

The Validity of Approximate Equations for k_c in Dynamic Nuclear Magnetic Resonance

By DANIEL KOST, ERIC H. CARLSON, and MORTON RABAN*

(Department of Chemistry, Wayne State University, Detroit, Michigan 48202)

Summary Rates of exchange at coalescence in d.n.m.r. spectroscopy obtained using approximate equations: (a) $k_c = (\pi/\sqrt{2})\Delta\nu$ and (b) $k_c = (\pi/\sqrt{2})\sqrt{(\Delta\nu)^2 + 6J^2}$, have been compared with those obtained by complete line shape analysis and have been found to give reliable estimates of free energies of activation within specified limits for coalescing singlets, doublets and AB quartets.

D.N.M.R. spectroscopy is one of the most powerful tools for the evaluation of rate constants for conformational changes with energies of activation in the range *ca.* 6—25 kcal mol⁻¹. Rate constants at the coalescence point (k_c) are usually evaluated using approximate equations: (a) $k_c = (\pi/\sqrt{2})\Delta\nu$, for the coalescence of singlets associated with uncoupled diastereotopic atoms or groups,² and (b) $k_c = (\pi/\sqrt{2})\sqrt{(\Delta\nu)^2 + 6J^2}$, for the coalescence of the coupled AB spin system to a singlet.³ Although the use of these approximate equations has been recently criticized as an unreliable procedure,^{1a} it has been shown, in some cases, that free energies of activation using approximate equations are in good agreement with the results of complete line shape analysis.⁴ Some of the errors in the use of approximate equations have been discussed previously.⁵

In order to determine the general validity of the approximate equations, we have carried out a systematic comparison of the rate constants obtained using equations (a) and (b) with those obtained by complete line shape analysis. We have also tested the validity of (a) for the coalescence of unequally intense singlets and for the coalescence of pairs of equally intense and unequally intense doublets into a single doublet as is encountered in the coalescence of isopropyl groups containing diastereotopic methyl groups or phenethyl methyl groups which exchange between diastereomeric environments. An additional approximate method for the evaluation of k_c for coalescence of unequally intense singlets, suggested by Shanan-Atidi and Bar-Eli,⁶ has also been compared with the results of complete line shape analysis.

In making comparisons between rates obtained using equation (a) and (b) and complete line shape analysis, it is important to realise that errors of 10, 25, and 100% in rate constants produce errors in ΔG^\ddagger of only 0.06, 0.1, and 0.4 kcal mol⁻¹ respectively, at 300 °K. An experimental error of $\pm 2^\circ$ corresponds to an error of *ca.* 1% in ΔG^\ddagger , (if T_c is near 300 °K) or *ca.* 0.1—0.2 kcal mol⁻¹. Since this is the generally accepted accuracy of temperature measurements, we have taken agreement of rates within 25% as acceptable,

† The coalescence point is defined such that a minimum between two coalescing signals has just vanished, *i.e.* $\partial G/\partial\nu = \partial^2 G/\partial\nu^2 = 0$.

‡ In cases where populations of sites are not equal because of an equilibrium constant different from unity, two rate constants (and free energies of activation) are involved corresponding to forward and backward reaction, $k_1/k_{-1} = K$. In subsequent discussion we shall refer to the higher of the two rate constants as k_1 or k_e . The other rate constant k_{-1} , is readily obtained by division by K .

and suggest that the approximate equation be judged valid when agreement is within this range.

Equation (a) is derived from the complete line shape expression for equally intense coalescing singlets. Nevertheless, we have found that the values for k_c obtained by complete line shape analysis for equally intense coalescing singlets or doublets[§] are within 20% of the rates obtained using the approximate equation, when $\Delta\nu$ is greater than 3 Hz.[¶] At smaller values of the chemical shift difference the deviation increases, although it is only 80 and 20%, for 1 and 3 Hz respectively for singlets or doublets. Equation (a) affords a good estimate[¶] of the larger rate k_1 for both coalescing singlets and doublets with different intensities so long as $\Delta\nu > 4$ Hz, e.g. Figure 1 shows the result obtained for an equilibrium constant, $K = 2$. The procedure of Shanan-Atidi and Bar-Eli yields estimates that are significantly closer to the complete line shape analysis rate

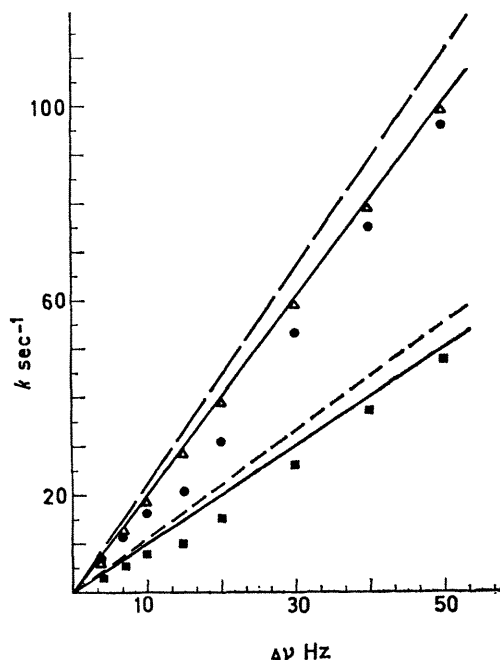


FIGURE 1. Rate constants determined at coalescence for singlets and pairs of doublets with $K = 2$. By approximate methods: — from $k_1 = (\pi/\sqrt{2})\Delta\nu$; - - - from $k_{-1} = (\pi/K\sqrt{2})\Delta\nu$; ——— k_1 and k_{-1} from the procedures used in ref. 6. By complete line shape analysis: Δ k_1 for singlets; \bullet k_1 for doublets and \blacksquare k_{-1} for doublets.

