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Spectroscopy Letters

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597299>

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To cite this Article Berger, S.(2000) 'Gradient Selected Constant Time Cosy', Spectroscopy Letters, 33: 1, 1 – 8

To link to this Article: DOI: 10.1080/00387010009350054

URL: <http://dx.doi.org/10.1080/00387010009350054>

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GRADIENT SELECTED CONSTANT TIME COSY

KEYWORDS: 2D-NMR, COSY, Pulsed Field Gradients

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ABSTRACT

A gradient selected constant time COSY pulse sequence is investigated and compared with other standard COSY techniques. It is shown that this variety of COSY has some advantages for routine spectroscopy in service laboratories.

INTRODUCTION

COSY (correlation spectroscopy)^{1,2} is certainly the most well known and often used 2D NMR method for structural elucidation of organic

compounds^{3,4}. It provides correlation signals for H,H spin pairs indicating connectivities over two, three and four bonds and can therefore be used to elucidate a molecular structure. A very large number of varieties have been described in the literature of the last 25 years⁵ where the COSY procedure was used extensively. We focus here on the application of the COSY technique in the routine service laboratory for organic chemistry. In this field the gradient selected absolute value COSY^{6,7} has become standard⁸ since the average customer is only interested in connectivities, but not in spin coupling constants. The virtues of this particular COSY technique are its robustness and speed; with typically one or two transients per FID one is finished after at most, 10 minutes and any other new proposed method must compete with this.

Nevertheless the experiment still suffers from deficiencies. Particularly in crowded regions near the diagonal one often has difficulties to obtain the correct connectivities. Smaller coupling constants which are slower evolving lead to cross peaks with reduced intensity. Very early in the COSY literature there was the ω_1 decoupled technique introduced⁹ where a 180° pulse was shifted through the t_1 period and the distance between the 90° excitation pulse and the mixing pulse was left constant. This constant time COSY was discussed in considerable detail by Ernst and co-workers¹⁰ and later Girvin¹¹ pointed out the advantages within the field of structural biology. Although the constant time principle is now a standard feature in 3D sequences for protein NMR, the method seems not to be used widely for the case of the simple COSY. For most of the standard 2D NMR techniques there are, by now, gradient selected versions reported, however to the best of our knowledge, for the simple constant time COSY a gradient selection was not looked at. We report here our findings and propose that this method should be considered as one of the methods for routine service.

EXPERIMENTAL

The spectra given in the Figures were measured in 3% solutions of strychnine in CDCl_3 or sucrose in D_2O using a Bruker DRX-400 spectrometer equipped with a multinuclear inverse probe head with additional coils for z -gradients. The gradient length was set to 1 ms with a strength in the order of 0.01 T/m. The 2D spectra for **1** were obtained with 1 scan for each of 256 fid's, a relaxation delay of 2 s and a time domain of 2 k were employed. For **2** 128 fid's of 1 k length were sampled. The constant time delay was set to 35 ms for **1** and 64 ms for **2**. The spectra were processed in the quadrature off mode using an exponential filtering in F_2 with $\text{lb} = 2.5$ Hz and a $\pi/3$ shifted squared cosine window in F_1 and were not symmetrized. The total time required for the spectra shown was 10 min.

RESULTS AND DISCUSSION

One of the difficulties of the constant time COSY, as pointed out by Freeman, is the accuracy of the 180° pulse. It was desirable that a gradient selected version should account for this. Therefore, we chose to employ the gradients one before and one after the 180° pulse and a final one before acquisition. Since the 180° pulse is embedded between two gradients these will control any imperfections of the 180° pulse. The pulse sequence is given in Fig. 1 together with one minor phase cycle, although, in practice it may be used only with one scan per fid. We compare the results on strychnine (**1**) and sucrose (**2**), which have become standards for introducing new NMR methods in the field of organic chemistry.

In Fig 2 an extension of the aromatic region of **1** is given, where a displays the result from the standard gradient selected COSY and b from

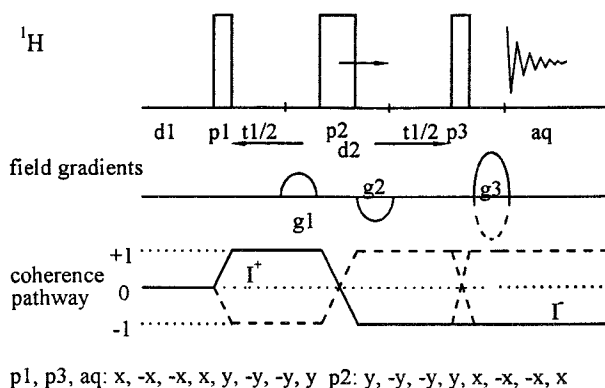
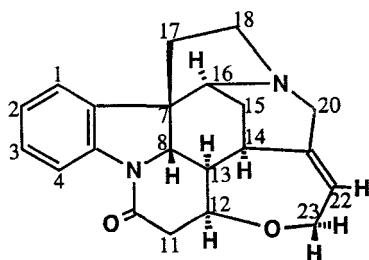


FIG. 1 Pulse sequence for gradient selected constant time COSY

the gradient selected constant time COSY. The spectra were plotted at the same level and the processing was identical. We observe two expected results. First, the sensitivity of the cross peaks is higher and the diagonal peaks are diminished. Due to the ω_1 decoupling the assignment of the cross peaks near the diagonal is much easier. These are certainly the main advantages of the techniques and we wonder, why the method is not that popular.

