LONG-RANGE 2D INADEQUATE IN STRUCTURE DETERMINATION

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It is demonstrated that the 2D INADEQUATE experiment utilizing long-range $^{13}C-^{13}C$ spin–spin couplings is feasible and that it can solve structural or assignment problems when one-bond connectivities do not provide sufficient clue for structure determination. In such cases, the long-range 2D INADEQUATE can be used instead of the standard 2D INADEQUATE since it also yields the one-bond connectivities in addition to the connectivities over more bonds. The two types of connectivities are easily distinguished according to satellite separations. Because of similar magnitudes of various long-range $^{13}C-^{13}C$ couplings, the method of "*J*-resolved INADEQUATE" suggested earlier for such purpose is unlikely to provide unambiguous results. The proposed method is utilized for complete assignment of ^{13}C and ^{1}H NMR spectra of dicyclohexylphenylphosphine.

Among the many NMR methods now available for the structure determination of organic compounds INADEQUATE experiments[1 – 5] are certainly most powerful. However, they are plagued by low sensitivity which calls for a large amount of the sample or for an excessive measuring time. Though several approaches to enhance the sensitivity of these experiments (for example by polarization transfer[6 – 8]) have been successfully tried, the experiments are used only in the important cases when the extensive use of the spectrometer time is justified or when the problem at hand cannot be solved by some other method.

An example of the latter kind is provided by the cyclohexyl part of NMR spectra of dicyclohexylphenylphosphine. As it is apparent from Fig. 1, the ^{1}H NMR spectrum of this compound is not sufficiently resolved at 500 MHz to permit its assignment and analysis. Moreover, the spectrum looks to a certain degree suspicious as high frequency part ($\delta = 1.4 - 1.9$) is less resolved than the low frequency part. The ^{13}C NMR spectrum (Fig. 2) is well resolved into six doublets (due to $^{31}P-^{13}C$ coupling) labelled from left *A*, *B*, *C*, *D*, *E*, and *F* (the lowest frequency doublet *F* appears as a singlet under the conditions employed). Because of the complexity of the ^{1}H NMR spectrum mentioned above, the usual heteronuclear $^{1}H-^{13}C$ experiments are of no help for assigning these doublets to the twelve cyclohexyl carbon nuclei in the molecule. Only the APT experiment[9] unambiguously confirmed that the doublet *A* belongs both to C-1 and C-1′ carbons. The results of the standard 2D INADEQUATE (utilizing one-bond ^{13}C–^{13}C coupling) experiment are compatible with two assignments:

assignment	doublet					
	A	*B*	*C*	*D*	*E*	*F*
I	C-1	C-2 & C-6		C-3 & C-5C		C-6
	C-1′		C-2′ & C-6′		C-3′ & C-5′	C-6′
II	C-1	C-2	C-6	C-3	C-5	C-6
	C-1′	C-2′	C-6′	C-3′	C-5′	C-6′

In the assignment *I* the two cyclohexyl rings are not equivalent but equivalent are the carbon atoms symmetrically disposed around the planes of symmetry of each cyclohexyl ring. In the assignment *II* the situation is reversed, the rings are equivalent but the carbon atoms are not.

According to the assignment *I* there should be no long-range coupling between carbons giving rise to the doublets *B* and *C* as they belong to different cyclohexyl rings but if the assignment *II* is correct, carbons C-2 and C-6 as well as carbons C-2′ and C-6′

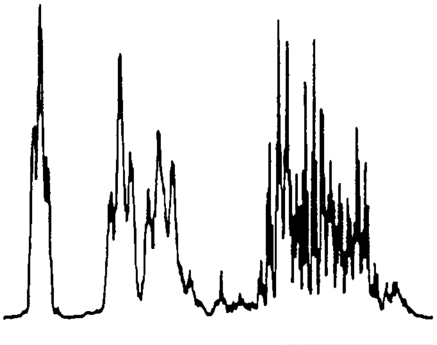

FIG. 1
^{1}H NMR spectrum of dicyclohexylphenylphosphine. Cyclohexyl proton part only, external referencing, spectral width 5 kHz, acquisition time 4.0 s, no data weighting, zero filling to 64 Kb, 4 scans with relaxation delay 5.0 s

