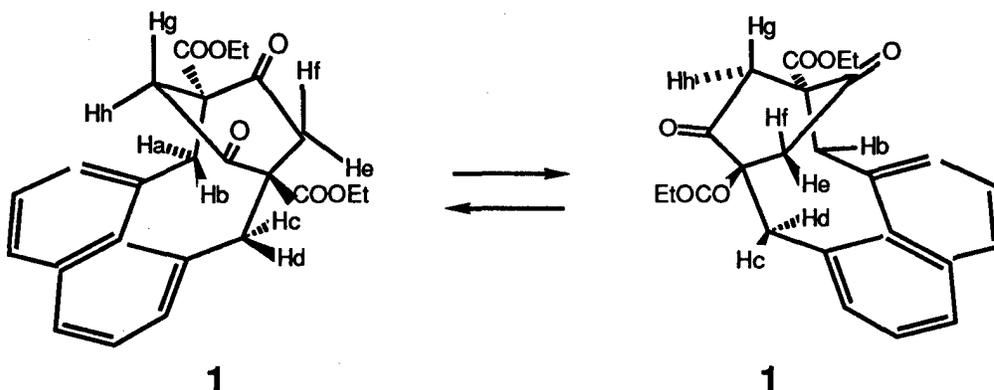


**SIGNALS ARISING SIMULTANEOUSLY DUE TO NOE AND NOE-TRANSFER  
IN DOUBLE RESONANCE DIFFERENCE SPECTROSCOPY.**

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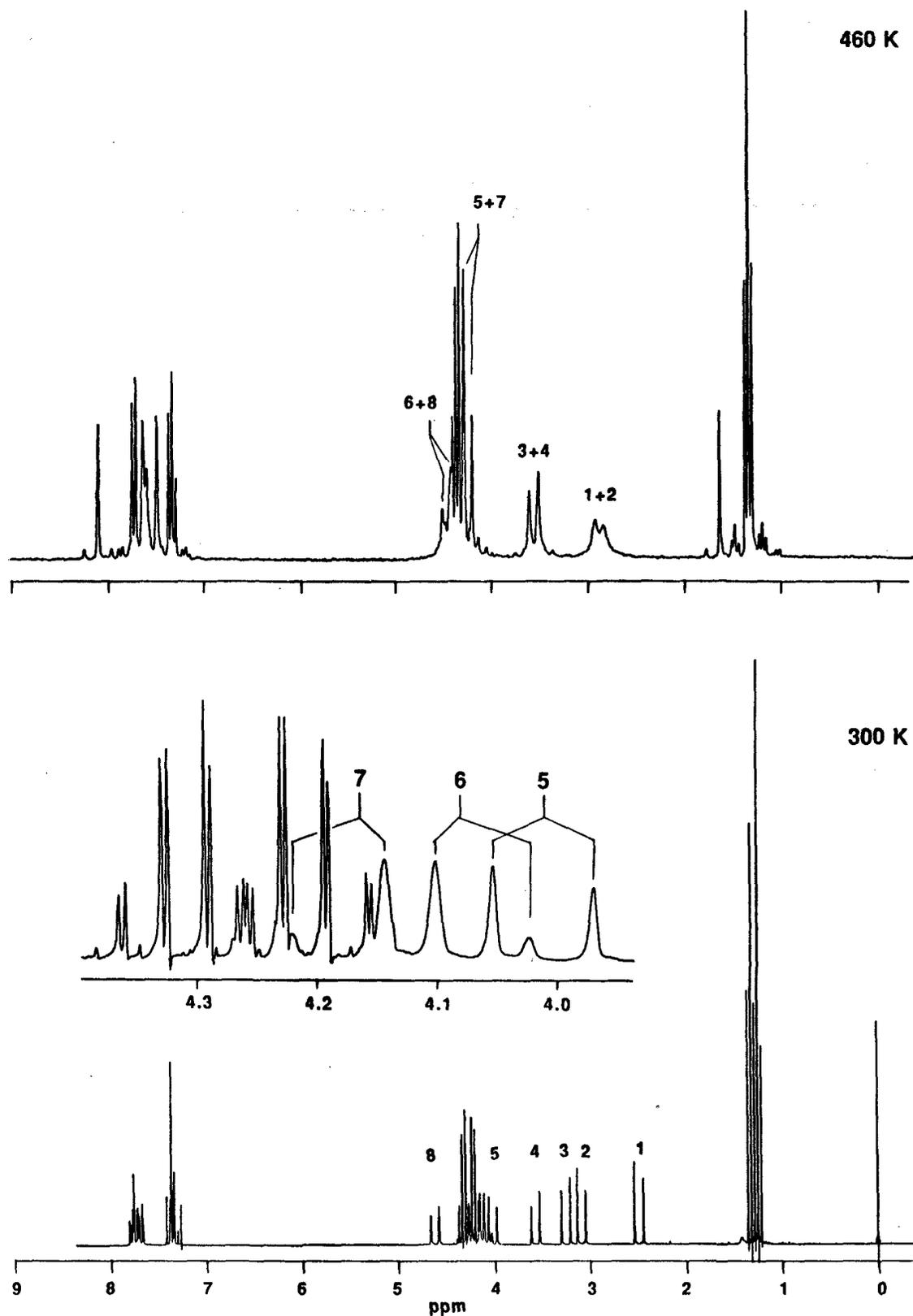
**Scheme 1**

