trum in fact told him not the relaxation properties but the pattern of couplings between the spins. Although similar information could be obtained from a series of double-resonance experiments performed in the frequency domain, Jeener saw that the new 2D technique gave a very clear picture of the connectivities and that the sensitivity was essentially as high as a conventional 1D experiment. Unfortunately, these first 2D spectra were never published; the only reference to this work is in a set of lecture notes for a summer school (*17*).

This technique, which was comprehensively analyzed and put into practice by Ernst (*18*), became known as correlation spectroscopy (COSY). The spectrum consists of two types of response: diagonal peaks, which have the same frequency coordinates in both dimensions and reflect the conventional 1D spectrum, and cross peaks, which are responses that lie off the main diagonal and indicate which diagonal peaks are connected by spin coupling (Figure 6). This graphic representation of the network of scalar couplings has proved surprisingly useful as a general method for assigning NMR spectra. More important, as demonstrated by Ernst (*18*, *19*), it is the prototype of an entire family of 2D experiments discovered during the past 15 years.

Of particular importance to the study of biochemical molecules is an offshoot of COSY known as nuclear Overhauser enhancement spectroscopy (NOESY) applied to 2D proton NMR. The interaction responsible for forming cross peaks is the nuclear Overhauser effect, the enhancement of the intensity of one NMR line when the resonance of a close neighbor is saturated. Only if there is a significant dipole–dipole interaction between the two spins is there an Overhauser enhancement. Because this effect falls off as the inverse sixth power of distance, it provides a sensitive criterion for proximity within the molecule. An enormous amount of work on the structure and conformation of proteins in solution hinges on this particular experiment (*20*).

An organic chemist concerned with the structure of small molecules might be more attracted to a third

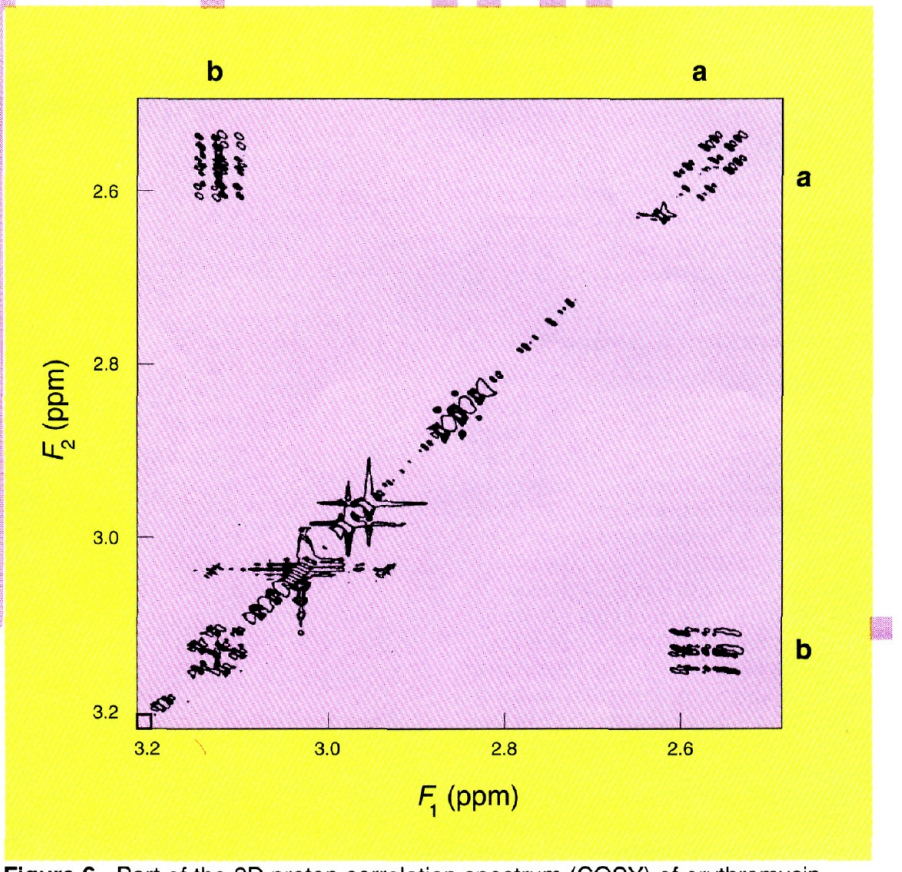

Figure 6. Part of the 2D proton correlation spectrum (COSY) of erythromycin showing a single pair of cross peaks, indicating that proton *a* is spin-coupled to proton *b*.