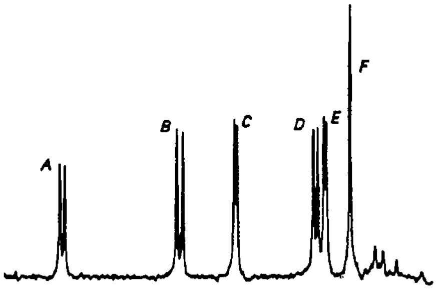

FIG. 2
^{13}C NMR spectrum of dicyclohexylphenylphosphine. Cyclohexyl carbon part only, referenced to the line of solvent $\delta(C_6D_6)$ = 128.00. Doublets due to ^{31}P–^{13}C coupling labelled arbitrarily from left to right *A* through *F*. Spectral width 1 200 Hz, acquisition time 1.0 s, exponential data weighting with *lb* = 3.7, zero filling 4 Kb, 4 scans with relaxation delay 2.0 s

are coupled through a geminal $^{2}J(^{13}C-^{13}C)$ coupling. The two assignments can be differentiated by a 2D INADEQUATE experiment utilizing double quantum coherence between geminal ^{13}C carbon nuclei. Such long-range 2D INADEQUATE experiments have much wider applicability and for that reason some details of the experiment are discussed in this paper.

EXPERIMENTAL

The sample, dicyclohexylphenylphosphine, was prepared as described previously[10], its 30% solution in hexadeuteriobenzene was sealed under argon atmosphere in a 5 mm NMR tube (Royal Imperial type from Wilmad, N. J.). All the NMR experiments described here were performed on a Varian UNITY 500 spectrometer operating at 499.843 MHz and 125.697 MHz for ^{1}H and ^{13}C NMR measurements, respectively. All the measurements of ^{13}C NMR spectra used 5 mm broad band probe with the transmitter power set so that the 90° pulse width was 10.3 μs, temperature was held at 30 °C, and the sample was spinning. The spectrometer was equipped with Sun 3/50 computer which run the standard software (VNMR version 2.2).

Preliminary measurements of spin-lattice relaxation times T_1 of cyclohexyl carbons by the standard inversion recovery method provided the following values of T_1 for the doublets shown in Fig. 2: *A* 0.38, *B* 0.21, *C* 0.20, *D* 0.21, *E* 0.21, and *F* 0.18 s.

All the pulse sequences used for 2D measurement were derived from the standard INADEQUATE pulse sequence provided by the manufacturer. The pulse sequence was programmed according to the original description of the experiment[3] but the phase cycling employed 45° phase shifts and allowed hypercomplex data handling[11] for pure absorption phase presentation. Long-range 2D INADEQUATE used the delay for the creation of the double-quantum coherence corresponding to $J = 2.1$ Hz. The pulse sequence for "*J*-resolved INADEQUATE" replaced the fixed time delay for the double-quantum formation by the variable time t_1 and held constant, 10 μs, the delay between the last two pulses.

RESULTS AND DISCUSSION

Both 1D and 2D INADEQUATE experiments[1,3] require prior knowledge of an approximate value of $^{13}C-^{13}C$ coupling constant. Using this *J* value, the delays τ for creation of double quantum coherence in the pulse sequence are set to

$$\tau = (2n + 1) / (4J)$$

(though any number *n* can be used for optimum coherence transfer, the longer delay means higher loss of the signal by relaxation).

Thus by selecting the *J* value corresponding to the one-bond $^{13}C-^{13}C$ coupling constant these constants can be measured through 1D INADEQUATE experiments or one-bond connectivities can be determined through the 2D version of the experiment. Bax et al.[1] have shown that for 1D experiments the value of *n* can be chosen in such a way that the delay allows simultaneous measurement of ^{13}C satellites due to both one-bond and long-range couplings. Whether the *J* doublet of satellites appears in the "up-down" or "down-up" antiphase configuration depends upon whether *n* is even or odd.

When no prior knowledge of the value of $^{13}C-^{13}C$ coupling is available, the coupling constants can be determined by another closely related method proposed also by Bax et al.[2]. The method, which has not gained much popularity, replaces the fixed delay 2τ of 1D INADEQUATE by the variable evolution period t_1 and produces two-dimensional spectra where F_2 dimension carries the conventional ^{13}C spectral information with the strong central line suppressed and F_1 carries resonances at the frequencies of $\pm J/2$. We shall refer to this method as "J-resolved INADEQUATE", despite that full separation of coupling and shift information is not achieved[12] by this method. Results of "J-resolved INADEQUATE" applied to the dicyclohexylphenylphosphine are exemplified on Figs 3 and 4. From the overall picture (Fig. 3), two ranges of coupling constants are obvious, one-bond $^{13}C-^{13}C$ couplings around 32 Hz and long-range $^{13}C-^{13}C$ couplings around 2 Hz. More accurate values of the constants can be read from the appropriate traces of the 2D spectrum that was weighted along F_1 axis for resolution enhancement as shown on the right side of Fig. 4 for the doublet *A*. Obviously, the resolution is not sufficient to distinguish the two ^2J coupling constants one from the other or from the ^3J or ^4J couplings. (Similar results were obtained for all the other doublets.) The average value of long-range $^{13}C-^{13}C$ coupling constants was 2.1 Hz. Using this value the long-range 2D INADEQUATE experiment was set.