The nine-membered ring in the bicyclic compound **1** undergoes ring reversal associated with chemical interchange (topomerization<sup>1</sup>) of pairs of protons that is slow relative to the NMR time scale (Scheme 1). At room temperature the <sup>1</sup>H-NMR spectrum of **1** (Figure 1) features well resolved doublets corresponding to the ring-protons labeled H<sub>a</sub> - H<sub>h</sub>. At elevated temperatures extensive line broadening and overlap of signals take place, due to chemical exchange, and do not permit assignment of exchanging protons. We utilized difference <sup>1</sup>H-NMR NOE and saturation transfer spectroscopy<sup>2</sup> to make this assignment, and encountered a phenomenon of generation of a signal by two different and nearly independent magnetization transfers.

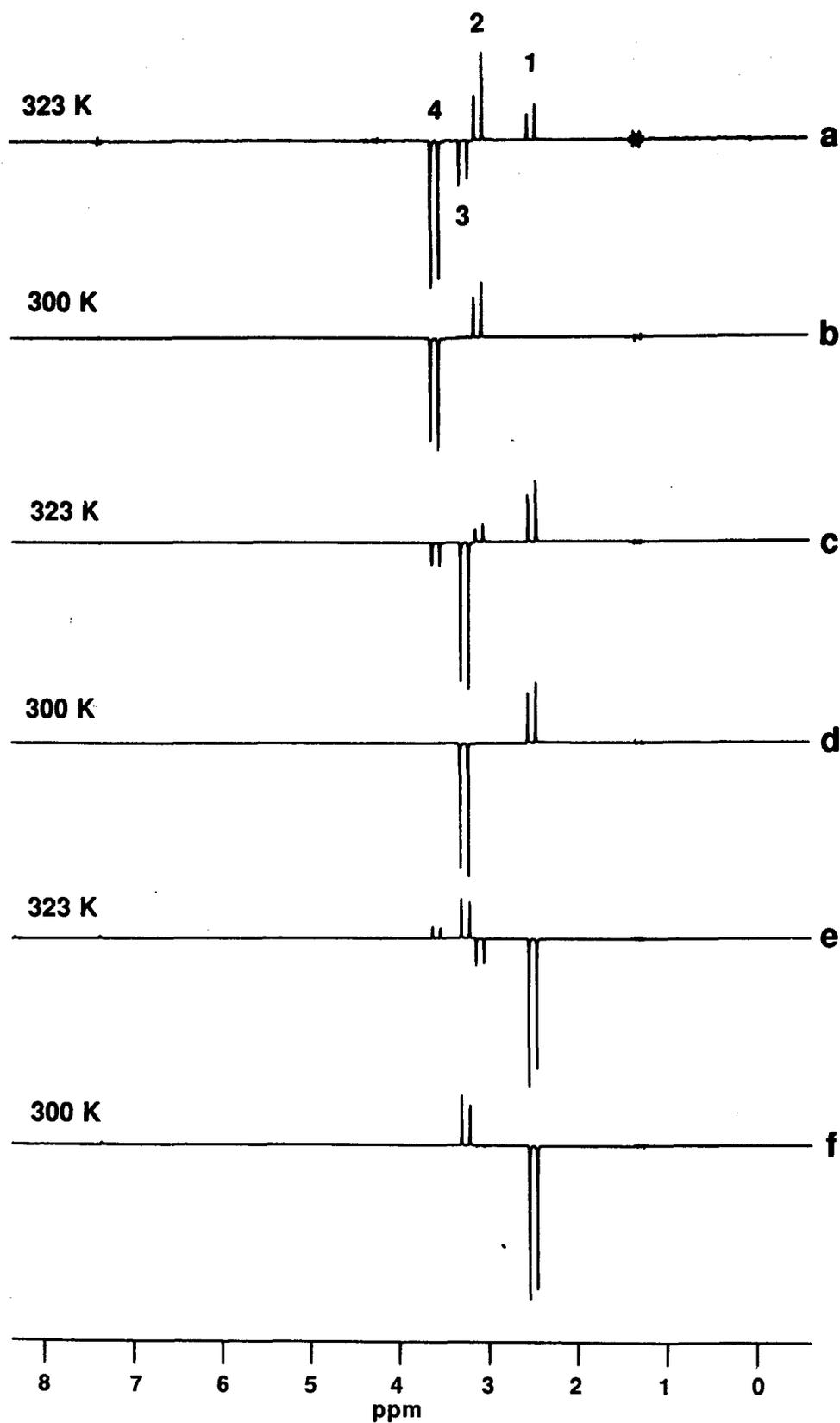
Difference spectra were measured at two temperatures, 300 K and 323 K (Figure 2). At the lower temperature, exchange was too slow to permit any significant

