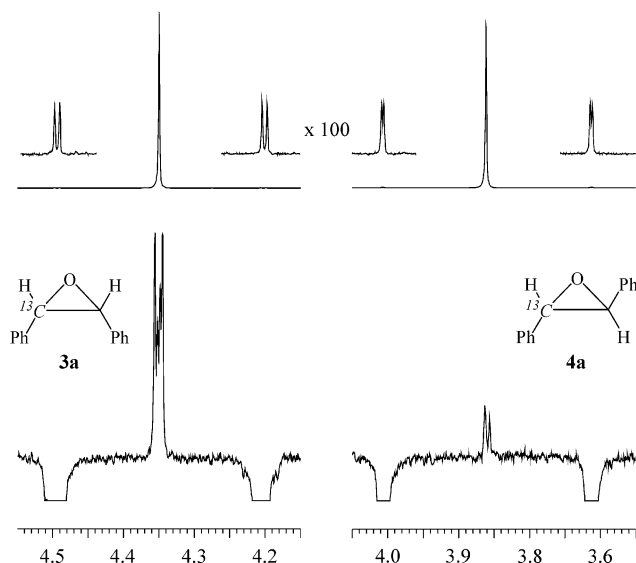
Figure 2. NOE experiments (600 MHz in CDCl$_3$) carried out by irradiation of the ^{13}C satellites of the methine hydrogens in the cis (left) and trans (right) isomers of stilbene oxide (see text).

It should be noticed that the NOE signal of **3a** (Figure 2, bottom left) displays four lines (a doublet of doublets) because, in addition to the mentioned $^3J_{HH}$ of 4.3 Hz, there is also a J^2 of 2.3 Hz, due to the coupling of this hydrogen with the ^{13}C separated by two bonds (^{13}C$-^{12}$C$-$H).[10]

The approach presented here is not confined solely to the case of cis and trans isomers and can be applied to all of the symmetric isomers having carbon bonded hydrogens with different interproton distances. For instance, it can be used to identify the 2,5-dimethylthiophene, **5**, from the isomeric 3,4-dimethylthiophene, **6** (see Supporting Information). In the isomer **5**, a positive NOE is observed when irradiating the ^{13}C satellites of the CH hydrogens in positions 3,4 because they are close to each other, whereas there is not any NOE effect when irradiating the CH$_3$ hydrogens that are farther apart. The opposite occurs in **6** where NOE is detected on irradiation of the CH$_3$ but not of the CH satellites (see Supporting Information).[11] Likewise, a positive NOE is detected for the ^{12}CH$_3$ methyl signal of 1,8-dimethylnaphthalene, **7**, on irradiation of the ^{13}C methyl satellites, while NOE is not observed in the case of the isomeric 1,5-dimethylnaphthalene, **8** (see Supporting Information).

Another interesting application of this approach concerns the structural assignment of the two atropisomers arising from the parallel and antiparallel disposition of two naphthyl substituents bonded to a benzene ring in an ortho relationship (Chart 2).

(10) We verified that this coupling is equal to that derived from the undecoupled ^{13}C spectrum of **3** (and of **4** as well). It should also be pointed out that the four lines of the NOE spectrum of **3a** (Figure 2, bottom left) are not first order and, in addition, are affected by the sequence employed, so that the height of the two inner lines is significantly lower than that of the outer lines. This explains why the NOE spectrum of **4a** (Figure 2, bottom right) displays two lines separated by 4.0 Hz, corresponding to the sum of $^3J_{HH}$ (1.7 Hz) and $^2J_{CH}$ (2.3 Hz). In this case, the two smaller inner lines are not resolved, due to the relatively broad width (1.8 Hz) of the intense outer lines, so that only the latter are clearly visible.

(11) It should be pointed out that, depending on the choice of the mixing time, a weak residual signal might occasionally be detected, even when a null NOE effect is expected to occur. Such a signal, however, has the typical anti-phase dispersive component due to the zero-quantum coherence contribution, a well-known feature of some NOESY spectra. Fortunately, this peculiar shape makes this signal clearly distinguishable from the pure absorption signal of a real NOE effect, see: Schulte-Herbrüggen, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 5270−5272 and references quoted therein. An example of this type is illustrated in the NOE spectrum of compound **6** (see Supporting Information).