Comparison of Fig 2a with Fig 2b demonstrates that the constant time variant, which can also be regarded as a long range COSY, gives more information since long range couplings also give rise to cross peaks. Thus, we observe clearly in figure 2b the meta couplings in the aromatic ring. This may be sometimes undesirable, especially if nothing at all is known about the compound investigated, but this is seldom the case.

In Fig 3 we show a comparison for sucrose (2). Here in the crowded aliphatic region the advantages of the constant time COSY become apparent and the structure elucidation with the ω_1 decoupled cross peaks is



1

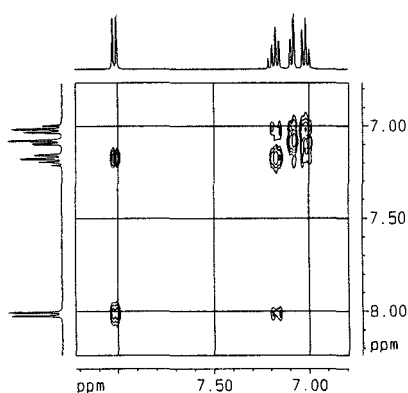


FIG. 2a

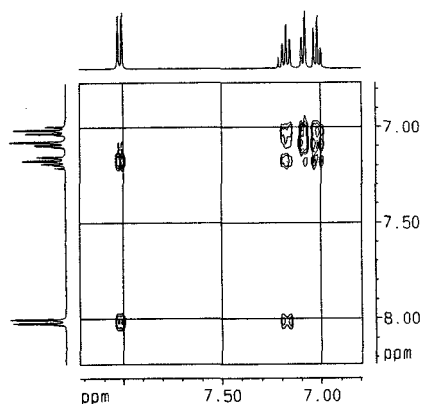


FIG. 2b

Expansion of the aromatic region of 1 using normal gradient COSY (a) and constant time gradient selected COSY (b)

definitively easier. However, close inspection of figure 3b also reveals an undesired result namely, two artefacts which can be seen in the F_1 column of the f_3 signal. It is not yet clear at present how one can avoid these artefacts.

The gradient technique employed here easily allows recording of the constant time COSY in the phase sensitive mode by using the echo anti-echo scheme. For this, the last gradient g_3 is changed in sign for every other

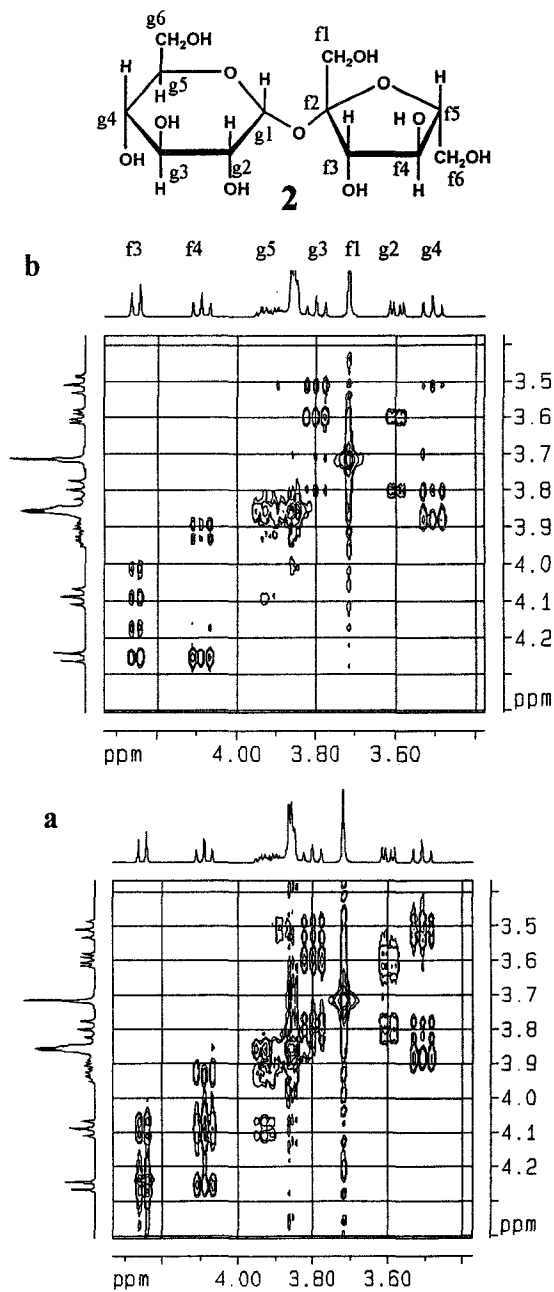


FIG.3

t_1 increment. We compared this result with a gradient COSY which was also recorded using the echo anti-echo principle. It was difficult to phase the constant time COSY in the F_1 dimension correctly. We feel that the value of this method is best if applied to the absolute value mode giving easier connectivity information than the standard method.

CONCLUSION

In this work we have demonstrated that the well known constant time COSY can be modified into a gradient selected version which is superior to the standard gradient selected COSY. We recommend considering it in routine applications for service laboratories.

ACKNOWLEDGEMENTS

This work was supported by the Fonds der Chemischen Industrie.

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Date Received: May 1, 1999

Date Accepted: September 1, 1999