The results of the long-range 2D INADEQUATE experiment are shown on Fig. 5, where the ellipses mark the long-range correlations decisive for the assignment problem. Assuming no long-range coupling between carbons of different cyclohexyl rings, the cross-peaks in the ellipses prove that the doublets *B* and *C* as well as *D* and *E* belong to the carbon atoms which are the parts of the same cyclohexyl ring. Thus, the assignment *I* is ruled out.

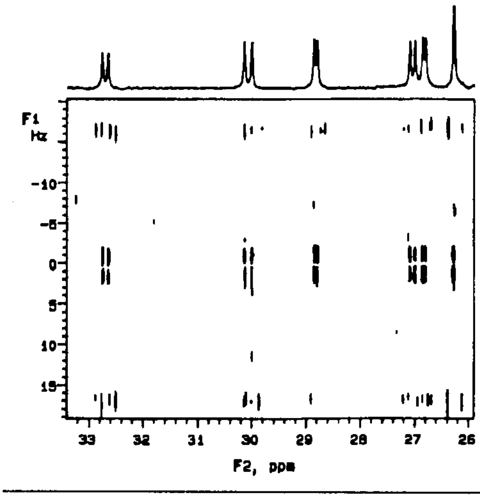

FIG. 3

"J resolved 2D INADEQUATE" ^{13}C NMR spectrum of the cyclohexyl carbons in dicyclohexylphenylphosphine. Pulse sequence of ref.[2], 128 transients accumulated for each of 40 increments, relaxation delay 4.0 s, spectral width 1 200 in F_2 axis and 50 Hz in F_1 axis, acquisition time for each transient 0.9 Hz, zero filled data matrices 256 × 8 192 weighted by Gaussian apodization in both directions, gf = 0.6 and $gf1$ = 0.3. Pure absorption phase sensitive presentation using States, Haberkorn and Ruben[11] method

In addition to the cross-peaks in the ellipse the spectrum shows a number of cross-peaks. Some of them are also due to long-range couplings (e.g. correlations between the doublets *B* and *D* or *E*, which are found in the 2D spectrum just above the larger ellipse) as indicated by the minimal separation of the satellites along the F_2 direction. Relatively large number of long-range correlations apparent from the 2D spectrum is in agreement with the failure of the "*J*-resolved INADEQUATE" experiment to resolve all the long-range couplings, they are of very close magnitude. Other correlations in the 2D spectrum, which are distinguished by about 35 Hz separation of the satellites along the F_2 axis, are due to the one-bond $^{13}C-^{13}C$ couplings (e.g. cross-peaks with the F_1 frequencies around 1 750 or 1 600). Since these two types of cross-peaks are so easily recognized, measuring of the long-range 2D INADEQUATE spectra appears to be of advantage since it contains considerably more information. In a number of instances the corresponding loss of the experiment's sensitivity due to the relaxation during the longer delay would be outweighed by the additional information gained.

With the completed assignment of the doublets in the ^{13}C NMR spectrum, a heteronuclear correlation can be utilized for the assignment of the ^{1}H NMR spectrum. From the HETCOR spectrum (Fig. 6) the cause for the apparent low resolution in the high frequency part of ^{1}H NMR spectrum is clear. This part of the spectrum originates in six protons the chemical shifts of which are very close. In the low frequency part, the signals of only five protons are observed and their chemical shifts cover the frequency range rather uniformly.

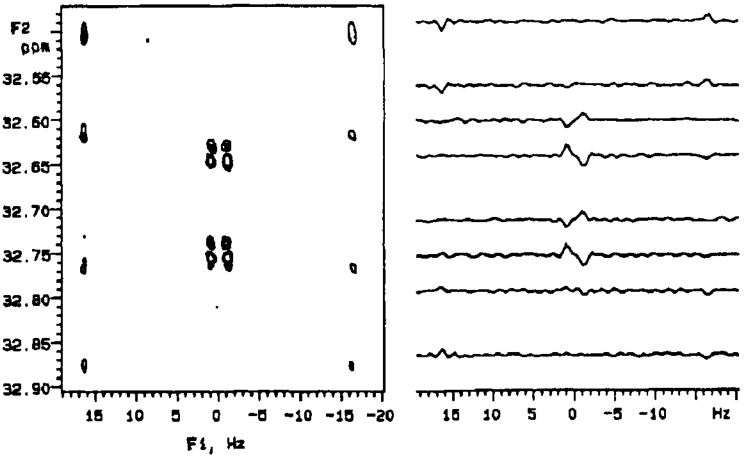

FIG. 4

Detail of doublet *A* of the "*J* resolved 2D INADEQUATE" ^{13}C NMR spectrum of dicyclohexylphenylphosphine. Left part contour map, right part traces along F_1 axis corresponding to maximum signals. The same experiment as shown in Fig. 3, except that the data were weighted for resolution enhancement, $lb = -0.37$, along t_1 axis prior to the second Fourier transformation