[§] For our calculations we assumed reasonable values of $T_2 = 0.4$ s and for doublets, J 7 Hz.

[¶] This is true for doublets except when the value of $\Delta\nu$ lies between $2J$ and $3J$. In this range the error rises to a maximum of about 70% corresponding to an error in ΔG^\ddagger of about 0.3 kcal/mol.

¹ For recent reviews on the theory and applications of d.n.m.r. see: (a) G. Binsch, in "Topics in Stereochemistry", Vol. 3, eds. E. L. Eliel and N. L. Allinger, John Wiley and Sons, New York, 1968, ch. 2; (b) R. Lynden-Bell, in "Progress in Nuclear Magnetic Resonance Spectroscopy," Vol. 2, eds. J. W. Emsley, J. Feeney, and L. H. Sutcliffe, Pergamon Press, Oxford, 1967, ch. 4; (c) C. S. Johnson, jun., in "Advances in Magnetic Resonance," Vol. 1, ed. J. S. Waugh, Academic Press, New York, 1965, ch. 2; (d) A. Rauk, L. C. Allen, and K. Mislow, *Angew. Chem. Internat. Edn.*, 1970, **9**, 400; (e) J. M. Lehn, *Fortschr. Chem. Forsch.*, 1970, **15**, 311; (f) J. B. Lambert, in "Topics in Stereochemistry," Vol. 6, eds. E. L. Eliel and N. L. Allinger, John Wiley and Sons, 1971; (g) H. Kessler, *Angew. Chem. Internat. Edn.*, 1970, **9**, 219; (h) W. E. Stewart and T. H. Siddal, *Chem. Rev.*, 1970, **70**, 517.

² J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, 1959, p. 223.

³ R. J. Kurland, M. B. Rubin, and M. B. Wise, *J. Chem. Phys.*, 1964, **40**, 2426.

⁴ (a) K. I. Dahlqvist, S. Forsen, and T. Alm, *Acta Chem. Scand.*, 1970, **24**, 651; (b) E. H. Carlson, F. B. Jones, jun., and M. Raban, *Chem. Comm.*, 1969, 1235; (c) M. Raban, F. B. Jones, jun., E. H. Carlson, E. Banucci, and N. A. LeBel, *J. Org. Chem.*, 1970, **35**, 1496; (d) W. Egan, R. Tang, G. Zon, and K. Mislow, in the press.

⁵ A. Allerhand, H. S. Gutowsky, J. Jonas, and R. A. Meinzer, *J. Amer. Chem. Soc.*, 1966, **88**, 3185.

⁶ H. Shanan-Atidi and K. H. Bar-Eli, *J. Phys. Chem.*, 1970, **74**, 961.

constants, but the difference in the rate constants using this procedure and equation (a) is always within 15%, whatever the value of the chemical shift difference or equilibrium constant. As illustrated, the lower rate is within acceptable agreement with either the estimate of Shanan-Atidi and Bar-Eli or the equation $k_{-1} = (\pi/K\sqrt{2})\Delta\nu$.

When coalescing nuclei are spin coupled to one another approximate equation (a) ceases to be accurate. For the coalescing AB quartet (Figure 2) equation (b) was in

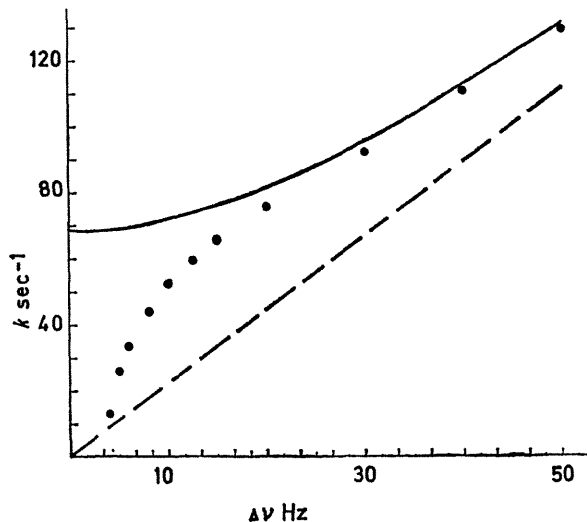


FIGURE 2. Rate constants determined at coalescence for an AB quartet with $J_{AB} = 12.5$ Hz. By approximate equations: — $k_c = (\pi/\sqrt{2})\sqrt{(\Delta\nu^2 + 6J^2)}$; - - - $k_c = (\pi/\sqrt{2})\Delta\nu$. By complete line shape analysis: \bullet .

acceptable agreement with the results of line shape analysis for $\Delta\nu > J$. Equation (a) was within an acceptable range only when $\Delta\nu/J > 3$, as the two functions began to converge. At lower values of the chemical shift difference the complete line shape rate constants began to deviate considerably and approached zero while equation (b) approaches a lower limit of $k_c = (\pi\sqrt{3})J$.

Thus equation (a) yields reliable estimates of rates of coalescence, in most cases, when nuclei are not spin coupled, and the coalescence rate constants of spin coupled nuclei (AB spin system) can be approximated using equation (b), but only if the chemical shift difference exceeds the coupling constant.

(Received, April 14th, 1971; Com. 535.)