Chart 2
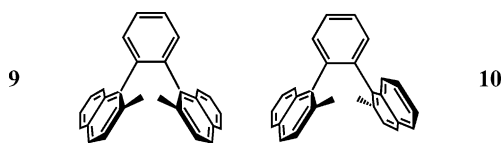
The 1,2-bis(2-methyl-1-naphthyl)benzene of Chart 2 exists, in fact, as two stable syn and anti isomers.[12] As shown in the Supporting Information, isomer **9** (mp 180 °C) yields a substantial NOE effect on irradiation of the satellites of the ^{1}H methyl signal, whereas isomer **10** (mp 163 °C) does not. Thus, the syn structure must be assigned to **9** and the anti structure to **10** because the average distance between the methyl hydrogens is relatively small in the former and quite large in the latter (3.15 and 5.31 Å, respectively).

Finally, the method has been successfully tested also on derivatives possessing multiple double bonds such as 1,3-cyclooctadiene (**11**) and cyclohepta-1,3,5-triene (**12**): on irradiation of the appropriate satellites, both compounds showed substantial NOE enhancement of the signals due to the pair of equivalent (homotopic) CH hydrogens (the NOE spectrum of **12** is reported in the Supporting Information).

Experimental Section

A mixture of the two isomers of dimethyl stilbene, cis and trans stilbene oxide, 1,5-dimethylnaphthalene, 1,8-dimethylnaphthalene, and 2,5-dimethylthiophene were commercially available and were used without further purification. 1,3-Cyclooctadiene and cyclohepta-1,3,5-triene were commercially available and were redistilled before use. 3,4-Dimethylthiophene[13] and the two atropisomers of 1,2-bis(2-methyl-1-naphthyl)benzene[12] were prepared according to the literature. A typical sample was prepared dissolving the compound (15−25 mg) in 0.7 mL of CDCl$_3$ or DMSO-d_6. The sample was degassed by bubbling argon directly into the solution in the NMR tube for about 30 min and was sealed to avoid contamination from air.[14] NMR spectra were obtained on an indirect triple resonance probe at 600 MHz (Varian INOVA, equipped with a waveform generator), using the standard DPFGSE-NOE sequence proposed by Shaka et al.[7] Double frequency selective

saturation of the ^{13}C satellites was obtained with a phase shifted laminar pulse, following the method proposed by Patt.[15] The spectra were obtained with the transmitter offset on one of the two ^{13}C satellites (usually the low-frequency one), and, by using a standard software (Pbox), a two-band 10 Hz selective pulse was calculated, with a refocusing-SNOB shape and a pulse width of 185 ms. We have chosen the SNOB family shape because it is the one which gives the maximum excitation profile as well as the lowest pulse width.[16] Even though a shorter 20 Hz pulse of 94.5 ms can be used when the $^1J_{CH}$ is larger than 150 Hz, the choice of the 10 Hz pulse guarantees that the central signal is not saturated at all. To minimize interferences and distortions arising from J-couplings, a mixing time similar to T_1 should be used (between 2 and 3 s for **1**−**10**), with an acquisition time of 3 s, and a recycling delay of 2 s. In the case of **11** and **12**, very long mixing times (6 and 11 s, respectively) and a recycling delay (10 s) had to be used. Typically, 512−2048 scans were acquired, resulting in a total acquisition time of 1−5 h, depending on the mixing time used.

Note Added after ASAP Publication: References were inadvertently omitted in the version published on the Web August 20, 2004. The following should be added: This is a more straightforward approach than other related procedures published previously. See: (a) Kawabata, J.; Fukushi, E.; Mizutani, J. *J. Am. Chem. Soc.* **1992**, *114*, 1115−1117. (b) Hoffman, R. E.; Shenhar, R.; Willner, I.; Bronstein, H. E.; Scott, L. T.; Rajca, A.; Rabinovitz, M. *Magn. Reson. Chem.* **2000**, *38*, 311−314. (c) Berger, S.; Wagner, R. *Magn. Reson. Chem.* **1997**, *35*, 199−202. The version published August 27, 2004, and the print version are correct.

Supporting Information Available: Alternative NOE spectrum of compound **1** and NOE spectra of compounds **5**−**10** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA047887+

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(13) Consiglio, G.; Arnone, A.; Spinelli, D.; Noto, R.; Frenna, V.; Fisichella, S. *J. Chem. Soc., Perkin Trans. 2* **1985**, 519−522. (In our synthesis, MeI rather than dimethyl sulfate was employed.)

(14) Sealing the tube is not necessary if the sample is degassed immediately before acquisition.

(15) Patt, S. L. *J. Magn. Reson*. **1992**, *96*, 94−102.

(16) Kupče, E.; Boyd, J.; Campbell, I. D. *J. Magn. Reson., Ser. B* **1995**, *106*, 300−303.