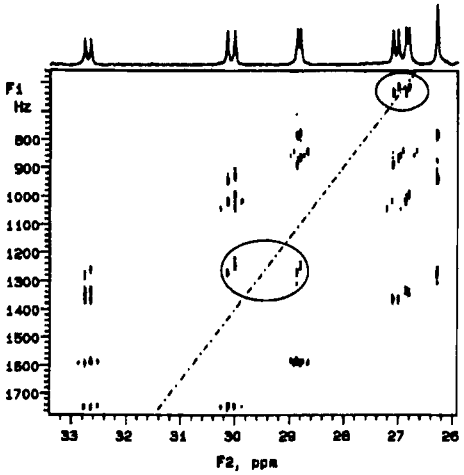

FIG. 5

Significant part of the long-range 2D INADEQUATE ^{13}C NMR spectrum of dicyclohexylphenylphosphine and its 1D ^{13}C NMR spectrum on the top. The broken line is the diagonal, ellipses mark the correlations decisive for the assignment. 128 transients accumulated for each of 70 increments, relaxation delay 3.0 s, spectral width 1 200 in F_2 axis and 2 400 Hz in F_1 axis, acquisition time for each transient 0.9 Hz, zero filled data matrices 1 024 × 8 192 weighted by Gaussian apodization in both directions, *gf* = 0.6 and *gf*1 = 0.3.

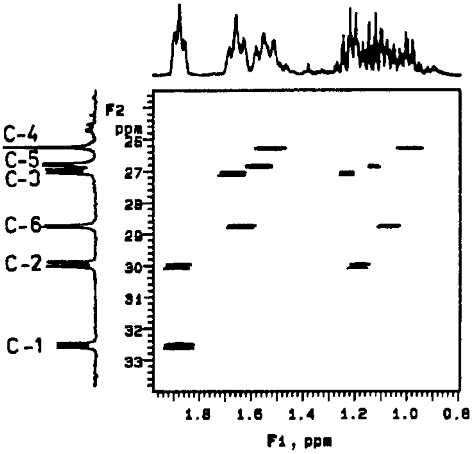

FIG. 6

HETCOR (^{13}C–^{1}H) 2D spectrum and the correlated 1D spectra of dicyclohexylphenylphosphine (cyclohexyl part only). Absolute value presentation of the 2D spectrum, 8 transients accumulated for each of 512 increments, relaxation delay 1.0 s, spectral width 1 200 in F_2 axis and 5 000 Hz in F_1 axis, acquisition time for each transient 0.5 Hz, zero filled data matrix 2 048 × 4 096 weighted by an exponential with *lb* = 1.0 along t_2 axis and by sine bell *sb*1 = 0.02 along t_1 axis.

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REFERENCES

1. Bax A., Freeman R., Kempsell S. P.: J. Am. Chem. Soc. *102*, 4849 (1980).
2. Bax A., Freeman R., Kempsell S. P.: J. Magn. Reson. *41*, 349 (1980).
3. Bax A., Freeman R., Frenkiel T. A.: J. Am. Chem. Soc. *103*, 2102 (1981).
4. Bax A., Freeman R., Frenkiel T. A., Levitt M. H.: J. Magn. Reson. *43*, 478 (1981).
5. Mareci T. H., Freeman R.: J. Magn. Reson. *48*, 158 (1982).
6. Sørensen O. W., Freeman R., Frenkiel T. A., Mareci T. H., Schuck R.: J. Magn. Reson. *46*, 180 (1982).
7. Sparks S. W., Ellis P. D.: J. Magn. Reson. *62*, 1 (1982).
8. Podkorytov I. S.: J. Magn. Reson. *89*, 129 (1990).
9. Patt S. L., Shoolery J. N.: J. Magn. Reson. *46*, 535 (1982).
10. Hjorkjaer J., Heinrich B., Čapka M.: Appl. Organometal. Chem., in press.

11. States D. J., Haberkorn R. A., Ruben D. J.: J. Magn. Reson. *48*, 286 (1982).
12. Hull W. E. in: *Pulse Methods in 1D and 2D Liquid-Phase NMR* (W. S. Brey, Ed.), p. 67. Academic Press, San Diego 1987.

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