saturation transfer, and only strong NOE signals were found for each of the ring protons due to its geminal neighbor. Let us analyze traces **a** and **b** in Figure 2: low power irradiation at the doublet labeled **4** for several seconds prior to the observation pulse, at 300 K (trace **b**), resulted in positive NOE at site **2**, the signal due to the geminal partner of the irradiated proton. Thus the series of difference spectra measured at 300 K enabled straightforward identification of all geminal proton pairs (Table 1), an assignment also confirmed by a COSY spectrum at room temperature.

At the higher temperature (323 K, trace **a**), two additional doublets appeared upon irradiation at the same frequency, in addition to the NOE of the geminal proton **2**: the first of these (labeled **3**) is due to transfer of saturation from doublet **4** by chemical exchange, and readily allows assignment of that signal to the exchange partner of the irradiated signal **4**.



**Figure 1:** 200 MHz  $^1\text{H}$ -NMR spectra of **1**. Lower trace: Spectrum in  $\text{CDCl}_3$  solution at 300 K (The reference spectrum used for the difference-NOE measurements). Inset shows detail between 3.9 and 4.4 ppm, and the AB quartet labeled 6,7, which cannot be shown in the full spectrum due to overcrowding. Upper trace: Spectrum taken at 460 K in  $d_5$ -nitrobenzene solution, near the fast exchange limit. The four doublets are labeled according to the low temperature pairs of doublets which have coalesced into each one.



**Figure 2:** Difference NOE and saturation transfer spectra for 1. The relatively large negative doublet in each trace represents the irradiated (saturated) signal. Temperatures are marked on each trace.

The small positive doublet labeled 1 originates from two *simultaneous*, nearly independent, different magnetization transfer processes: It arises from indirect NOE due to the partly saturated signal 3, representing the geminal neighbor of the latter, as well as by chemical transfer of NOE ("negative saturation transfer") from doublet 2 through exchange. Both of these contributions are positive and add up to form signal 1. The indirect NOE behaves normally, in the sense that a negative signal at site 3 gives rise to a positive contribution (enhancement) at site 1. However, the transfer of magnetization due to chemical exchange is also positive, and is *opposite* to that usually expected for exchange signals. This is because the exchange now is not with a saturated nucleus (i.e., one in which the excited level is populated in excess to the Boltzmann equilibrium distribution), but rather with one in which the population of the *ground* level is enhanced, represented by the positive doublet 2.

The double-resonance difference-NMR experiments described here led to a complete and unequivocal assignment of the set of exchanging as well as geminal

proton-pairs, and eventually also to the individual proton assignments, as shown in Table 1.

The immediate consequence of this unique formation of a signal by two different magnetization transfers is that its intensity no longer corresponds in a simple manner to either the exchange rate or the proximity of the nuclei, but to a combination of both.

### Acknowledgments

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### References

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**Table 1:** Geminal and Exchange Connections and Proton Assignments in the NMR Spectrum of 1.<sup>a</sup>

Doublet:	1	2	3	4	5	6	7	8
Geminal:	3	4	1	2	8	7	6	5
Exchange:	2	1	4	3	7	8	5	6
Proton assignment:	H <sub>h</sub>	H <sub>e</sub>	H <sub>g</sub>	H <sub>f</sub>	H <sub>b</sub>	H <sub>c</sub>	H <sub>d</sub>	H <sub>a</sub>

a. Doublet labels are as in Figure 1. Proton labels are as in the left hand structure 1 in Scheme 1. Connections are to be read vertically: Doublet 1 forms a geminal pair with 3, exchanges with 2, and corresponds to H<sub>h</sub>.